Non pediatric Brain tumors treated with PBS Proton therapy

Educational Course

Prof. Dr.med. Damien Charles Weber

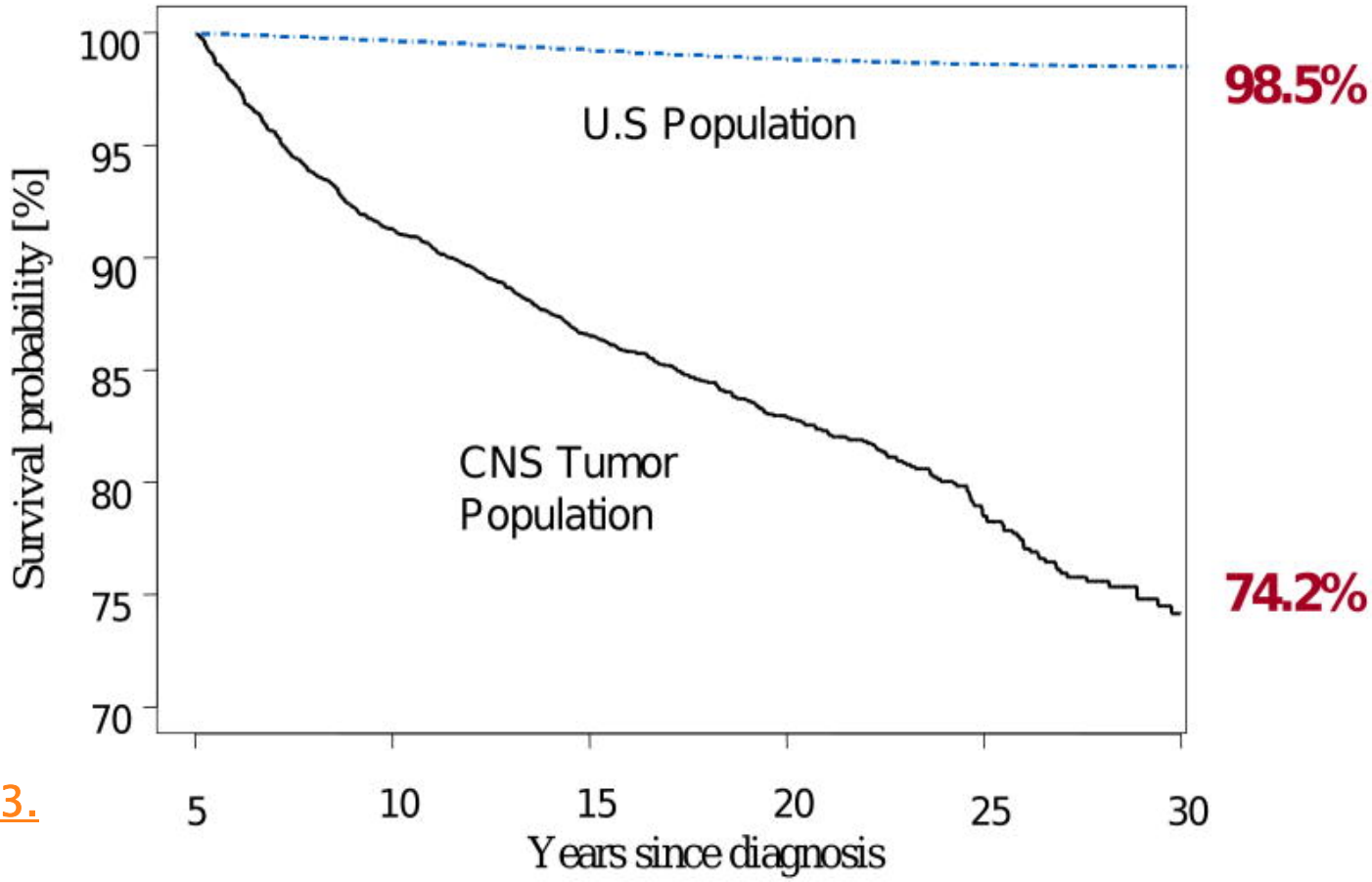
PTCOG 54, San Diego, CA

May 19th 2015 9:30-10:00 AM

Introduction

- RT plays a critical role in the local tumor control of brain tumors (meningiomas/LGG)
- The longer the survivorship, the better the therapeutic ration of PT.
- PT can be used for dose-escalation and/or
- PT can be used for decreasing the likelihood of radiation induced-toxicity
- Will limit this educational session to
  - Meningiomas
  - LGG

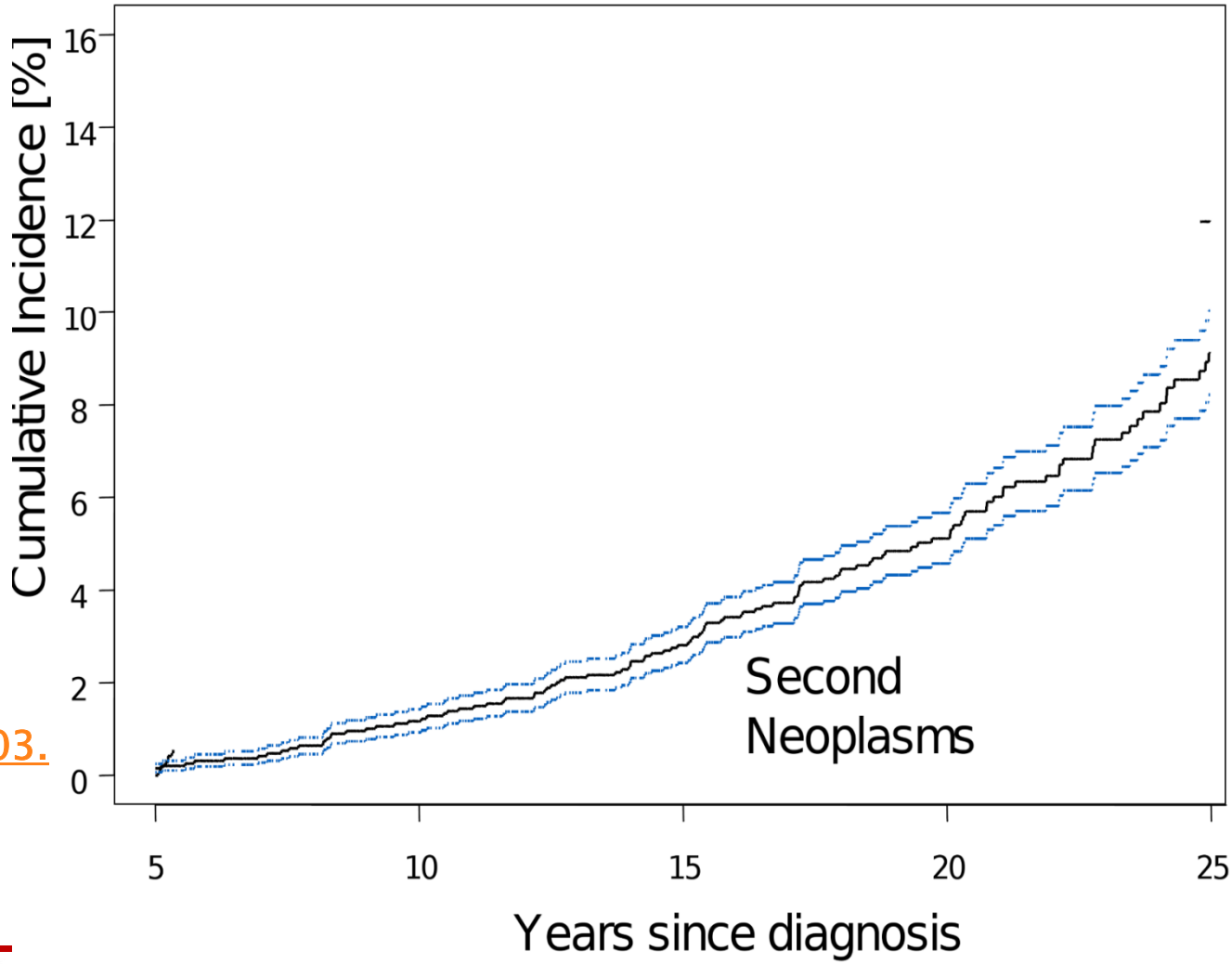
Why protons



Eur J Paediatr Neurol. 2010 July; 14(4): 298–303.

Long-term Survivors of Childhood Central Nervous System Malignancies: The Experience of the Childhood Cancer Survivor Study Gregory T. Armstrong, MD, MSCE

Why protons



10.7%

Eur J Paediatr Neurol. 2010 July; 14(4): 298–303.

Introduction

CNS Tumors (2014): 46.7%

*REG001-09 Enrollment by Disease Site – as of 31Apr2015

Meningioma & other benign tumors	19 (17.3%)
CNS tumors	32 (29.4%)
Chordoma	17 (15.6%)
Chondrosarcoma	7 (6.4%)
Soft tissue tumors	16 (14.7%)
Bone tumors	8 (7.3%)
H&N tumors	9 (8.3%)
Other	1 (0.9%)
Total	109 (100%)

Disease Site	Grand Total
Breast	200
CNS Adult	492
CNS Pediatric	335
Colorectal/Anal	64
Esophagus	68
Eye	58
Head & Neck	415
Liver	41
Lung	299
Lymphoma	86
Other	182
Pancreas	26
Prostate	2265
Sarcoma/Chordoma	322
Grand Total	4853

17%

PCG Proton Collaborative Group

Meningioma

- Majority are benign meningiomas
- Atypical (Grade II) or malignant (Grade III) account for 4.7 – 7.2% and 1.0 – 2.8% of all resected meningiomas
- Complete resection of Grade I meningiomas results 68 -92% long term control

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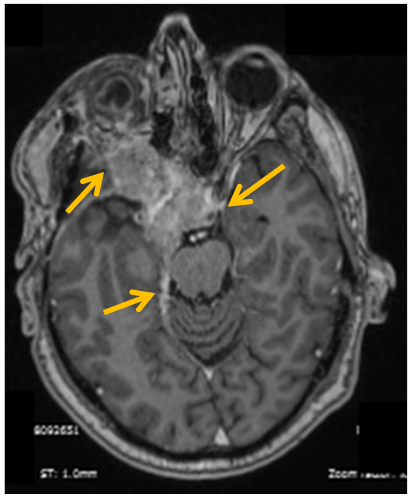
RT (open questions)

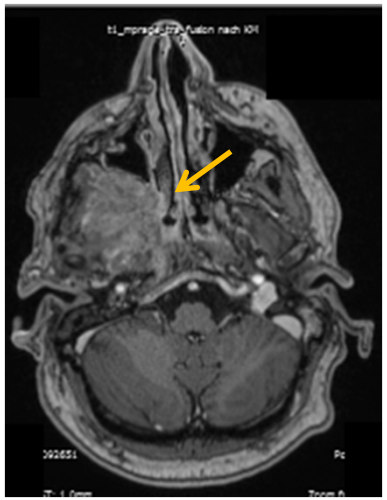
- Dose escalation EORTC 22042 / RTOG 0539
- Atypical (ROAM EORTC 1308) 'R0' (Simpson 1-3)

Proton Indication at PSI: complex benign meningiomas
atypical meningiomas
malignant meningiomas

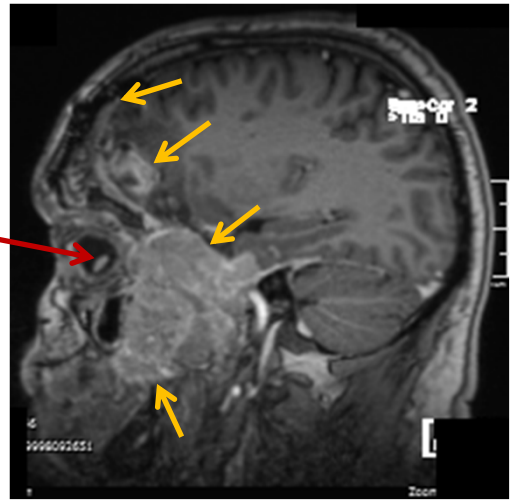
Meningioma – PSI Series

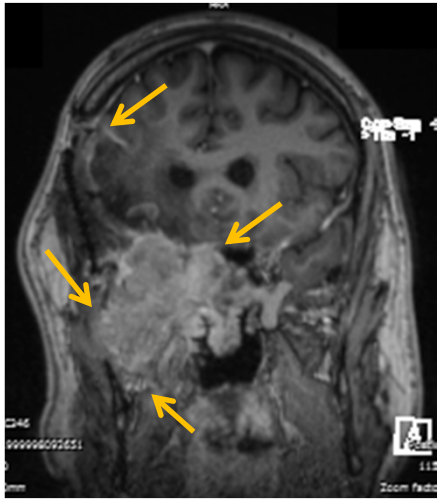
VOLUMETRICALLY CHALLENGING



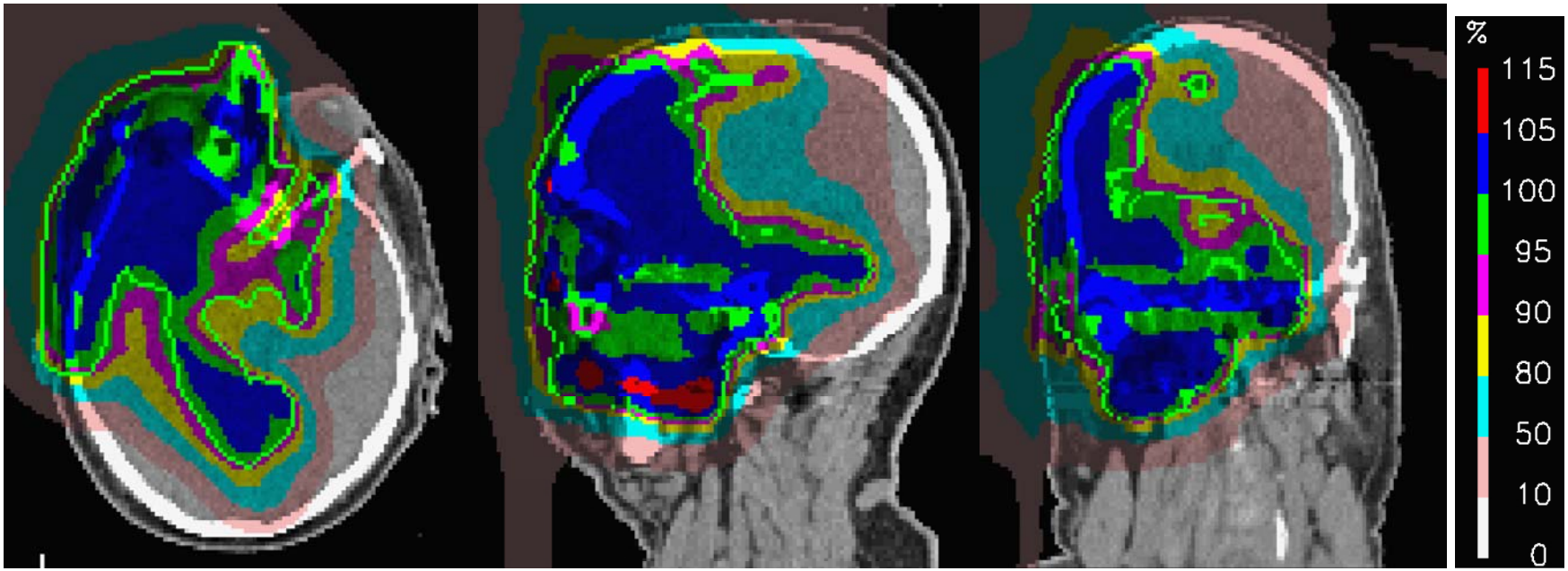


Subluxated Lens



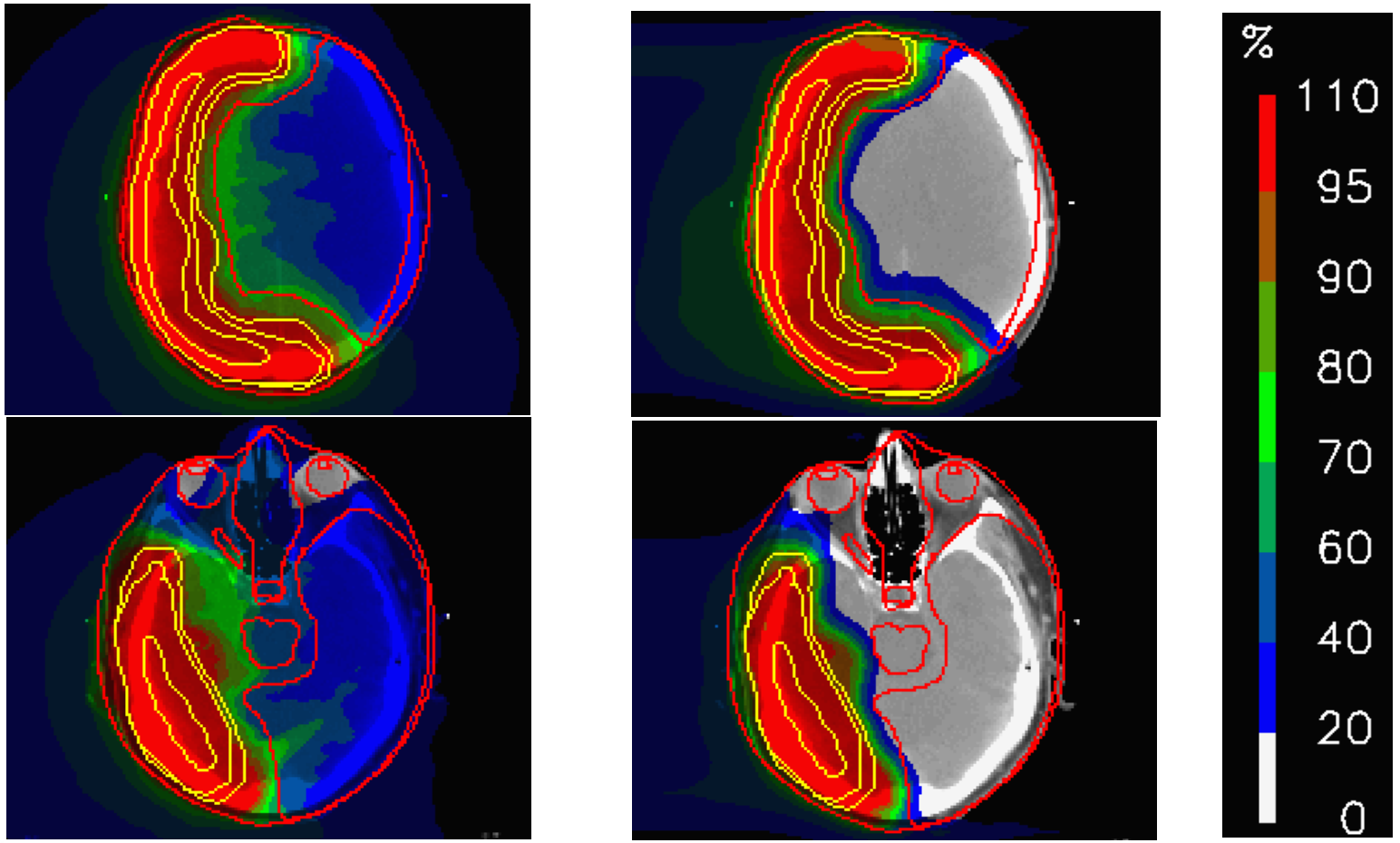


Meningioma – PSI Series



Meningioma

Tomotherapy **IMPT**

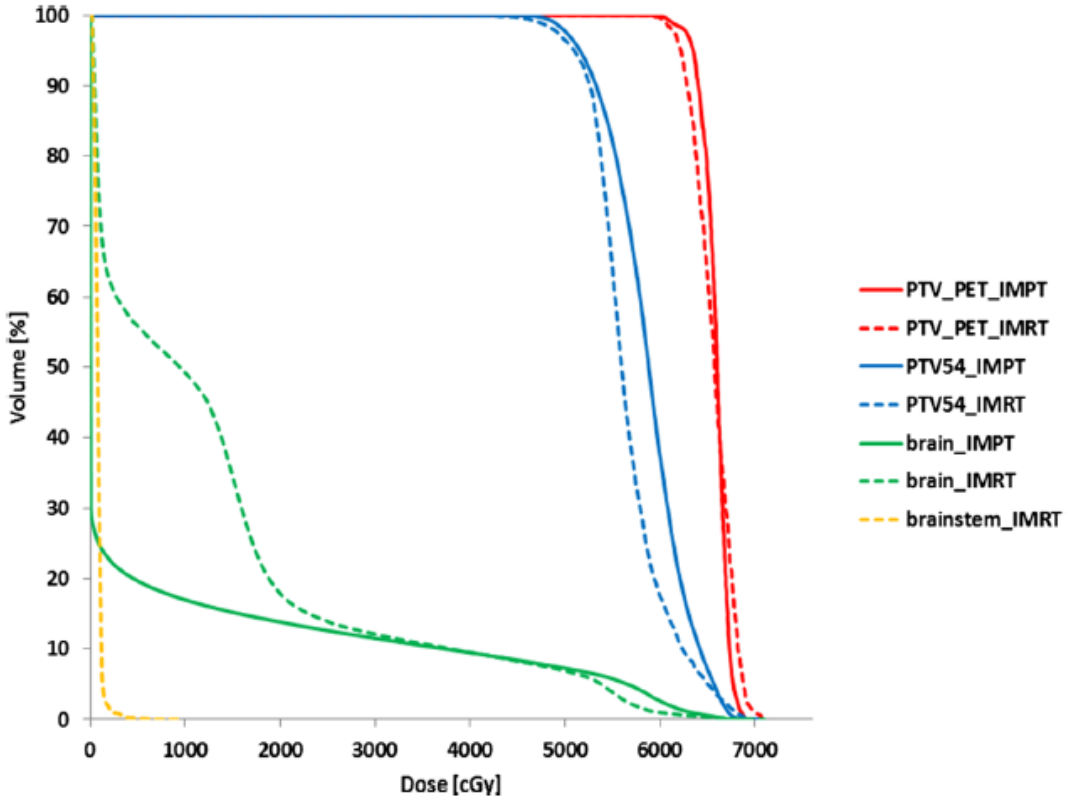


RADIATION ONCOLOGY

Meningioma

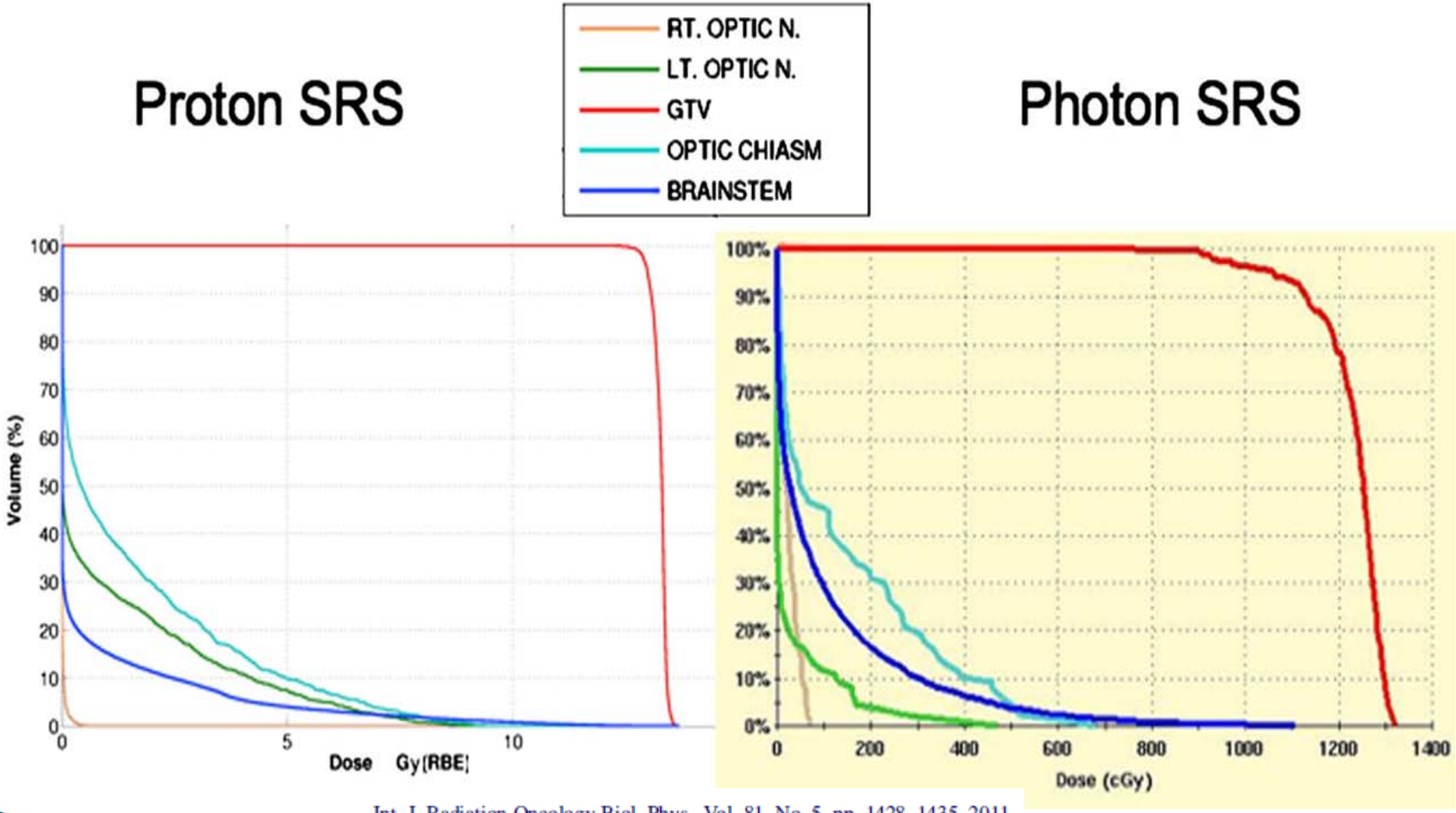
Dose-painting intensity-modulated proton therapy for intermediate- and high-risk meningioma

Indira Madani[1,2*], Antony J Lomax[1], Francesca Albertini[1], Petra Trnková[1] and Damien C Weber[1,3]



Madani *et al. Radiation Oncology* (2015) 10:72
DOI 10.1186/s13014-015-0384-x

PROTON STEREOTACTIC RADIOSURGERY FOR THE TREATMENT OF BENIGN MENINGIOMAS



Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 5, pp. 1428–1435, 2011

Meningioma

EORTC
European Organisation for Research and Treatment of Cancer

AISBL International Non-Profit Association under Belgian law IVZW

EORTC Data Center
Avenue E. Mounierlaan 83 / 11
Brussel 1200 Bruxelles
België - Belgique
Tel : +32 2 774 16 11
Fax : +32 2 772 35 45
E-mail : eortc@eortc.be
Web : http://www.eortc.be

EORTC Radiotherapy Group

EORTC Brain Tumor Group

Adjuvant postoperative high-dose radiotherapy for atypical and malignant meningioma: a Phase-II and observation study

EORTC protocol 22042_26042

PAUL SCHERRER INSTITUT PSI

Center for Proton Therapy

b UNIVERSITÄT BERN

Universität Zürich[UZH]

Meningioma

Study	Grade WHO	N=	Median Dose Gy RBE	Outcome
Orsay (2005)	1	51	60.6*	1/51 PD (G3)
Heidelberg (2011)	2-3	10	18 GyE	5yOS: 90% 10yOS:90%
MGH (2011)	1	50	13 pSRS	3yLC: 94%
LLMC (2012)	Cavernous sinus meningioma 1-2	72	57-59	LC 99% G1 LC 50% G2
PSI	1-3	39	56	LC 84.8% LC G1 100%
Orsay (2015)	1* (ONSM)	15	52.2*	LC 100%
Bloomington (2015)	2	22	63	**5yLC: 71.7%** < 60 Gy: 50% > 60 Gy 87.5%

Visual Toxicity

Toxicity type	N= (%)
Grade 4 Optic neuropathy	2 (5)
Grade 2 Retinis	2 (5)
TOTAL	4 (10)

Spot Scanning-Based Proton Therapy for Intracranial Meningioma: Long-Term Results From the Paul Scherrer Institute

Int J Radiation Oncol Biol Phys, Vol. 83, No. 3, pp. 865–871, 2012

J Neuroophthalmol. 2013 Jun;33(2):165-8. doi: 10.1097/WNO.0b013e31828292b8.

Radiation optic neuropathy after proton beam therapy for optic nerve sheath meningioma.

Siddiqui JD[1], Loeffler JS, Murphy MA.

1 patient treated with 50.4 Gy RBE. 27 months post PT, developp. of a RON

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

[a] Student *T*-test.

Radiotherapy and Oncology 81 (2006) 243–249

36 27 19 10 5 1

Meningioma – PSI Series

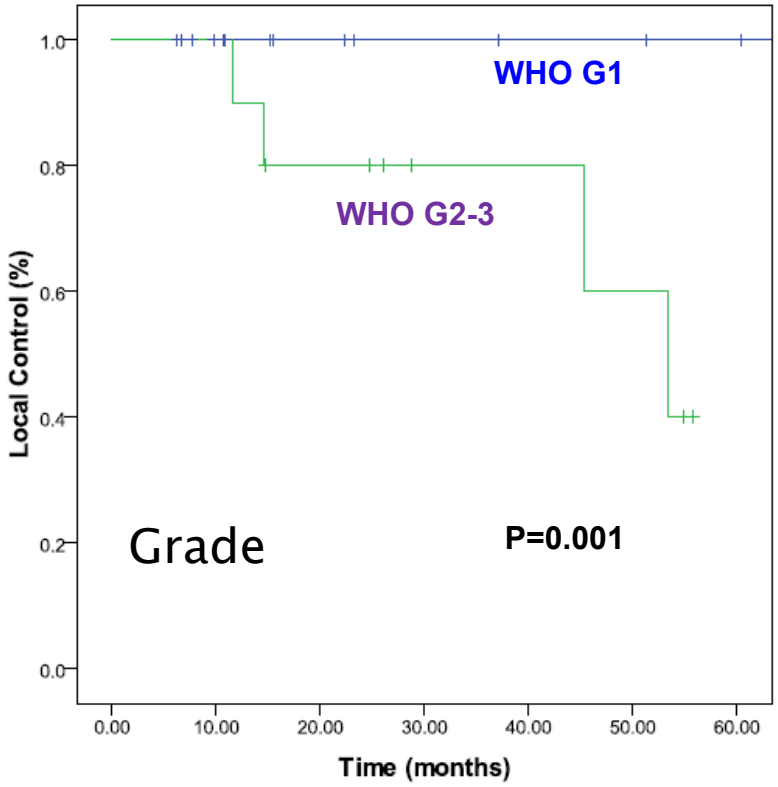
Weber *et al.* Int J Radiat Oncol Biol Phys 2012;83(3):865–71

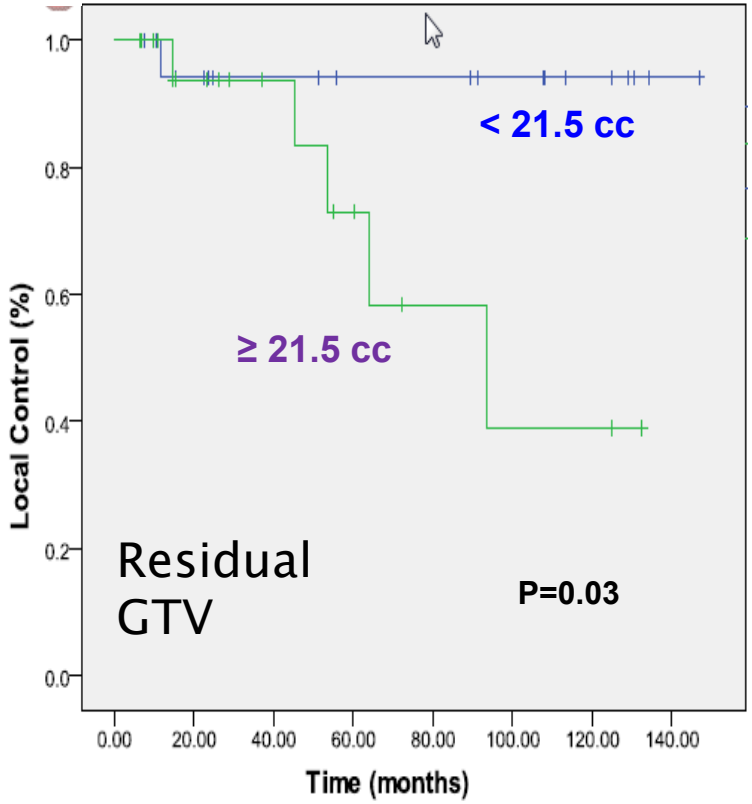
- **N = 39**
  - **24 benign**
  - **9 atypical**
  - **1 malignant**
  - **5 (radiological dx)**
- **1997 - 2010**
- **median prescribed dose 56 Gy(RBE) (range, 52.2–66.6)**
- **median follow-up 54.8 months (range, 6.23 – 146.7)**

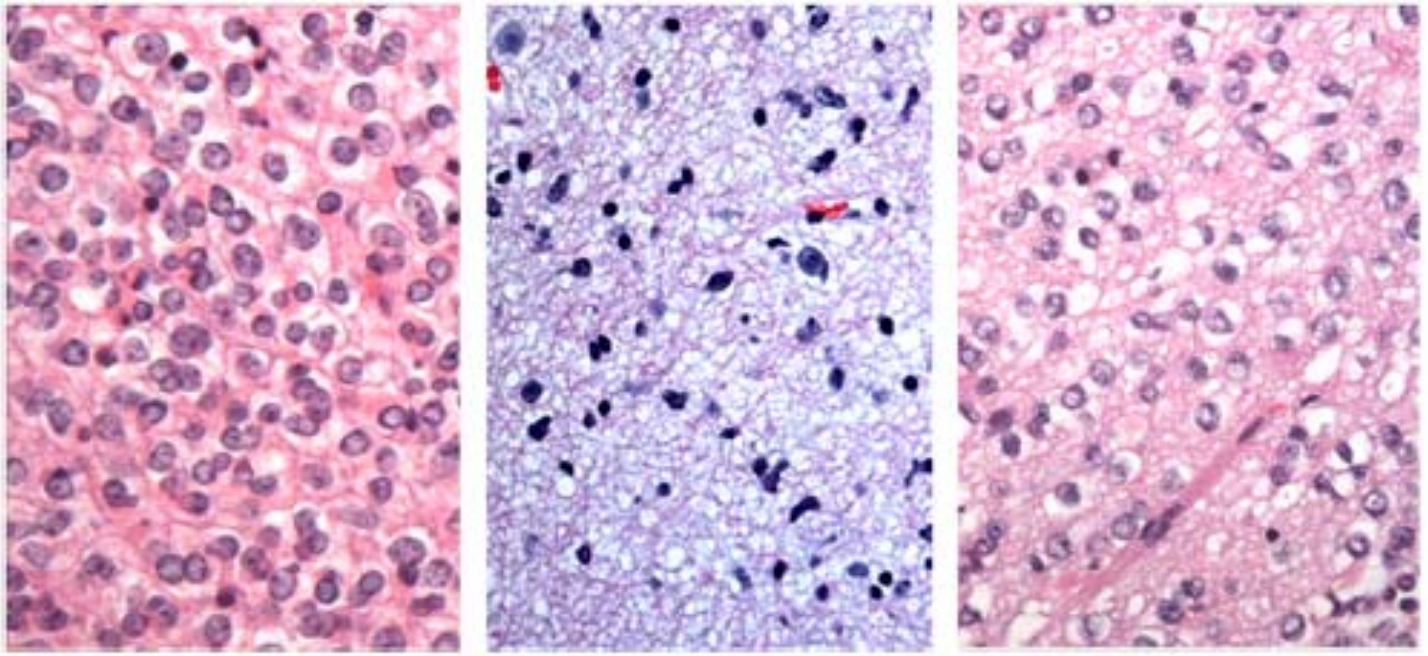
- **5-yr overall local control = 84.8%**
- **5-yr Grade I local control = 100%**
- **5-yr toxicity free survival = 84.5%**

Meningioma – PSI Series

Weber et al. Int J Radiat Oncol Biol Phys 2012;83(3):865-71





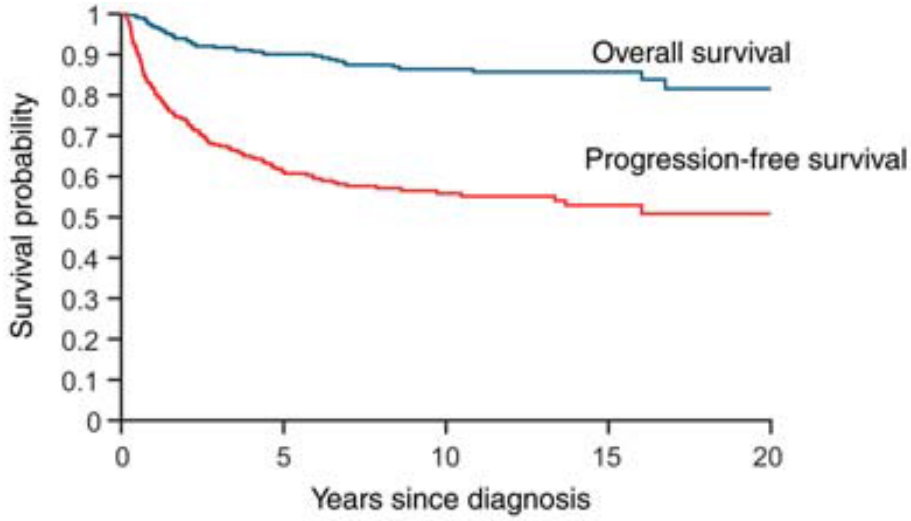


- generally have an indolent course **with longer-term survival** in comparison with high-grade gliomas (median OS 7-10 years)
- the impact of treatment on neurocognitive function and quality of life is of paramount importance.

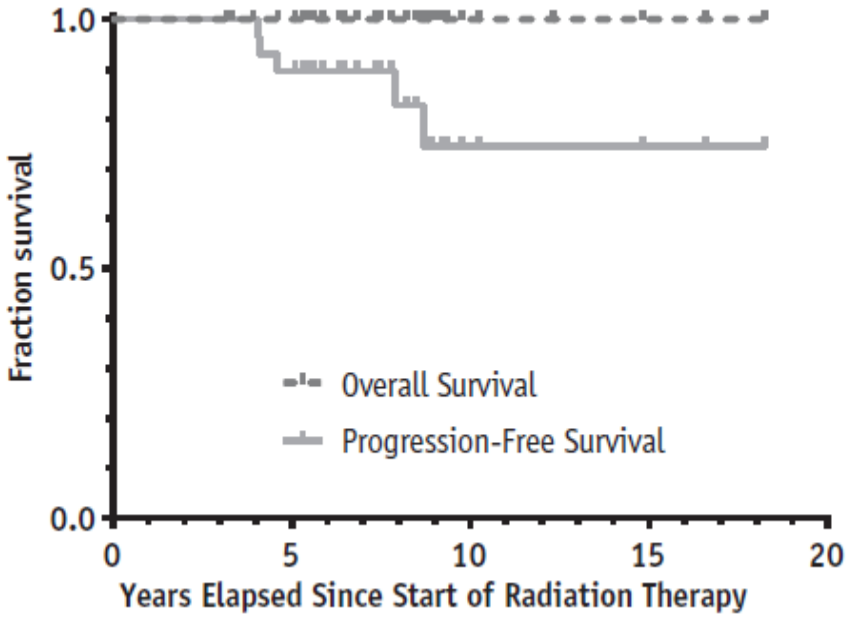
Low grade gliomas

Neuro-Oncology 13(2):223–234, 2011.
doi:10.1093/neuonc/noq178

Benjamin A. Greenberger, AB,* Margaret B. Pulsifer, PhD,† David H. Ebb, MD,‡ Shannon M. MacDonald, MD,§ Robin M. Jones, MD,‡,‖ William E. Butler, MD,¶ Mary S. Huang, MD,‡ Karen J. Marcus, MD,# Jennifer A. Oberg, ED,** Nancy J. Tarbell, MD,*,§ and Torunn I. Yock, MD§



OS	1.0 (361)	0.90 (250)	0.87 (138)	0.86 (60)	0.82 (11)
PFS	1.0 (361)	0.61 (163)	0.58 (81)	0.53 (36)	0.51 (8)



Int J Radiation Oncol Biol Phys, Vol. 89, No. 5, pp. 1060–1068, 2014

Gregory T. Armstrong, Heather M. Conklin, Sujuan Huang, Deokumar Srivastava, Robert Sanford, David W. Ellison, Thomas E. Merchant, Melissa M. Hudson, Mary Ellen Hoehn, Leslie L. Robison, Amar Gajjar, and E. Brannon Morris

Low grade gliomas

Treatment modality	Summary
Observation	May be reasonable in low-risk patients with minimal or no symptoms [4]. Less favored in patients with high-risk features [17, 22, 23]: • Age ≥40 • Astrocytic tumor type
Surger	from of
Radiati	dose all ant
Chemo	patients treated with temozolomide-based chemotherapy [17, 40]. Trend toward improvement in OS in 1p-deleted tumors treated with temozolomide [45]. Investigations are underway to evaluate role of combined chemotherapy/radiotherapy approaches [46].

May be reasonable in low-risk patients with minimal or no symptoms [4].

Less favored in patients with high-risk features [17, 22, 23]:

- Age ≥40
- Astrocytic tumor type
- Tumor size ≥6 cm
- Tumor crossing midline
- Presence of neurologic deficits

Forst D et al. The Oncologist 2014;19:403

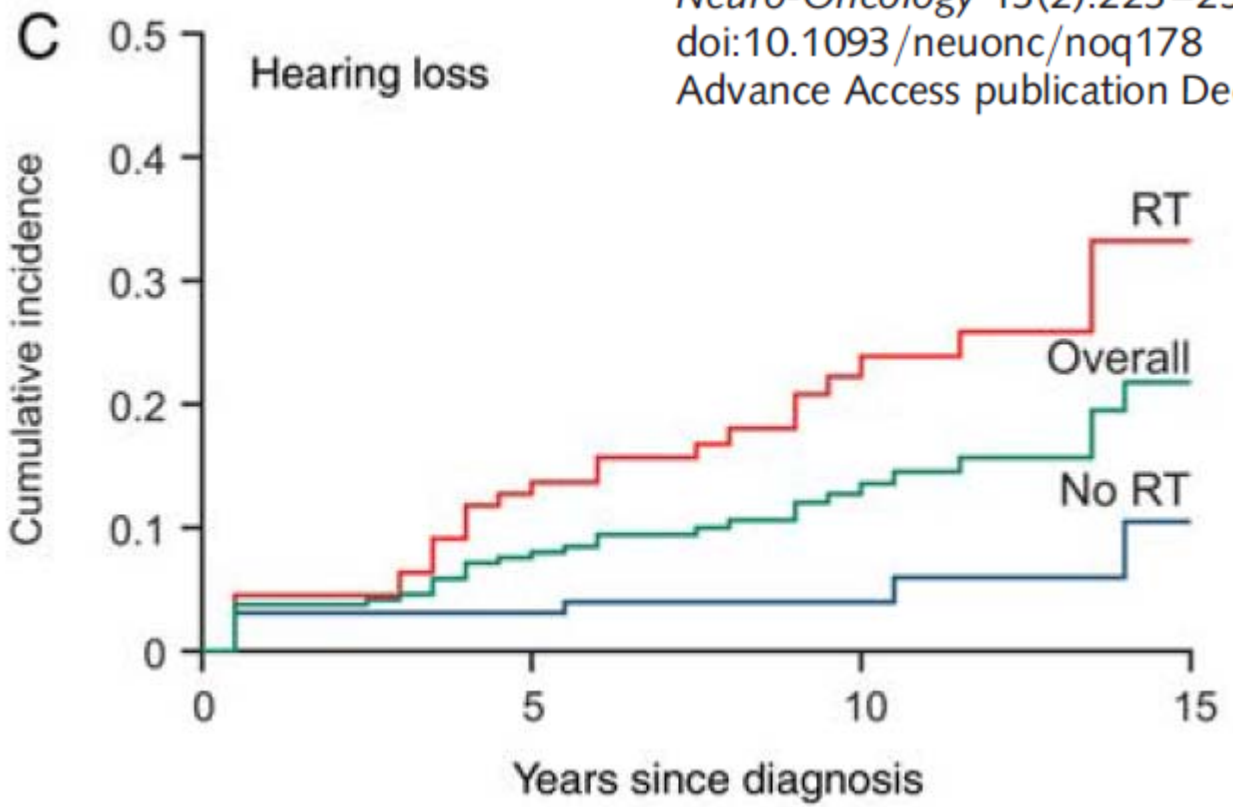
Low grade gliomas

Study	Patient N=	Treatement	Outcome

Radiotherapy is an Important comp. therapeutic startegy

Low grade gliomas

Neuro-Oncology 13(2):223–234, 2011.
doi:10.1093/neuonc/noq178
Advance Access publication December 22, 2010



Gregory T. Armstrong, Heather M. Conklin, Sujuan Huang, Deokumar Srivastava, Robert Sanford, David W. Ellison, Thomas E. Merchant, Melissa M. Hudson, Mary Ellen Hoehn, Leslie L. Robison, Amar Gajjar, and E. Brannon Morris

Greenberger BA et al. **Low grade gliomas** N=12/32

Int J Radiation Oncol Biol Phys, Vol. 89, No. 5, pp. 1060–1068, 2014

Type of cognitive test	Baseline mean (SD)	Follow-up mean (SD)	Mean change (SD of difference)	Paired sample 2-tailed Student *t* test *P* value	Median start of RT to max follow-up time, y (min, max)
Full-Scale IQ (n=11)	109.3 (9.3)	108.5 (12.3)	−0.7 (9.2)	.80	4.5 (1.2, 8.1)
Began RT at <7 years (n=4)	113.8 (10.2)	107 (15.1)	−6.75 (5.4)	.089	4.0 (1.9, 8.1)
Began RT at >7 years (n=7)	106.7 (8.4)	109.4 (11.6)	2.7 (9.3)	.47	4.5 (1.2, 7.8)
Supratentorial tumor (n=9)	111 (9.4)	110.8 (12.0)	−0.22 (9.5)	.95	4.4 (1.2, 8.1)
Infratentorial tumor (n=2)	101.5 (0.71)	98.5 (10.6)	−3 (9.9)	.74	5.5 (5.3, 5.7)
High-risk dose* (n=4)	107.3 (7.8)	97 (9.7)	−10.3 (2.5)	**.0038**	4.0 (1.9, 7.8)
Low-risk dose (n=7)	110.4 (10.4)	115.1 (8.1)	4.7 (6.5)	.10	4.5 (1.2, 8.1)
Verbal Comprehension Index (n=12)	113.2 (12.9)	112.7 (13.9)	−0.5 (11.7)	.88	4.9 (1.2, 8.1)
Began RT at <7 years (n=4)	126 (10.1)	114.5 (14.5)	−11.5 (6.4)	**.036**	4.0 (1.9, 8.1)
Began RT at >7 years (n=8)	106.8 (8.8)	111.8 (14.4)	5 (9.7)	.19	5.1 (1.2, 7.8)
Supratentorial tumor (n=9)	114.9 (13.8)	114.4 (14.8)	−0.44 (11.3)	.91	4.5 (1.2, 8.1)
Infratentorial tumor (n=3)	108 (10)	107.3 (11.0)	−0.67 (15.5)	.95	5.3 (2.9, 6.7)
High-risk dose* (n=4)	117.8 (17.6)	104.3 (17.8)	−13.5 (3.3)	**.0039**	4.0 (1.9, 7.8)
Low-risk dose (n=8)	110.9 (10.5)	116.9 (10.3)	6 (8.1)	.074	5.1 (1.2, 8.1)
Perceptual Reasoning Index (n=12)	107.7 (10.5)	107.5 (13.2)	−0.17 (9.8)	.95	4.9 (1.2, 8.1)
Began RT at <7 years (n=4)	102.3 (14.9)	105.5 (14.7)	3.3 (5.5)	.32	4.0 (1.9, 8.1)
Began RT at >7 years (n=8)	110.4 (7.2)	108.5 (13.3)	−1.9 (11.4)	.66	5.1 (1.2, 7.8)
Supratentorial tumor (n=9)	109.6 (11.4)	108.8 (14.0)	−0.78 (10.7)	.83	4.5 (1.2, 8.1)
Infratentorial tumor (n=3)	102 (4)	103.7 (11.9)	1.7 (8.1)	.76	5.3 (2.9, 5.7)
High-risk dose* (n=4)	100.5 (12.5)	97.8 (11.6)	−2.8 (13.9)	.72	4.0 (1.9, 7.8)
Low-risk dose (n=8)	111.3 (7.9)	112.4 (11.6)	1.1 (8.0)	.70	5.1 (1.2, 8.1)

* High risk is defined as receiving at least 15 Gy_{RBE} to 20% of the volume of the left temporal lobe or hippocampus.

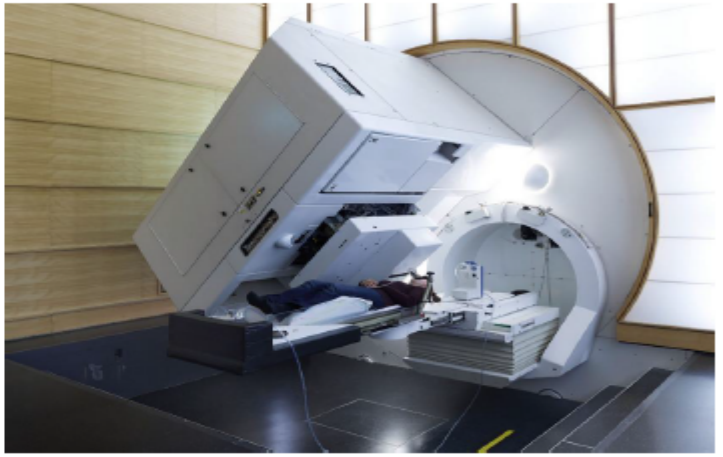
Low grade glioma – PSI Series

PFS	56%
OS	83.4%
Toxicity Grade 2-3 late **radiation necrosis** developed in one	2 (7%) and 1(4%)
Grade 2 hypopituitarism	8(29%)
Grade 2 memory or **cognitive impairment**	2 (7%)

Low grade glioma – PSI Series

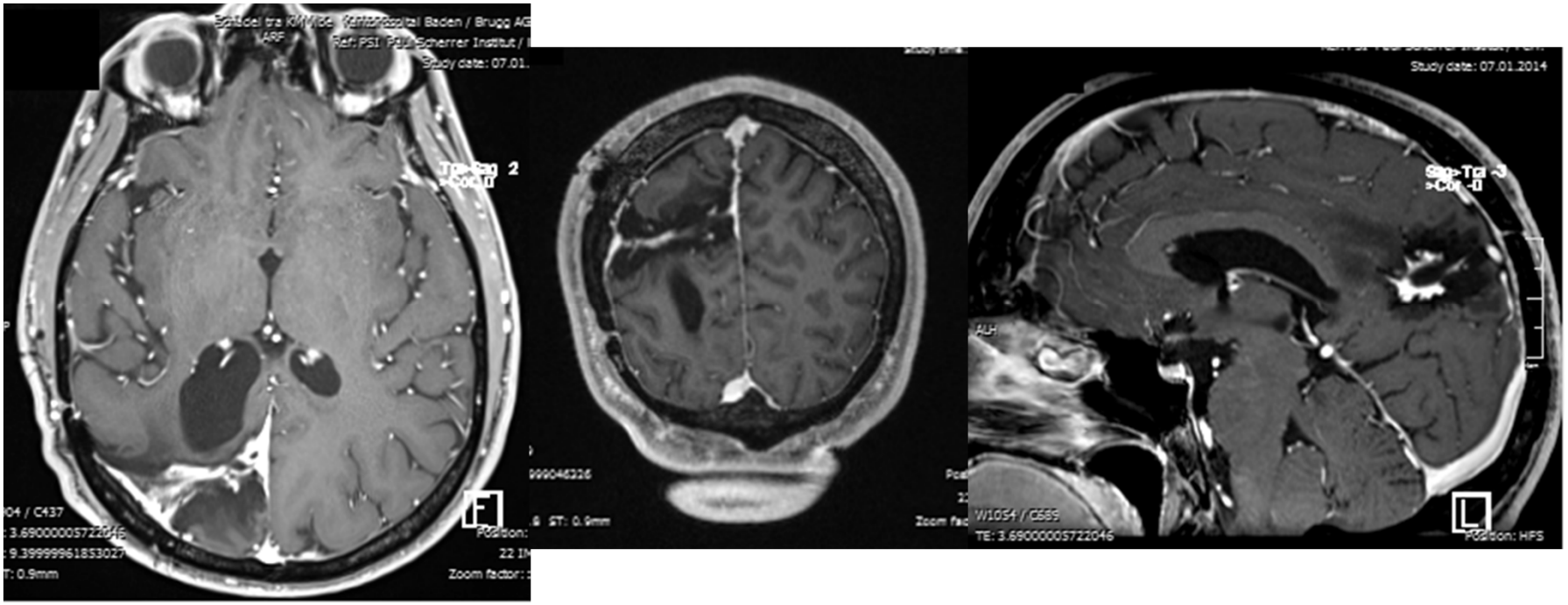
PAUL SCHERRER INSTITUT

Clinical and radiological outcomes of adults and children with low-grade glioma treated with pencil beam scanning proton therapy

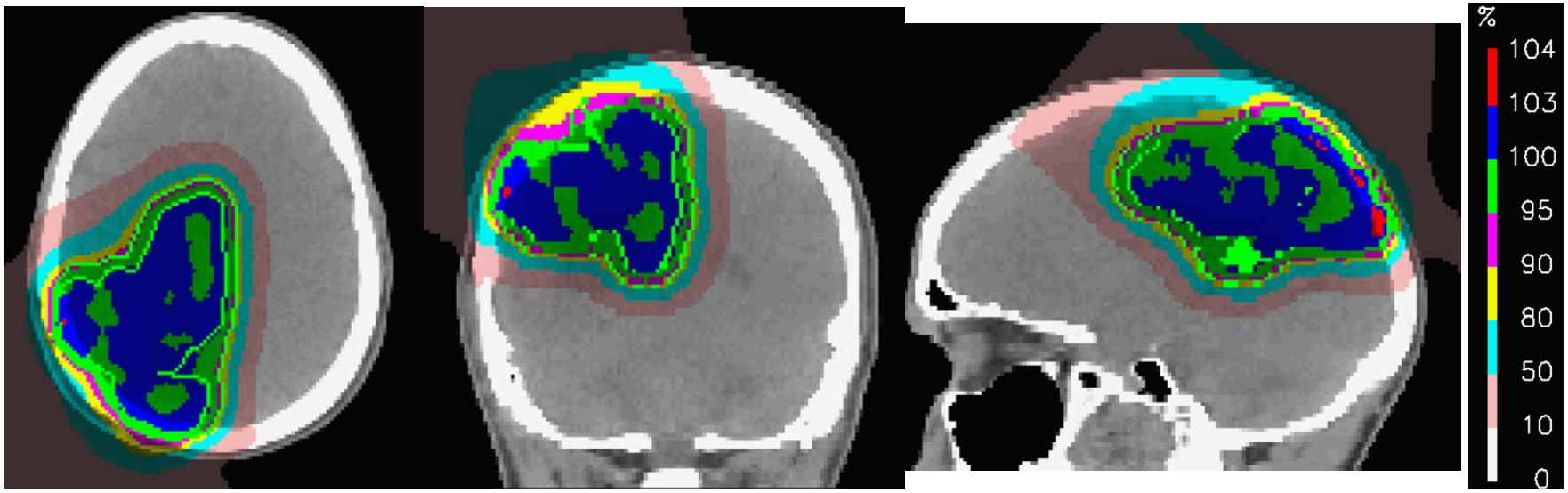


Shahed Badiyan MD
Center for Proton Therapy
Paul Scherrer Institute

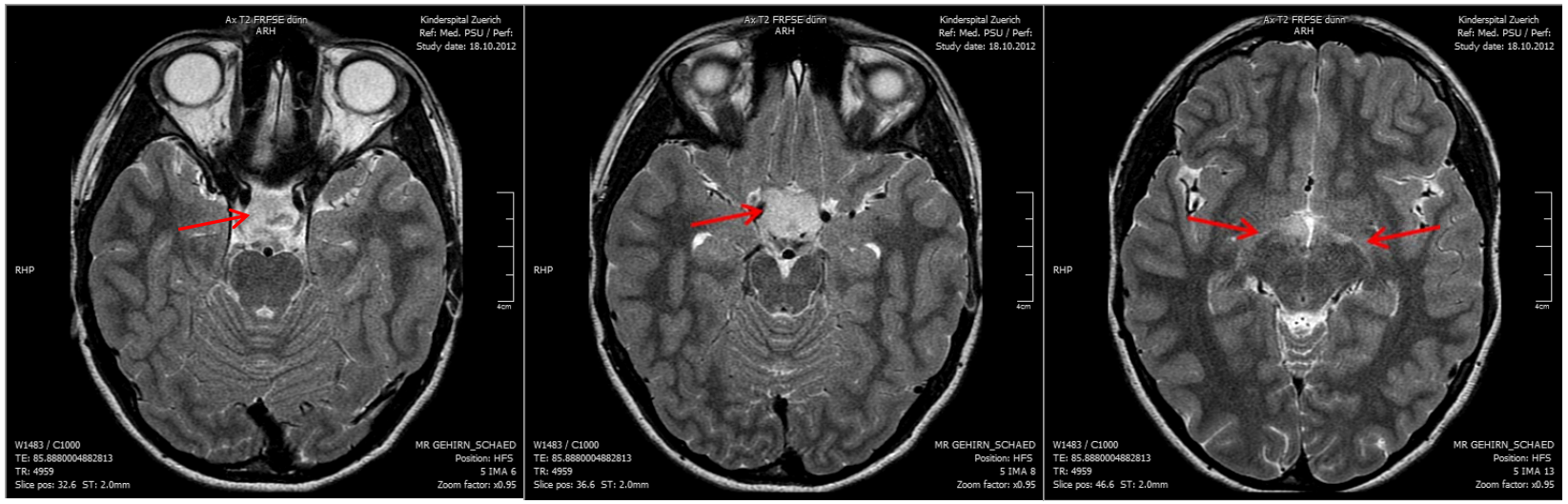
Low-grade gliomas

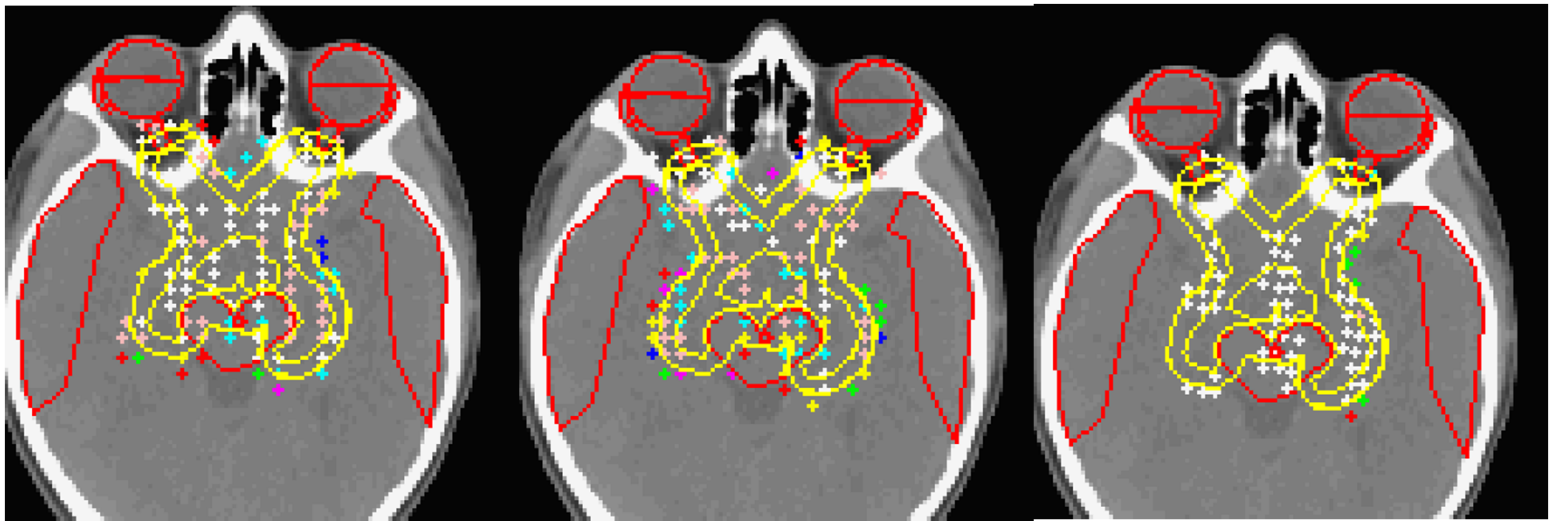


Low Grade Glioma

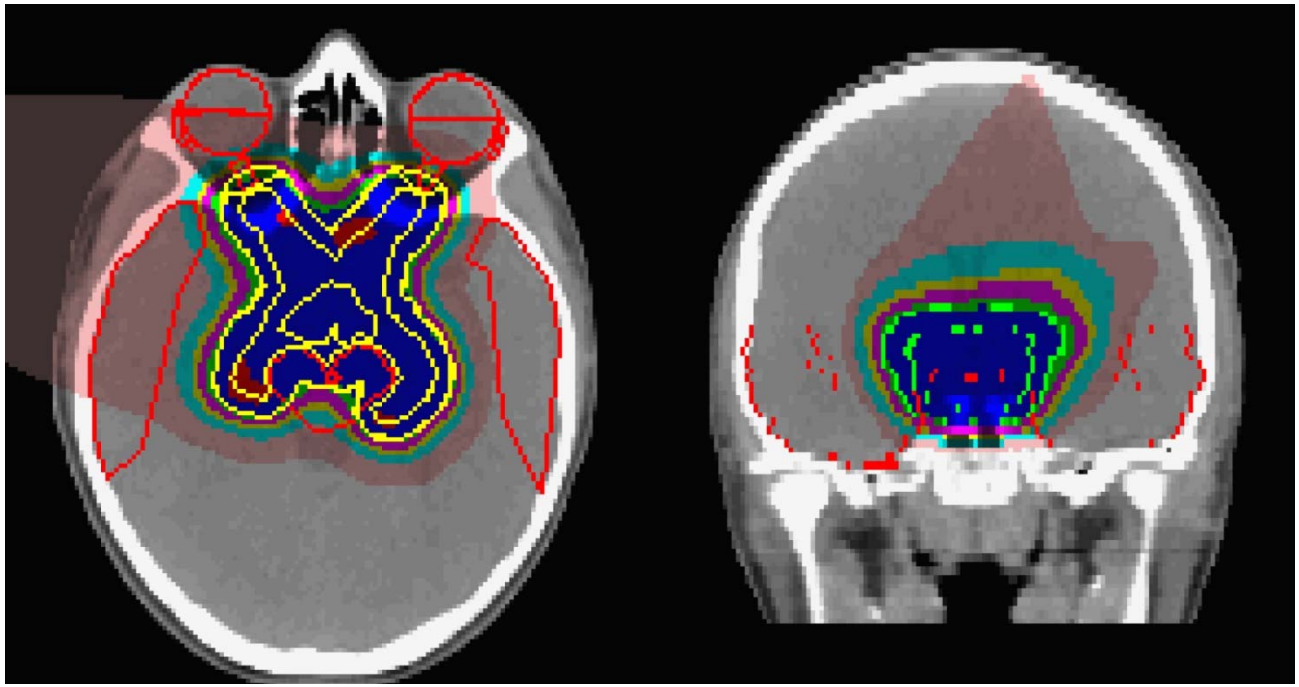


Optic Pathway Glioma





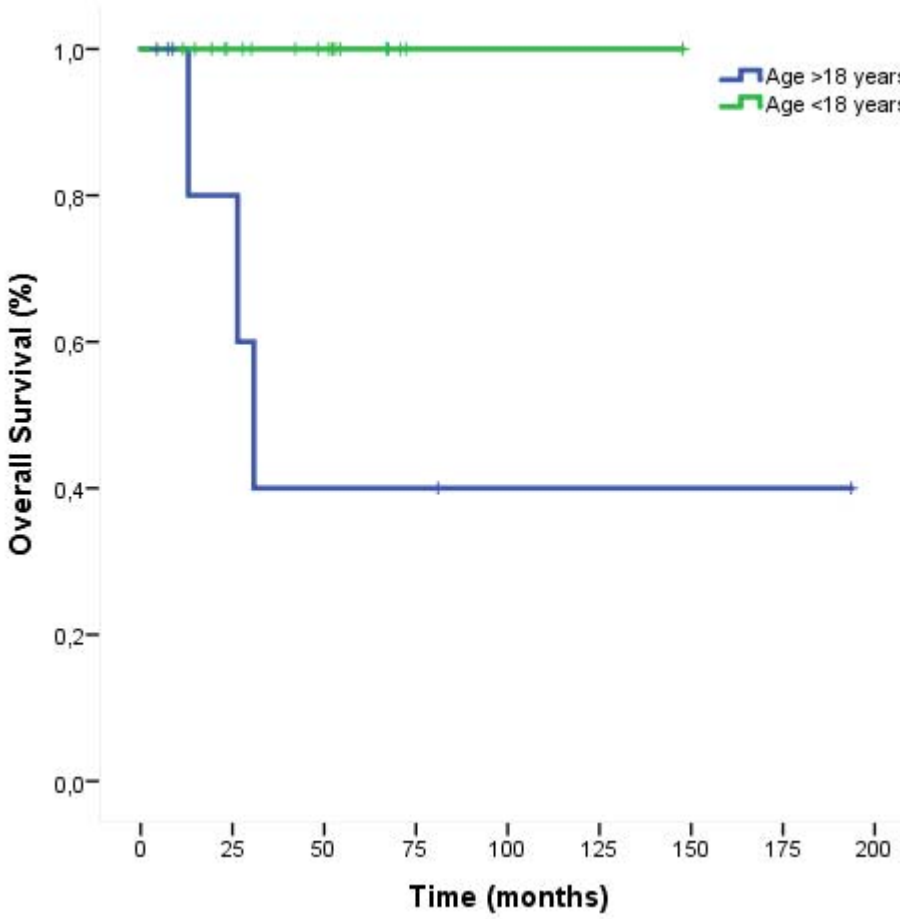
Optic Pathway Glioma

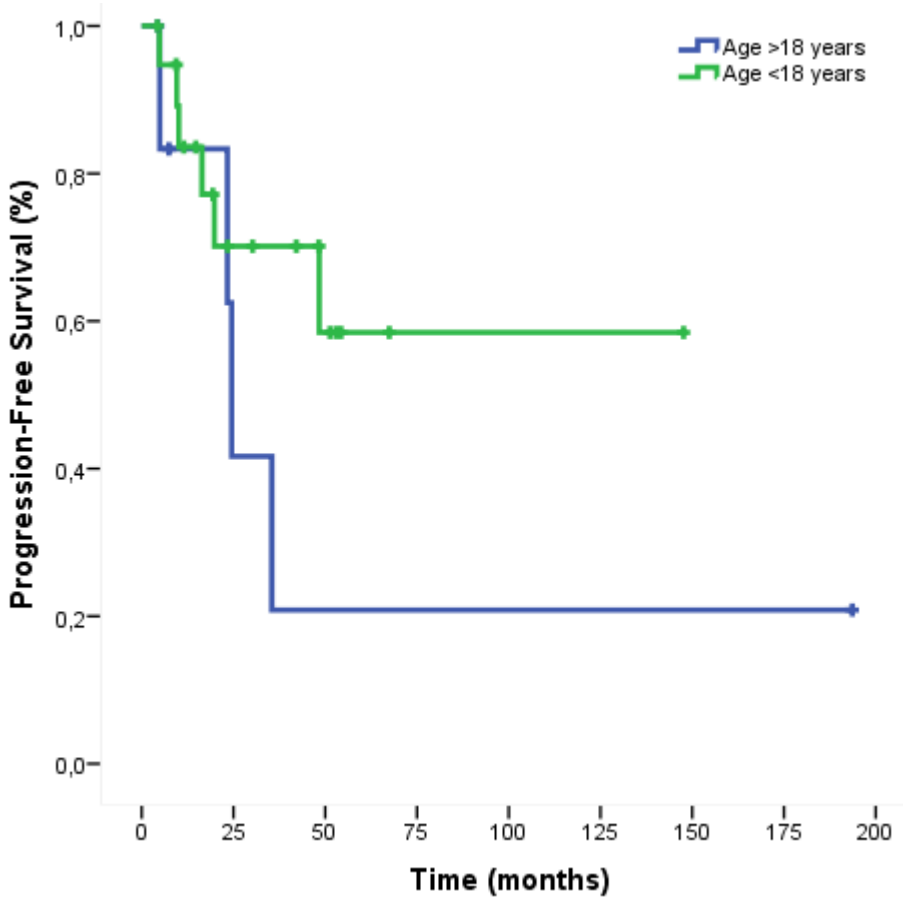


Low-grade gliomas

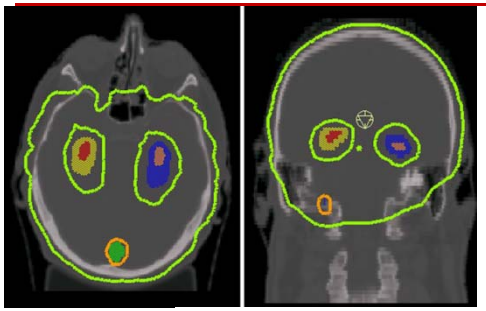
Study (year)	N=	LOC.	Mean age Years (range)	Mean FU Years (range)	Dose Gy RBE (Range)	Outcome
LLMC (2002)	27	Brain	8.7 (2–18)	3.3 (0.6–68)	55.2 (50.4–63.0)	*LC 87% *OS 93%
MGH (2014)	32	Brain & Spine	11 (2.7–21.5)	7.6 (3.2–18.2)	52.2 (48.6–54)	8y-PFS: 82.8% 8y-OS: 100%
MGH (2015)	20	Brain	37.5	5.1	54	3y-PFS: 85% 5y-PFS 40%
Heidelberg (2012)	19	Brain	29	0.4 (0–1.8)	54 (48.6–54)	12 SD; 1 pseudo PD; 2 CR
PSI (2015)	28	Brain	12.3 (2.2–53.0)	Min. 3 months	54	3y-PFS: 56% 3y-OS:83.4%

Low-grade gliomas

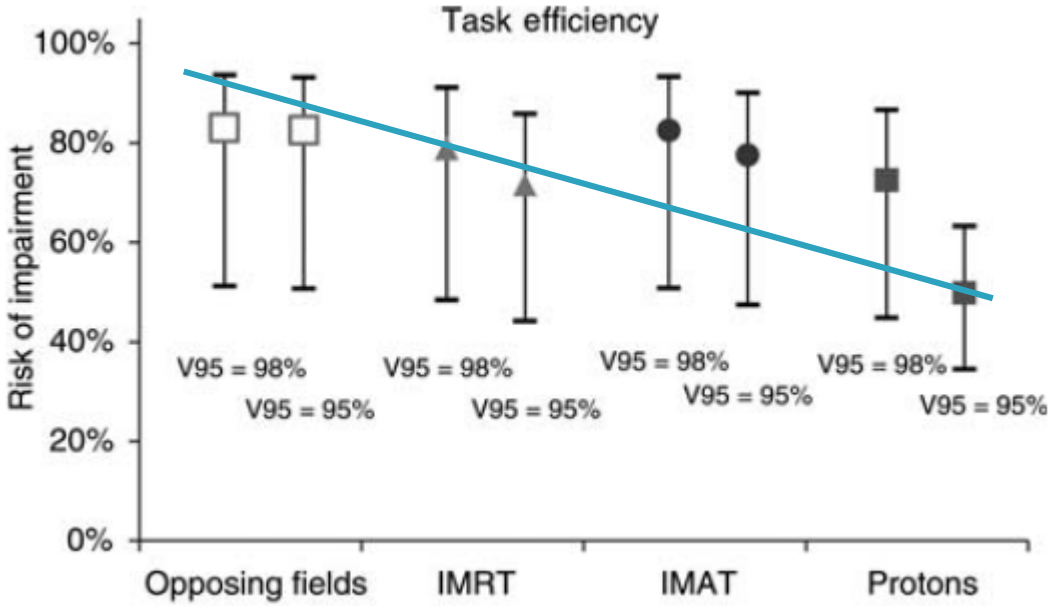




Low grade glioma hippocampal sparing



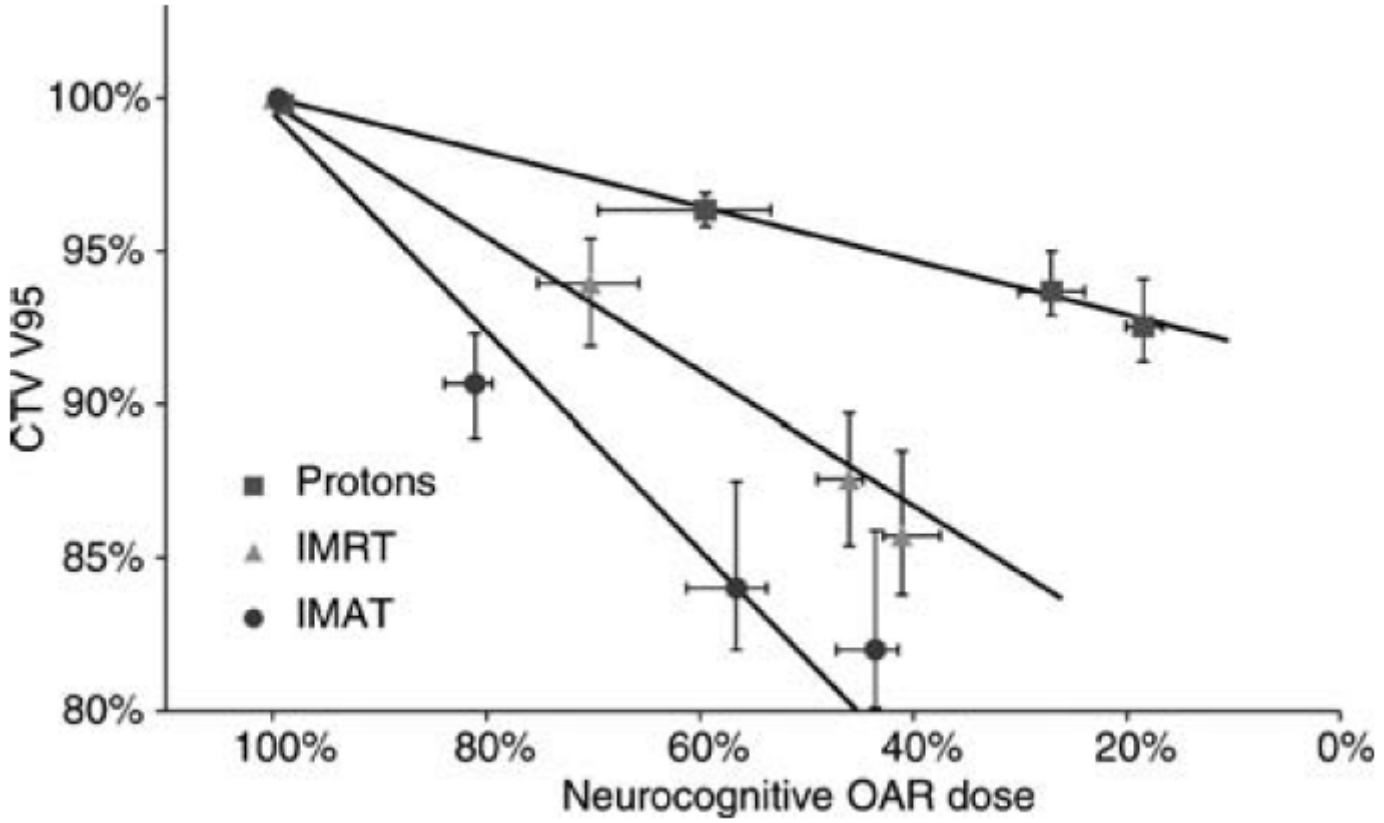
Estimated risks for developing memory impairment after a prescribed dose of 23.4 Gy were 44% (IMAT), 41% (IMRT), and 33% (IMPT).



Low grade glioma hippocampal sparing

Estimated clinical benefit of protecting neurogenesis in the developing brain during radiation therapy for pediatric medulloblastoma

Neuro-Oncology 14(7):882–889, 2012.
doi:10.1093/neuonc/nos120



Conclusions 1

- Volumetrically challenging Meningiomas can be treated with protons
- Some data suggests that Dose escalation for Grade 2-3 meningiomas would be beneficial.
- CAVE: dose constraints for optic apparatus (OSNM).
- The survivorship of LGG is good. Decreasing radiation-induced toxicity with protons?
- Limited number of series < 30 pts suggests that the outcome of pts treated with p+ is good.

Conclusions 2

- In practise: Meningioma G2-3 (dose escalation)
- Meningioma skull-base or hemisph. grade 1 meningioma, voumetrically challenging.
- Conservative dose constraints for the ON/OC
- Optic Nerve R/L 40 Gy(RBE)/<50 Gy(RBE) (Mean/Max)
- Chiasma 40 Gy(RBE)/<50 Gy(RBE) (Mean/Max)
- LGG +/- chemotherapy: children, young adults with hippocampal sparing

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PAUL SCHERRER INSTITUT
PSI

UNIVERSITÄT BERN

Universität Zürich[UZH]