Proton Therapy
for tumors of the skull base - RESULTS

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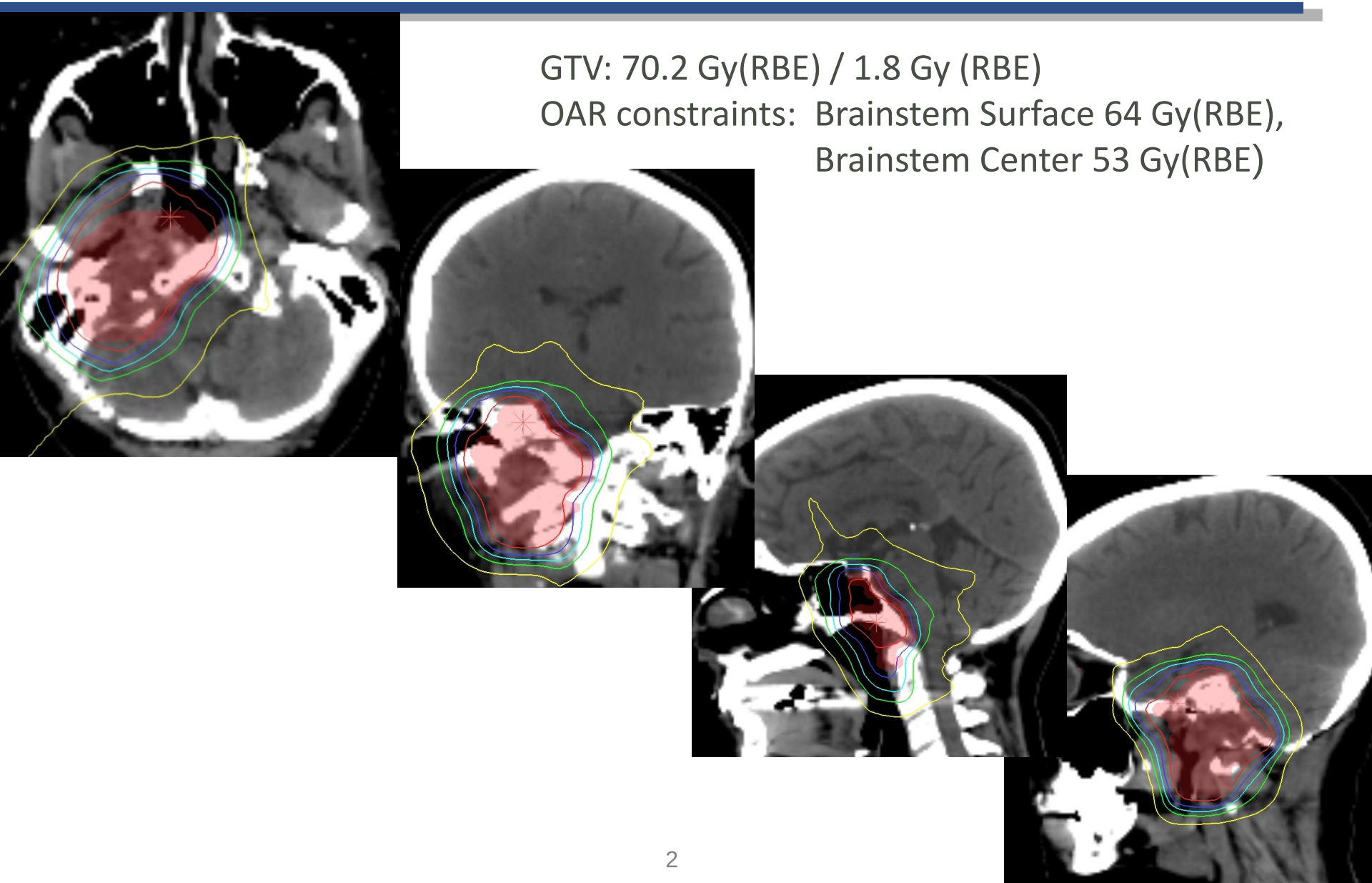
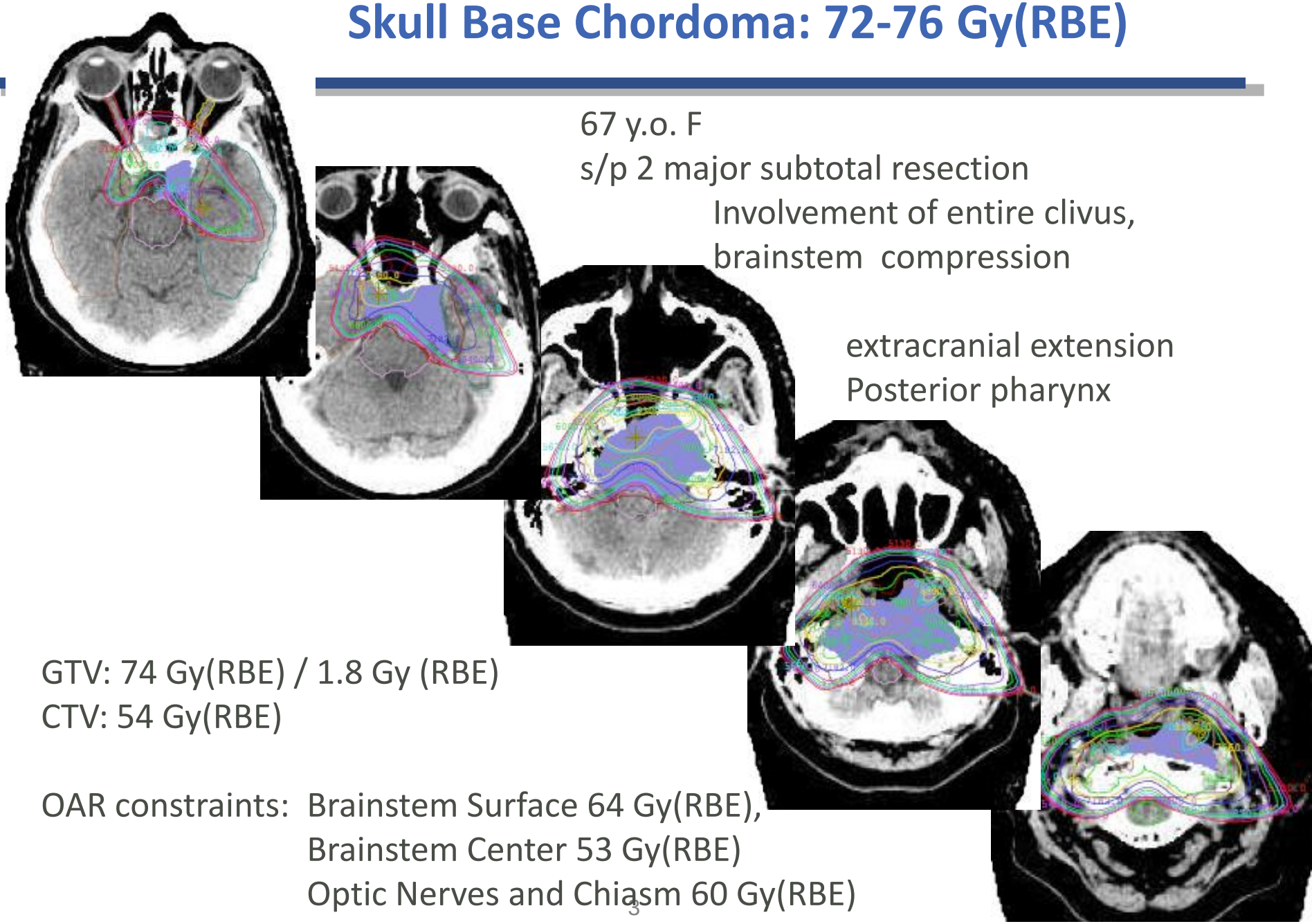
Petroclival Chondrosarcoma: 68 – 72 Gy(RBE) at 1.8 or 2.0 Gy(RBE)

GTV: 70.2 Gy(RBE) / 1.8 Gy (RBE)
OAR constraints: Brainstem Surface 64 Gy(RBE),
Brainstem Center 53 Gy(RBE)



Skull Base Chordoma: 72-76 Gy(RBE)



67 y.o. F
s/p 2 major subtotal resection
Involvement of entire clivus,
brainstem compression

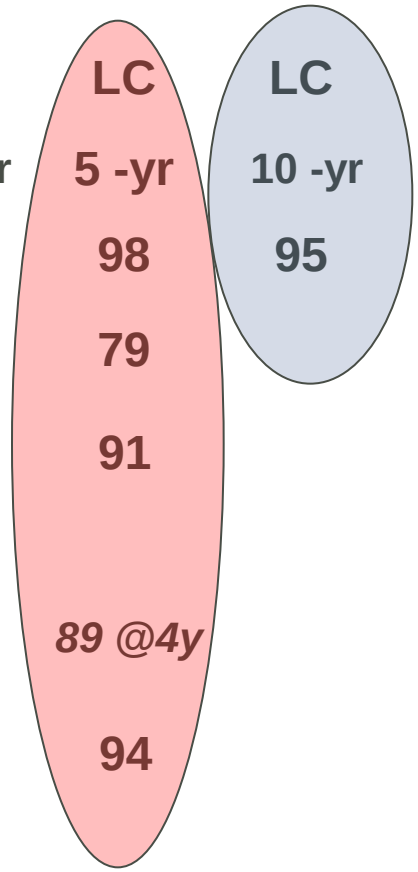
extracranial extension
Posterior pharynx

GTV: 74 Gy(RBE) / 1.8 Gy (RBE)
CTV: 54 Gy(RBE)

OAR constraints: Brainstem Surface 64 Gy(RBE),
Brainstem Center 53 Gy(RBE)
Optic Nerves and Chiasm 60 Gy(RBE)

Skull Base *Chondrosarcomas:*
Proton series

	n	Radiation	Mean dose	LC 3 -yr	LC 5 -yr	LC 10 -yr
Munz. MGH 1999	229	PT, RT	72		98	95
Hug, LLUMC1999	25	PT, RT	71		79	
Johnson, LLU '02	58	PT, RT	71		91	
Noel, CPO 2004	26	PT, RT	67	91		
Schulz-E., GSI 2007	54	*Carbon, RT*	60*	96	*89 @4y*	
Ares, PSi 2009	22	PT	68.4		94	



**at 3.0 CGE per fraction*

Skull Base Chordomas: Proton

			Pts	Tx	Mean dose	Local control 3 y	Local control 5 y
MUNZENRIDER	MGH	1999	290	PT, RT	76	67	73 ←
TERAHARA	MGH	1999	115	PT, RT	69		59
HUG	LLUMC	1999	33	PT, RT	71	67	59
NOEL	CPO	2005	100	PT, RT	67	86 (2 y)	53 (4 y)
SCHULZ-E	GSI	2007	115	Carbon RT	60*	81	70
ARES	PSI	2009	42	PT	74		81 ←

Protons: No large scale prospective or multicenter studies available

Contouring / Dose Prescription:

Similar Volume Definitions (GTV, CTV)

Similar Dose Prescriptions:

1.8 or 2.0 fraction dose

GTV 66-78 Gy(RBE) total dose – MGH up to 82 Gy(RBE) (selective only)

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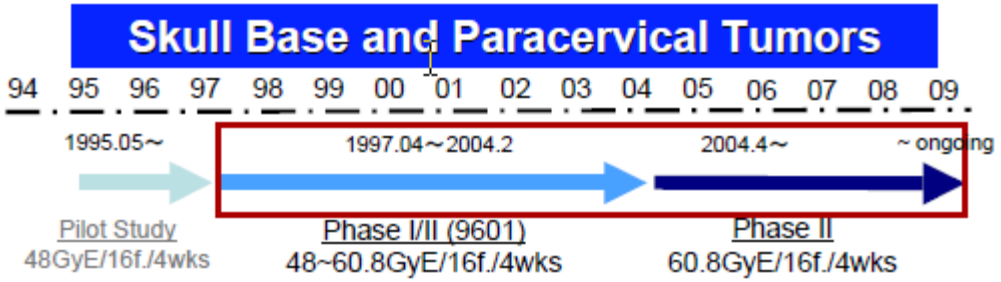
Carbon Ions for skull base *chordomas*: NIRS, Japan



Treatment Results in Skull base chordoma

	Authors	N	Median total dose	Median f/u (y)	Local control rate (%) 3-y	5-y	10-y
Photon	Catton et al. [1]	24	50.0	5.2		23	15
	Romero et al. [2]	18	50.1	3.1		17	
	Forsyth et al. [3]	39	50.0	8.3		39	31
	Magrini et al. [4]	12	58.0	6.0		25	25
Proton	Munzenrider et al. (MGH) [5]	169	66-83	3.4		73	54
(+/- photon)	Noel et al. (CPO) [6]	100	67.0	2.6	86 (2-y)	54 (4-y)	
	Igaki et al. (Tsukuba) [7]	13	72.0	5.8	67	46	
	Ares et al. (PSI) [8]	42	73.5	3.2 (Mean)		81	
Helium	Castro et al. (LB) [9]	53	65.0	4.3		63	
Carbon	Shults-Ertner et al. (GSI) [10]	96	60.0	2.6 (Mean)	81	70	
	NIRS	36	48-60.8	4.6		81	81 (SE ±08)
	NIRS	27	60.8	3.8		94 (SE ±06)	

1) Catton et al. Radiother Oncol 1996; 41: 67-72.
2) Romero et al. Radiother Oncol 1993; 29: 27-32.
3) Forsyth et al. J Neurosurg 1993; 78: 741-747.
4) Magrini et al. Acta Oncol 1992; 31: 847-851.
5) Munzenrider et al. Strahlenther Onkol 1999; 175: 3 -63.
6) Noel et al. Strahlenther Onkol 2003; 179: 241-248.
7) Igaki et al. Int. J. Radiation Oncology Bio. Phys 20 4; 60: 1120-26.
8) Ares et al. Int. J. Radiation Oncology Bio. Phys 200 ; 75: 1111-8.
9) Castro et al. Int. J. Radiation Oncology Bio. Phys 1 94; 29: 647-655.
10) Schulz-Ertner et al. Int. J. Radiation Oncology Bio Phys 2007; 68: 449-457.
11) Mizoe et al. Skull Base 2009; 19: 219-224.

From: Kamada, ESTRO Teaching Course 2012

Scanning-beam Proton Therapy for Chordomas and Chondrosarcomas of the Skull base

Ares, Goitein, Hug et al. - PSI **IJROBP 2009 Nov 15;75(4)**

- **N = 64 patients (Oct-98 Nov-05)**
  - **Chordoma 42 (65%)**
    Chondrosarcoma 22 (34%)

- **Mean age 44.5 years**
- **Mean follow-up 38 months(14 - 92 months)**

- **Prescription dose (mean) (at 2 CGE per frct.).**
  - **Chordoma (Ch) 73.5 CGE (range 67 - 74)**
    Chondrosarcoma(ChSa) 68.4 CGE (range 63 - 74)

- **GTV volume: mean 25.8 cc (1.5 -100.5 cc)**

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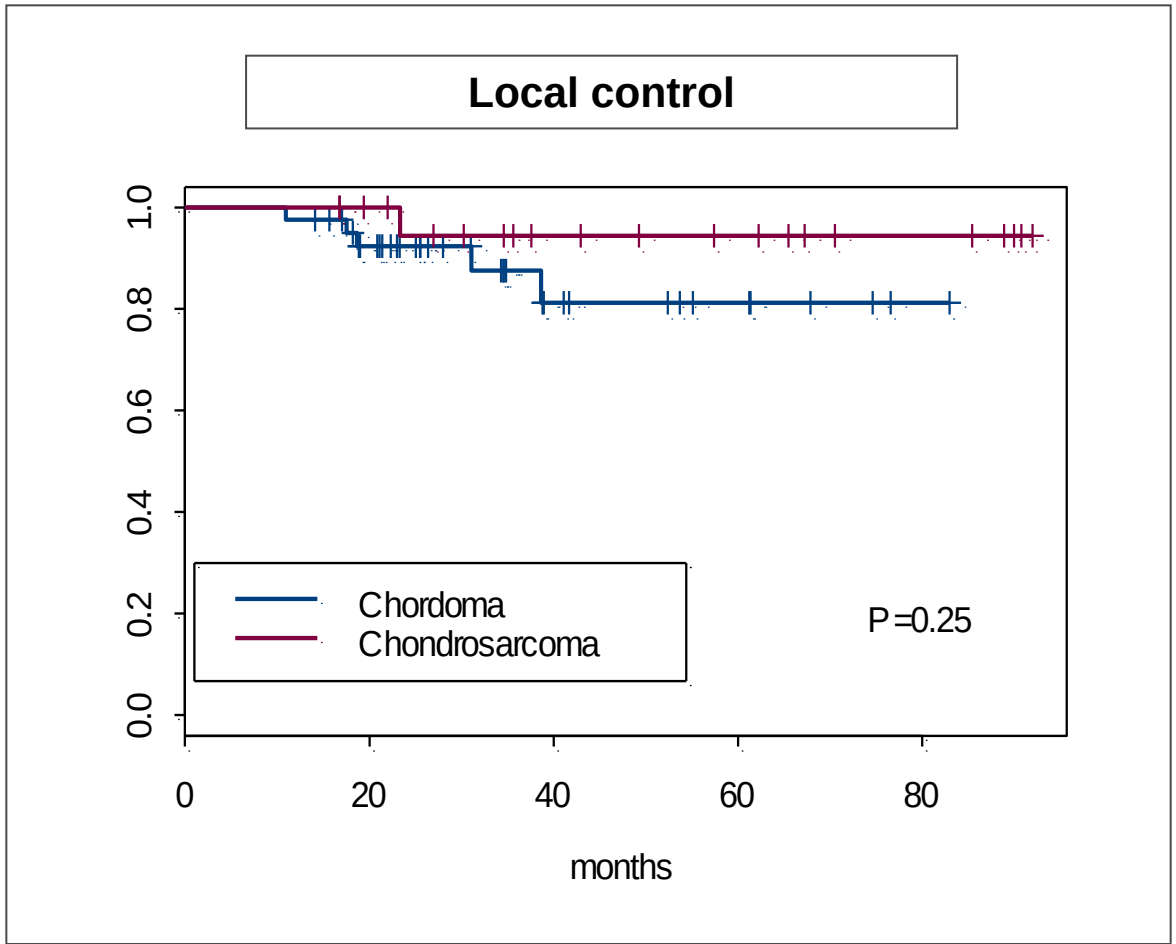
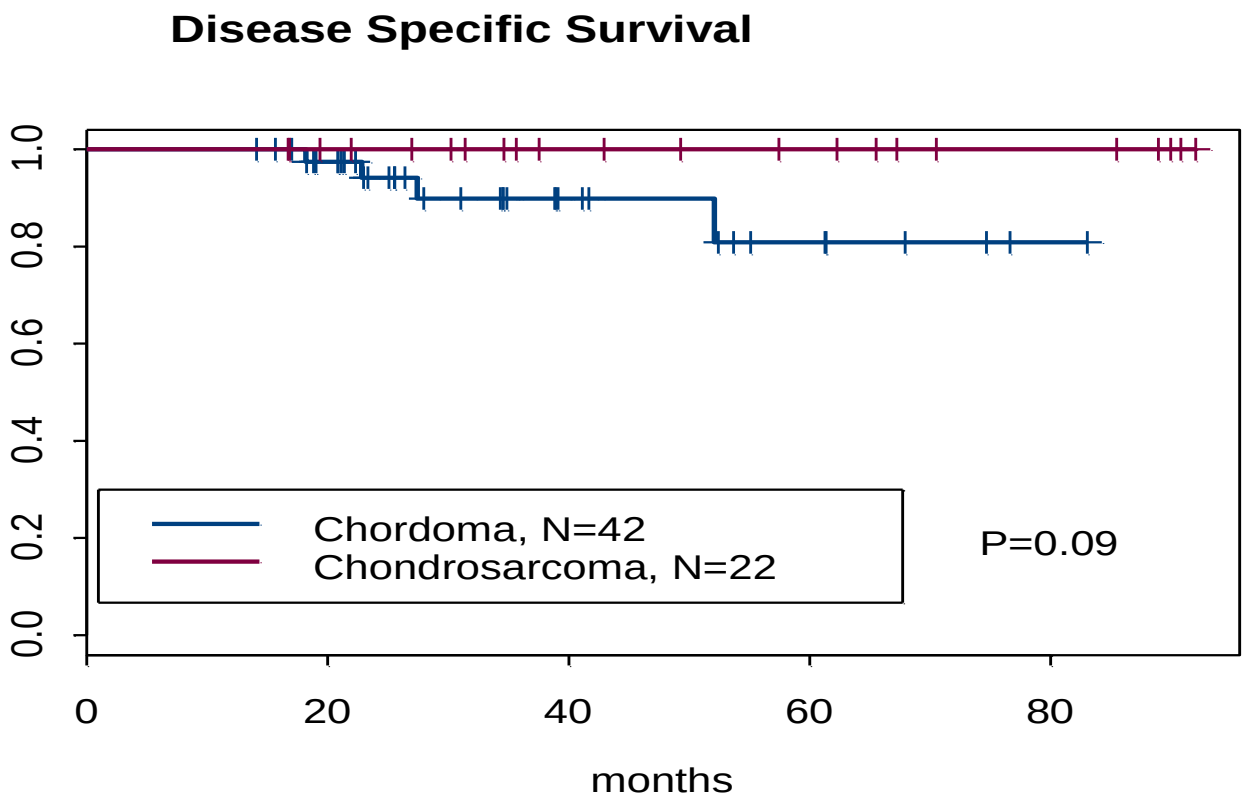
(Ares et al. cont.)

Actuarial Local Control	3 years	5 years
Chordomas	87 %	*81%*
Chondrosarcomas	94 %	*94 %*



(Ares et al. cont.)

Disease Spec. Survival	3 years	5 years
Chordomas	90%	81%
Chondrosarcomas	100 %	100 %



Radiation induced toxicity (CTCAE v3.0)

- ***High grade late toxicity (all Ch) → 4 pts (6%)***

– optic pathway	G 4 → 1 patient (unilat. blindness)
	G 3 → 1 patient (unilat. visual deficit)
– neurologic	G 3 → 2 patients (sympt. brain necrosis)

Actuarial Toxicity-Free Survival: 94%

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Proton-RT for Skull Base Chordomas

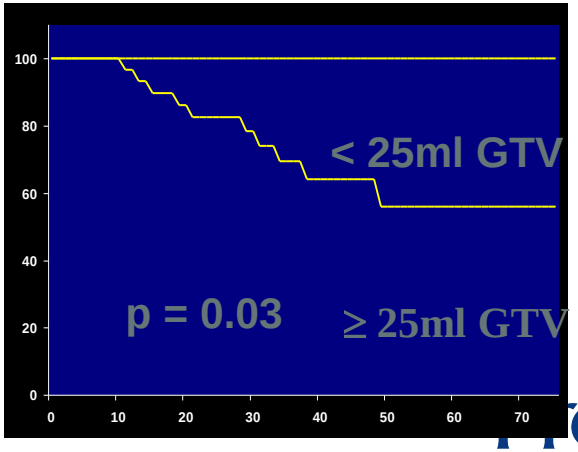
Prognostic Factor: Tumor Size and Local Control

Improved LC for "smaller" size

- **LLUMC: < 25 ml vs. > 25 ml (100% vs. 56%)** **p=signif.**
- **CPO: <29ml vs. > 29ml** **p=signif.**
- **PSI: > 25 ml vs. > 25 ml (90% vs. 74%)** **p=signif.**
- **MGH: < 70 ml vs. > 70 ml (disease-free survival)** **p=signif.**
- **LBL: < 20cc vs. <35 vs. > 35 cc (80% vs. 33%)** **p=signif.**

Loma Linda UMC Analysis

Hug, Laredo, et al.
J Neurosurg. 91:432-439, 1999



Proton-RT for Skull Base Chordomas

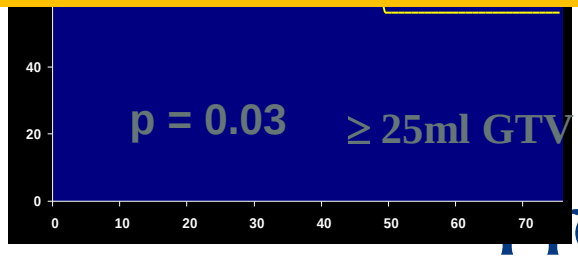
Prognostic Factor: Tumor Size and Local Control

Improve

- LL
- CP
- PSI
- MG
- LB

Note:
1) 5-year LC for 'small' lesions: approx. 85 – 95%
2) There is no evidence in the neurosurg. literature that local control is better following gross total resection compared to "small" residual

Hug, Laredo, et al.
J Neurosurg. 91:432-439, 1999

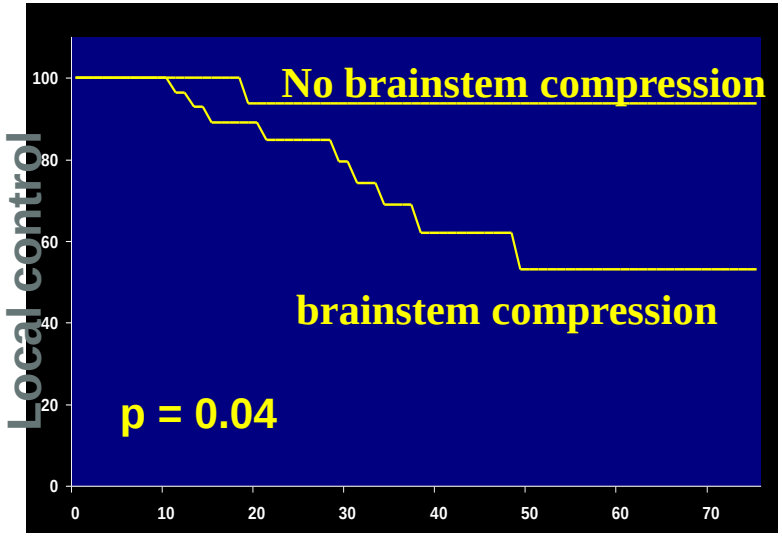


Skull Base Chordomas: Importance of high-dose

Tumor Compression of Critical Structures = under-dosage of GTV

Influence of tumor compression on local control

LLUMC: Hug, Laredo, et al.
J Neurosurg. 91:432-439, 1999



Orsay/France:
Noel, et al.
Acta Oncol 2005;44(7):700-8

- **95% GTV encompassed by 95% Isodose (p=0.01)**
- **Minimal dose < 56 Gy to GTV (p=0.04)**

Skull Base Chordomas: Importance of high-dose

Paul Scherrer Institute:

Ares C, Hug EB,et al. IJROBP 2009 Nov 15;75(4):1111-8

5/6 failures with brainstem compression **p=signif.**

Mass. General Hospital

Munzenrider JE, Liebsch NJ. Strahlenther Onkol. 1999 Jun;175 Suppl 2:57-63.

15/26 failures with BS or OC compression **p=signif.**

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Skull Base Chordomas: Importance of high-dose

- The majority of skull base tumors require 70-76 Gy(RBE) GTV-dose
- This exceeds all OAR constraints of brainstem, optic nerves, optic chiasm and most other structures
- Underdosage of tumor causes failures (approx. 2/3 of failures)
- Goal: minimize “GTV shoulder” on DVH

- Hence: surgical decompression of OAR’s recommended
- Hence: only high OAR constraint will permit adequate tumor dose in many / most patients

Skull base Chordomas and Chondrosarcomas: RS and Cyberknife LC data

	Chordomas		Chondrosarcomas	
	n	5-y LC	n	5-y LC
Krishan, 2005	25	32%	4	100%
Martin, 2007#	18	63%	10	80%
Hasegawa, 2007	30	72%	7	2/7 failed
Henderson, 2009	18	59%		
Liu, 2008	28	21%		
Kano, Pittsburg ,2011	71	66%		
Koga, U. Tokyo, 2010	14	combined Ch +ChS	43% 5-yr LC	

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Recent publication on photon- FSRT for Chordomas

Photon-based Fractionated Stereotactic Radiotherapy for Postoperative Treatment of Skull Base Chordomas

Darlene M. Bugoci, MD, Michael R. Girvigian, MD,* Joseph C.T. Chen, MD, PhD,† Michael M. Miller, MD,* and Javad Rahimian, PhD**

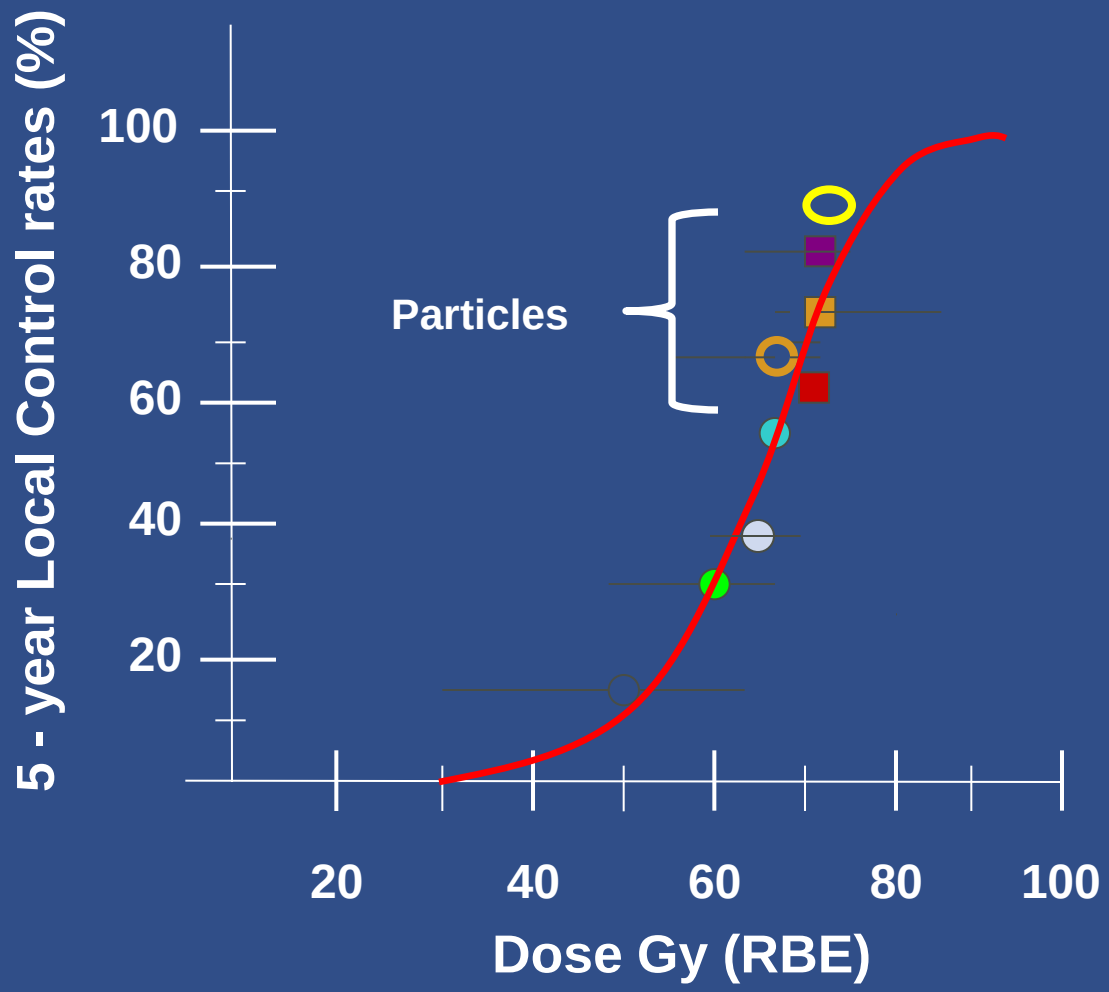
(*Am J Clin Oncol* 2012;00:000–000)

- Dept. of Rad. Onc, Kaiser Permanente, Los Angeles, CA
- OBJECTIVES:: Postoperative high-dose fractionated stereotactic radiotherapy (FSRT) as an alternative to proton radiotherapy (RT).
- FSRT between 2002 - 2009,
- 12 patients with skull base chordomas. IMRT and IGRT FSRT
- **Median dose of 66.6 Gy** (range, 48.6 to 68.4 Gy), at 1.8 Gy, prescribed to the 90% isodose line.
- Median follow-up 42 months.
- 5-year 0verall survival 76.4%
- **Progression-free survival 46.9% at 2-years and 37.5% at 5-years.**
- Author's CONCLUSIONS: "FSRT resulted in promising overall survival results comparable with the published literature of particle therapy without significant complications. Our technique for treating skull base chordomas can be considered a safe and less costly alternative to proton RT."

Note: Conclusion misleading. There is no salvage after failure. Patients will die of disease. Delay between LF and DoD about 2-3 years

What are the results comparing:

Particle Therapy vs. Stereotactic or conv. photons



Protons

Munzenrider	1999
Ares	2009
Hug	1999

C-Ions

Schulz-Ertner	
Mizoe	

Photons

Bugoci	2012
Romero	1993
Zorlu	2000
Debus	2002

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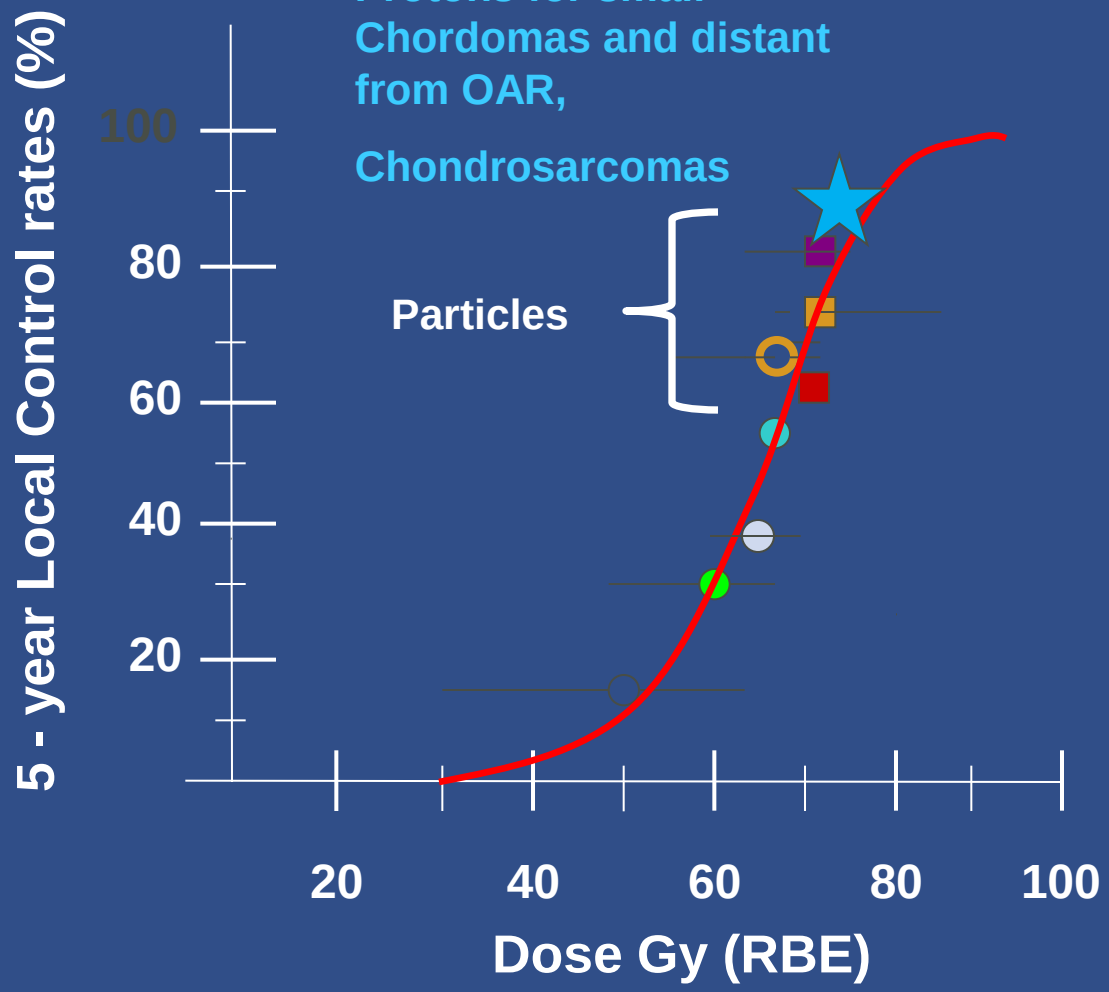
What are the results comparing:

Particle Therapy vs. Stereotactic or conv. photons



Protons

■	Munzenrider	1999
■	Ares	2009
■	Hug	1999

C-Ions

○	Schulz-Ertner	

Photons

●	Bugoci	2012
○	Romero	1993
●	Zorlu	2000
●	Debus	2002

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Long-term Side Effects of high-dose Proton Therapy for Skull Base Tumors:

The risks of severe (≥ Grade 3)side effects following high dose, precision RT depend on several variables:

Tumor size, tumor compression of normal brain, critical structure involvement, dose to normal tissues, number of prior surgeries, general medical risk factors (diabetes, HTN, smoking,), KPS

Rule of Thumb for Proton RT for Skull Base requiring > 70 Gy:

Low-risk group: < 5%

Mod.-risk group: 5-8%

High-risk group: > 8 % - ?? *

* PT as last modality after multiple failures

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High-Dose Proton Therapy to the Base of Skull: *Temporal Lobe Toxicity**

*** B. Pehlivan, C. Ares, T. Lomax, E. Hug et al. IJROBP. 2012 , 83(5):1432-40**

PSI: **64 Skull Base Patients treated at (40 Chordoma, 22 Chondrosarc.)**

7 pts. censored: Only 2 pts. With Gr. 3, and 5 pts. With Grade 1

Patient characteristics with G1 or G3 temporal adverse events

Patient #	Toxicity Grade	PT dose (Gy(RBE))	Overall F/U time (months)	LC	Dx of adverse event (months after PT)	Location temporal lobe change	Symptoms	Status MRI at last F/U
1	3	74	22	yes	12	Bilateral	Impaired short term memory, desorientation	Stable with edema reduction
2	3	74	23	yes	19	Bilateral	Impaired short term memory, desorientation	Stable with edema reduction
3	1	68	50	yes	35	Bilateral	N/A	stable on MRI
4	1	74	21	yes	10	Bilateral	N/A	resolution
5	1	74	61	yes	38	Left	N/A	no change
6	1	74	35	yes	31	Left	N/A	no change
7	1	74	21	yes	18	Right	N/A	increase

#: number; PT:proton-radiotherapy; F/U:follow-up; LC: local control; Dx: diagnosis; N/A: not applicable

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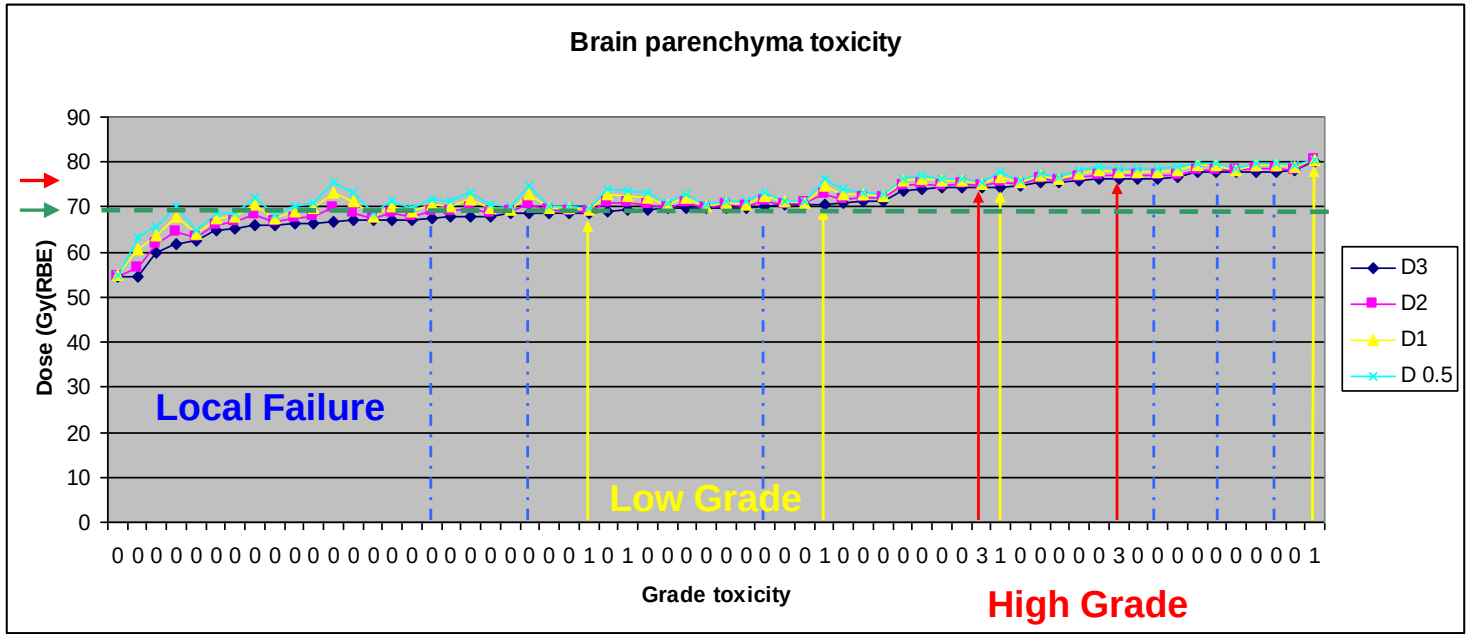
High-Dose Proton Therapy to the Base of Skull: ***Temporal Lobe Toxicity****

** B. Pehlivan, C. Ares, T. Lomax, E. Hug et al. Int. J Radiat. Oncol Biol. Phys. 2012 , 83(5):1432-40*

Threshold High Grade

Threshold Low Grade



cont. PT *Temporal Lobe Toxicity**

Table 3. Dose-volume values to 3 different neurological structures in relation with grade of CNS toxicity

Brain parenchyma

Grade Toxicity	D3 mean ± SD (Gy(RBE))	D2 mean ± SD (Gy(RBE))	D1 mean ± SD (Gy(RBE))	D0.5 mean ± SD (Gy(RBE))
0	70 ± 5	71 ± 5	72 ± 5	73 ± 5
1	73 ± 5	74 ± 5	75 ± 4	76 ± 4
3	75 ± 1	76 ± 2	76 ± 2	77 ± 2

Right temporal lobe

Grade Toxicity	D3 mean ± SD (Gy(RBE))	D2 mean ± SD (Gy(RBE))	D1 mean ± SD (Gy(RBE))	D0.5 mean ± SD (Gy(RBE))
0	50 ± 23	52 ± 23	56 ± 22	58 ± 22
1	67 ± 15	69 ± 12	73 ± 9	75 ± 7
3	71 ± 4	73 ± 3	75 ± 2	76 ± 2

Left temporal lobe

Grade Toxicity	D3 mean ± SD (Gy(RBE))	D2 mean ± SD (Gy(RBE))	D1 mean ± SD(Gy(RBE))	D0.5 mean ± SD (Gy(RBE))
0	53 ± 21	56 ± 21	59 ± 20	62 ± 19
1	57 ± 18	62 ± 15	67 ± 12	70 ± 9
3	68 ± 1	71 ± 0	74 ± 1	75 ± 1

** B. Pehlivan, C. Ares, T. Lomax, E. Hug et al. Int. J Radiat. Oncol Biol. Phys. 2012 ,*

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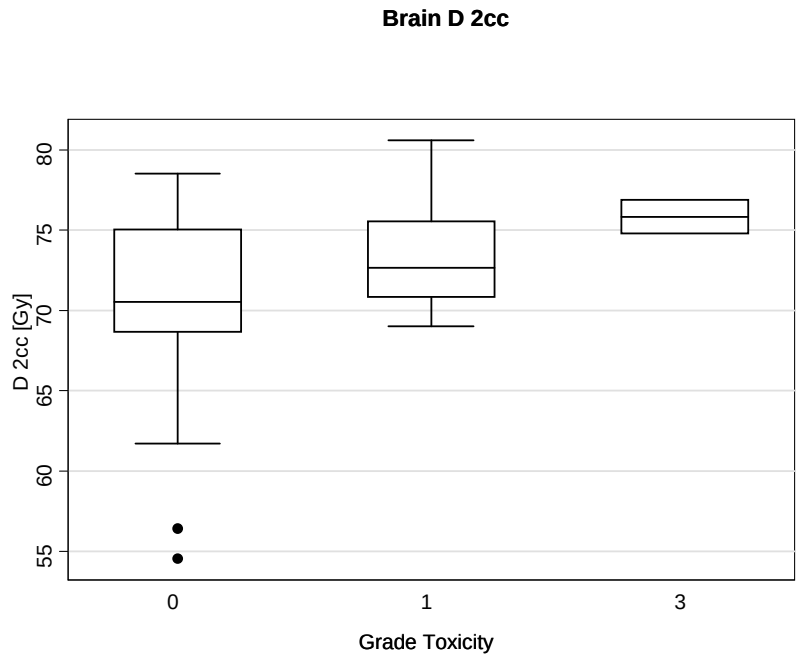
cont: PT *Temporal Lobe Toxicity**



Q: What is a „reasonable“ temp. lobe max. Dose Constraint, i.e. balancing toxicity risk with risk of failure ?

- ***D 2 = ≤ 70 or 72 Gy (RBE)?***

*** B. Pehlivan, C. Ares, T. Lomax, E. Hug et al. Int. J Radiat. Oncol Biol. Phys. 2012 , 83(5):1432-40**

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Constraints Temporal Lobe

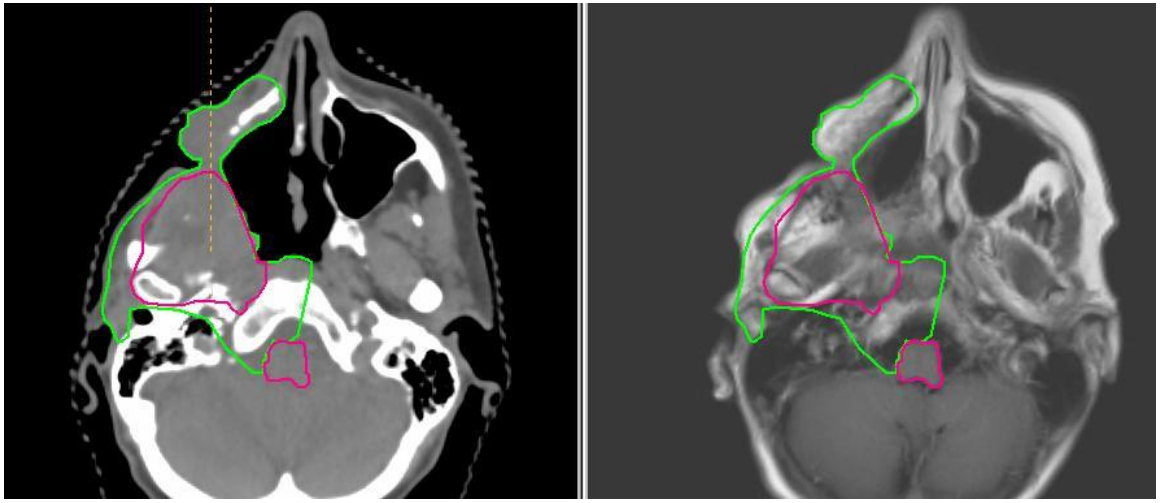
Temporal Lobe toxicity constitutes the most frequent high-grade adverse event in high-dose skull base treatments.
Approx. 3-5 %

Challenge: No clear tolerance threshold defined by ANY group
PTV of GTV frequently includes medial temporal lobes

Rec.: limit approx. 2 cc to $\leq$ 72 Gy(RBE)

Proton Radiation Therapy for *Adenoid-cystic Carcinoma* of the Skull Base

Adenoid Cystic Carcinoma with skull base invasion

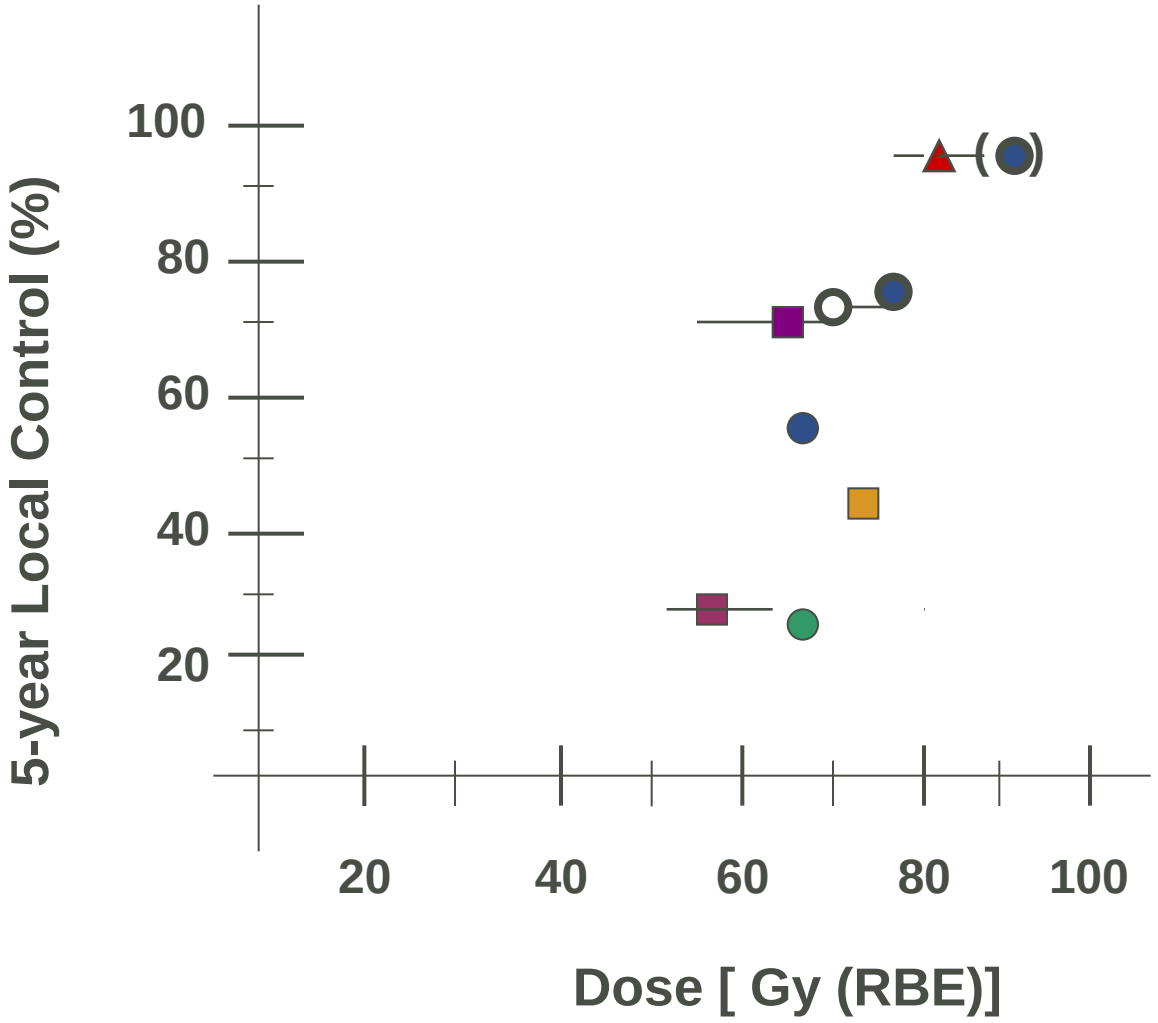


GTV: 72-74 Gy (RBE)

CTV: 60 Gy(RBE)

Institution/ Publication	Particle	# Pts.	Dose	Follow-up	Local control	Comments
MGH Pommier	Protons	23	Median 75.9 GyE at 1.8-2.0	Median 64 m	5-yr 93%	Mature f/u
NIRS Phase II 9602	Carbon	126	57.6 GyE then 64 GyE	Approx. 48 m	5-yr 76%	69 pts short f/U 95% to 64 GyE
GSI Schulz-Ertner	Carbon	29		Median 16 m	**4**-yr 77%	short f/u

Adenoid-Cystic Carcinomas
with infiltration of the skull base



Protons:

- Pommier et al. MGH, 2006

C-Ions:

- Schulz-Ertner et al. GSI – U Heidelberg
- Tsuji et al. NIRS

Photons:

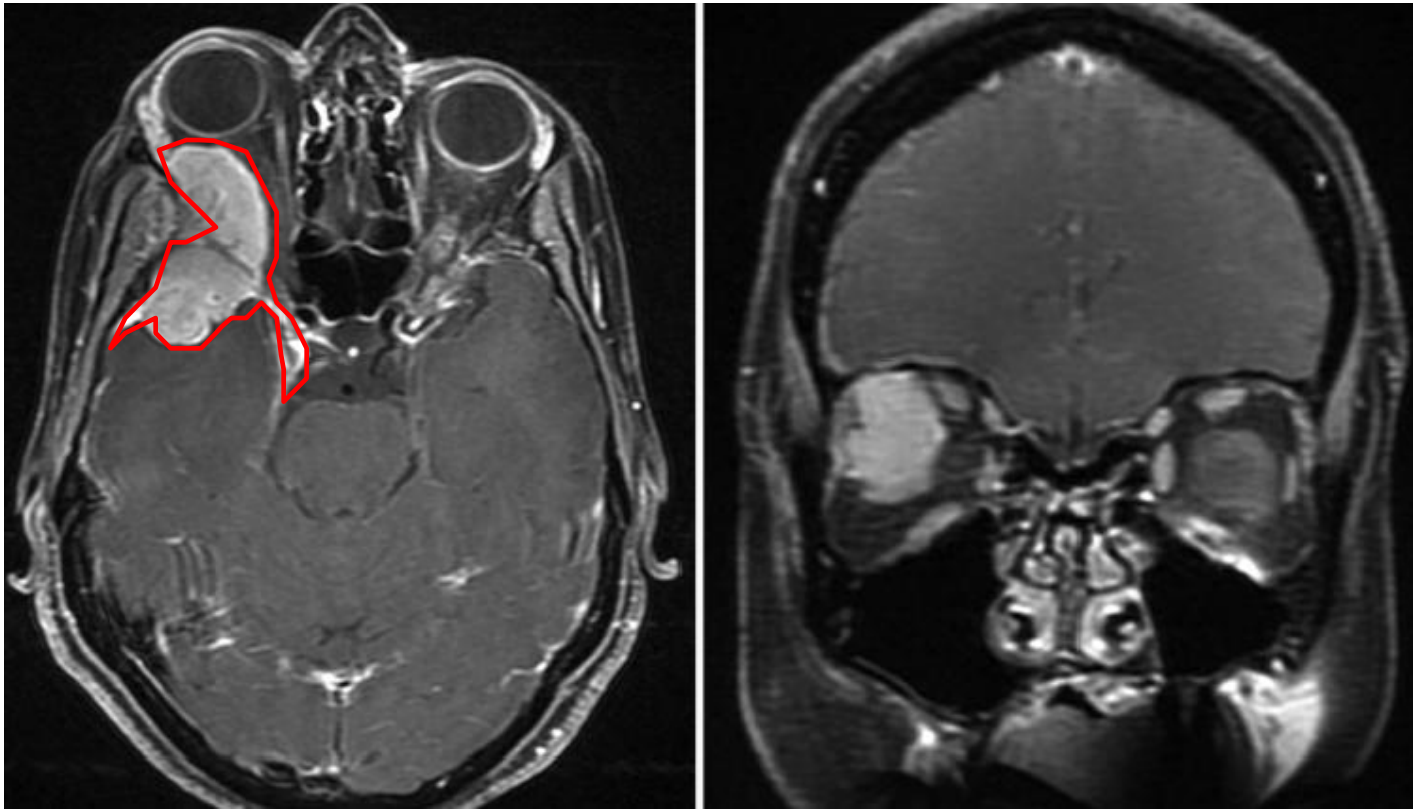
- Mendenhall (2004)
- Chen (UCSF, 2006)
- Historic data

Neutrons (Seattle):

- without
- with SB invasion

Proton Radiation Therapy for *Meningiomas* of the Skull Base and complex anatomic configuration

Proton-Radiotherapy for skull base tumors: ***Benign meningioma***



Axial and coronal Gd-enhanced T1-wMRI

Spheno-orbital meningioma.

Spot scanning based Proton Therapy at PSI for Meningiomas – 5-year actuarial data

Weber et al. IJROBP Dec. 2011

- 39 patients,
- Proton Therapy between 1997 – 2/2010. (exclusively protons)
- Age: 3.2 – 76 years (3 pediatric pats.)
- Gender: M:F = 9:30

- Histology: 34 histologically proven, 5 radiographic Dx.
- Histology: WHO (2007): Grade I: 23(58%), II: 10(25%), III: 2(5%)
- Location: 32(83%) skull base, 7(17%) Non-skull base

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Spot scanning based Proton Therapy at PSI for Meningiomas – 5-year actuarial data

Weber et al. IJROBP Dec. 2011

- **GTV:** range: 0.76 cc – 546 cc (mean: 56 cc)
- **PT:** fractionated, at 1.8-2.0 Gy(RBE)
- **Total Dose:** 52.2 – 68.4 Gy(RBE) (mean: 57.5)
- **Follow-up:** 6.2 – 147 months (mean: 63 months)

- **Local Control:** 33 pts., LF: 6 pts.
- **Overall Survival:** 6 pts. D, 4 pts. DoD
- **Late, high-grade Toxicity: 5 pts.**

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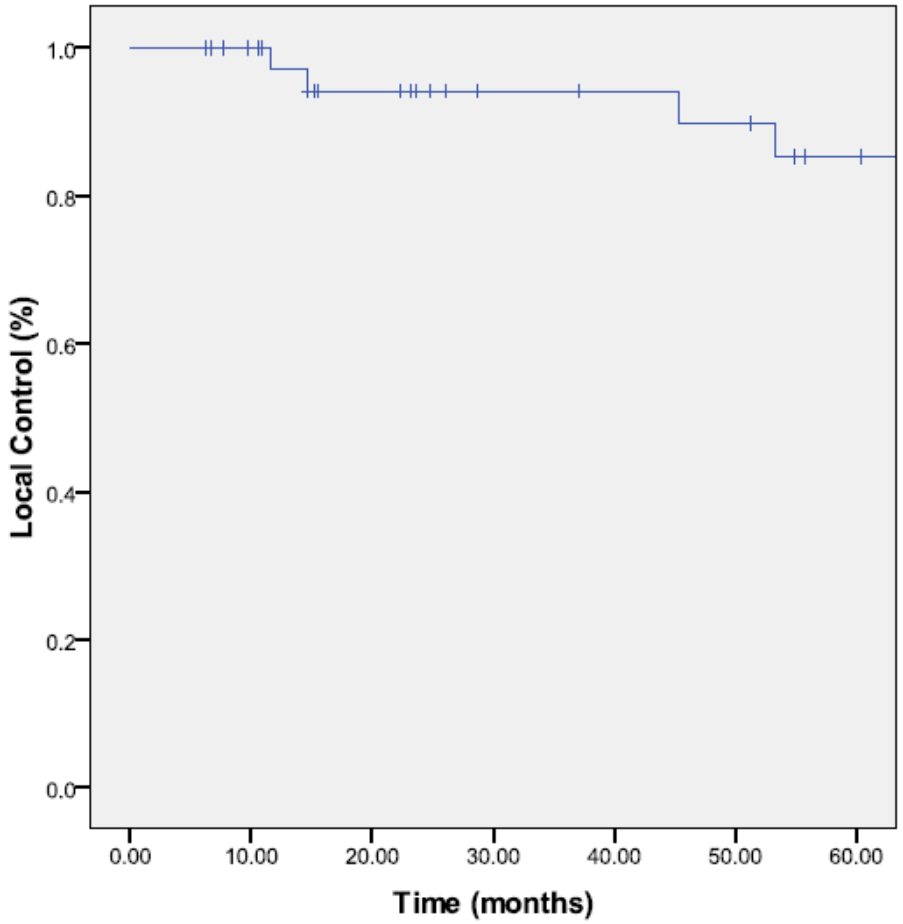
Local control

LC: 85% at 5 years – 39 pts.



Weber et al. IJROBP Dec. 2011

Local control

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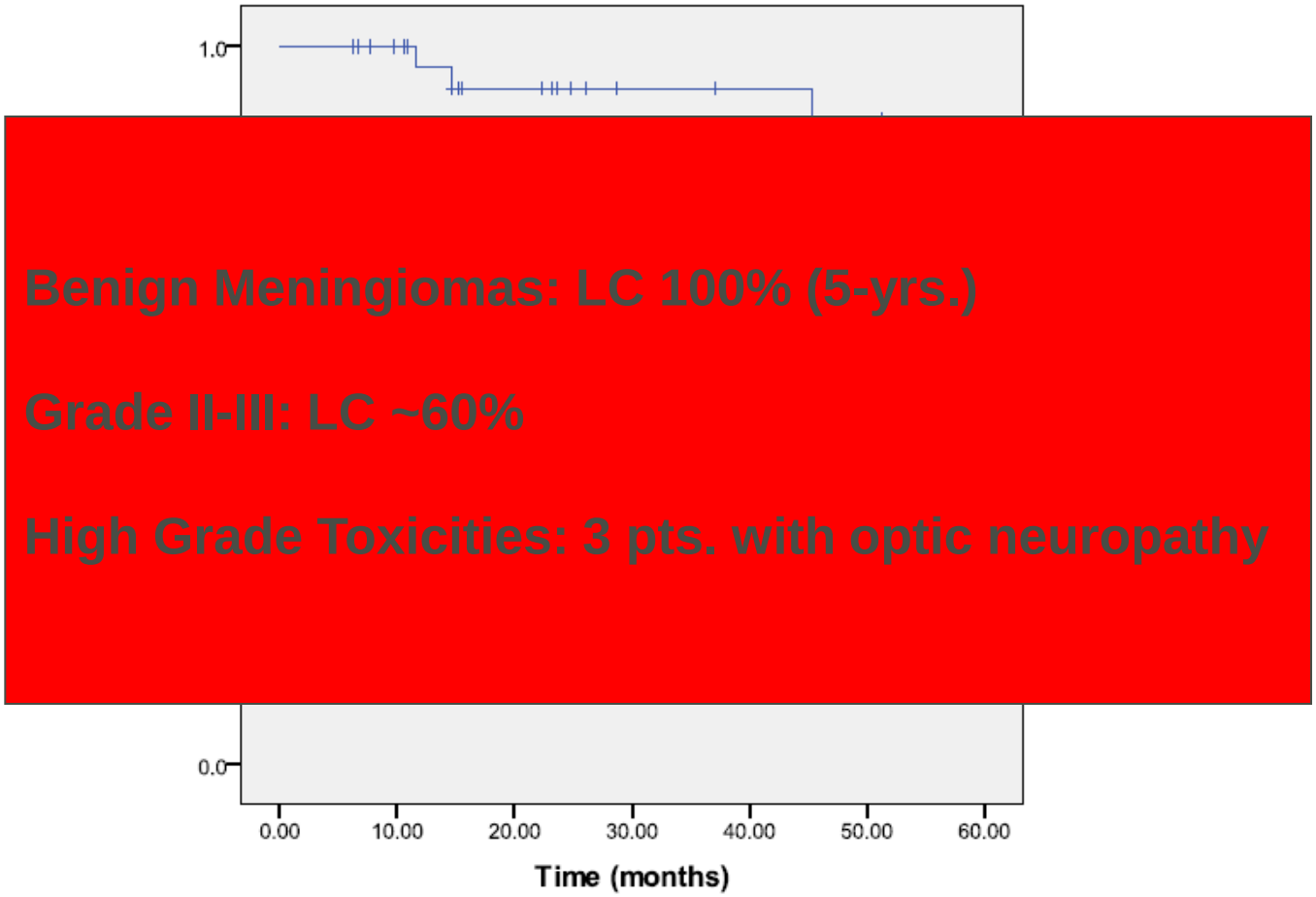

Benign Meningiomas: LC 100% (5-yrs.)

Grade II-III: LC ~60%

High Grade Toxicities: 3 pts. with optic neuropathy

Meningiomasa

Institution/ Publication	Particle	# Pts.	Dose	Follow-up	Local control	Comments
GSI/Heidelberg Combs 2010 Radiother Oncol 95(1)	Carbon	10 atypical anaplastic	18 GyE carbon boost 50.4 Gy photons	77 m median	5yr 86% for „primary RT“ = 6 / 8 patients	Statistical power of 5-yr rates(?)
PSI Weber (IJROBP 2011)	Protons	39 29 benign 10 atypical or malignant	53-58 GyE benign 60-66 GyE atyp or anapl.	55 m median	5-yr 100% benign 5-yr 58% atyp. or anaplastic	
MGH Wenkel 2000; 84(5)	Protons	46 Benign only	Mean 59 Gy(RBE)	53 m median	5-yr 100% benign	10-yr LC 88%
MGH Hug (J Neuroonc. 2000; 48(2)	Protons and photons	31 15 atypical 16 malignant	< 60Gy>	Mean 59 m	5-yr 38% atyp 5-yr 52% mal. 5-yr 80% with protons vs. 17% photons (signif).	8-yr LC 19% atyp and 17% mal.

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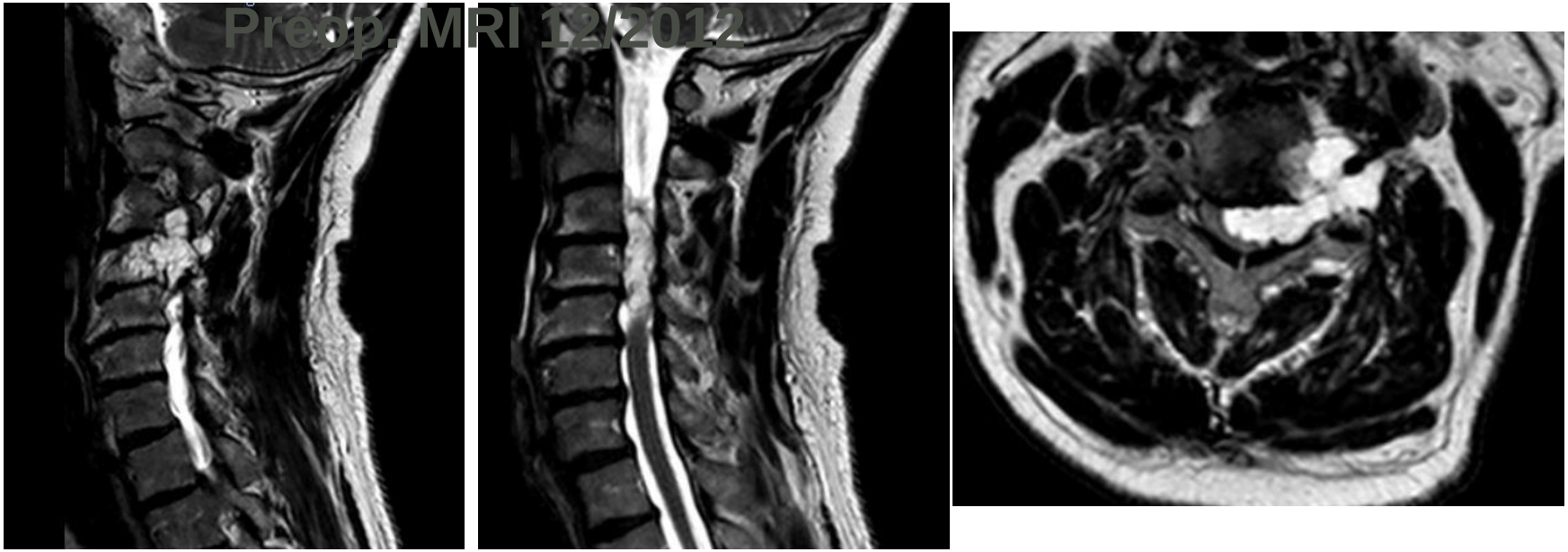
Chordoma of the Cervical Spine

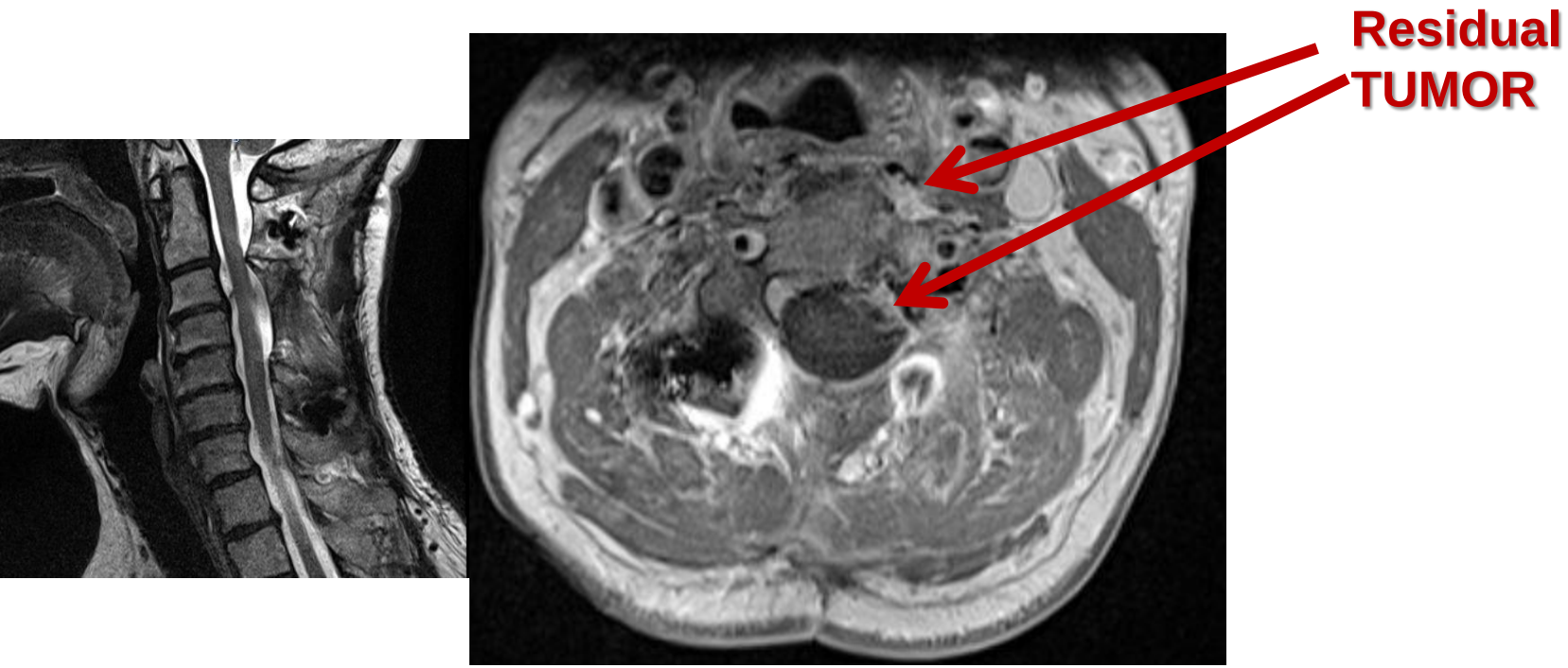
Patient: V.Y. 63 y.o. M; Hx of left sided weakness, sensory deficits, and neck pain



Chordoma of C4 Vertebral body, extensive spinal cord compression, involvement of left vertebral artery

Chordoma of the Cervical Spine

Patient: **63 y.o. M;** **Postop. MRI 2/2013**

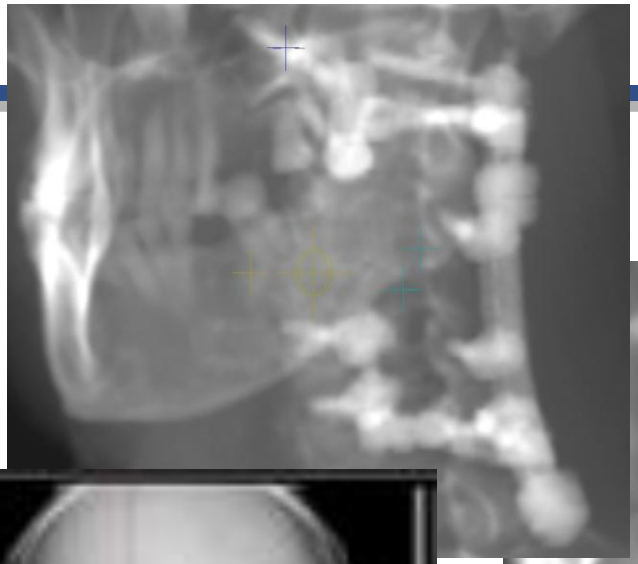


Posterior approach: Laminectomy, Facetectomy, Currettage of C4, subtotal resection
Stabilisation with rods and screws. Note: no ipsilateral rod

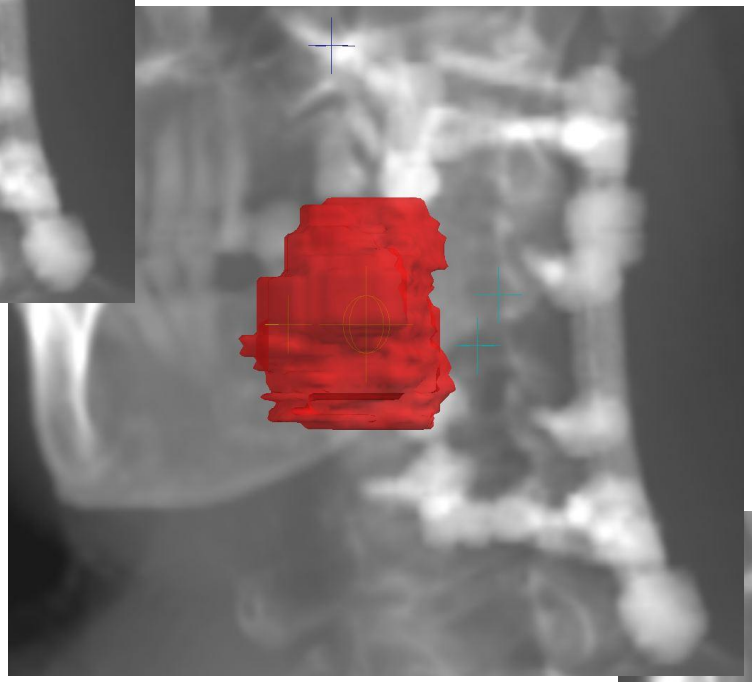
Chordoma of the Cervical Spine

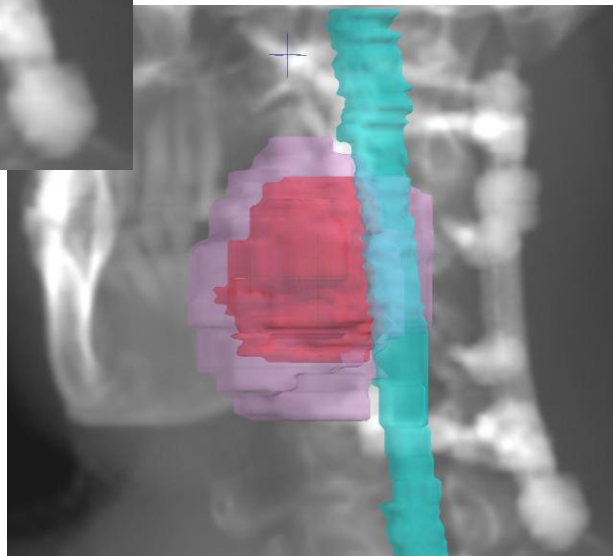
ProCure

Chordoma of the Cervical Spine



Patient: **V.Y. 63 y.o. M;**

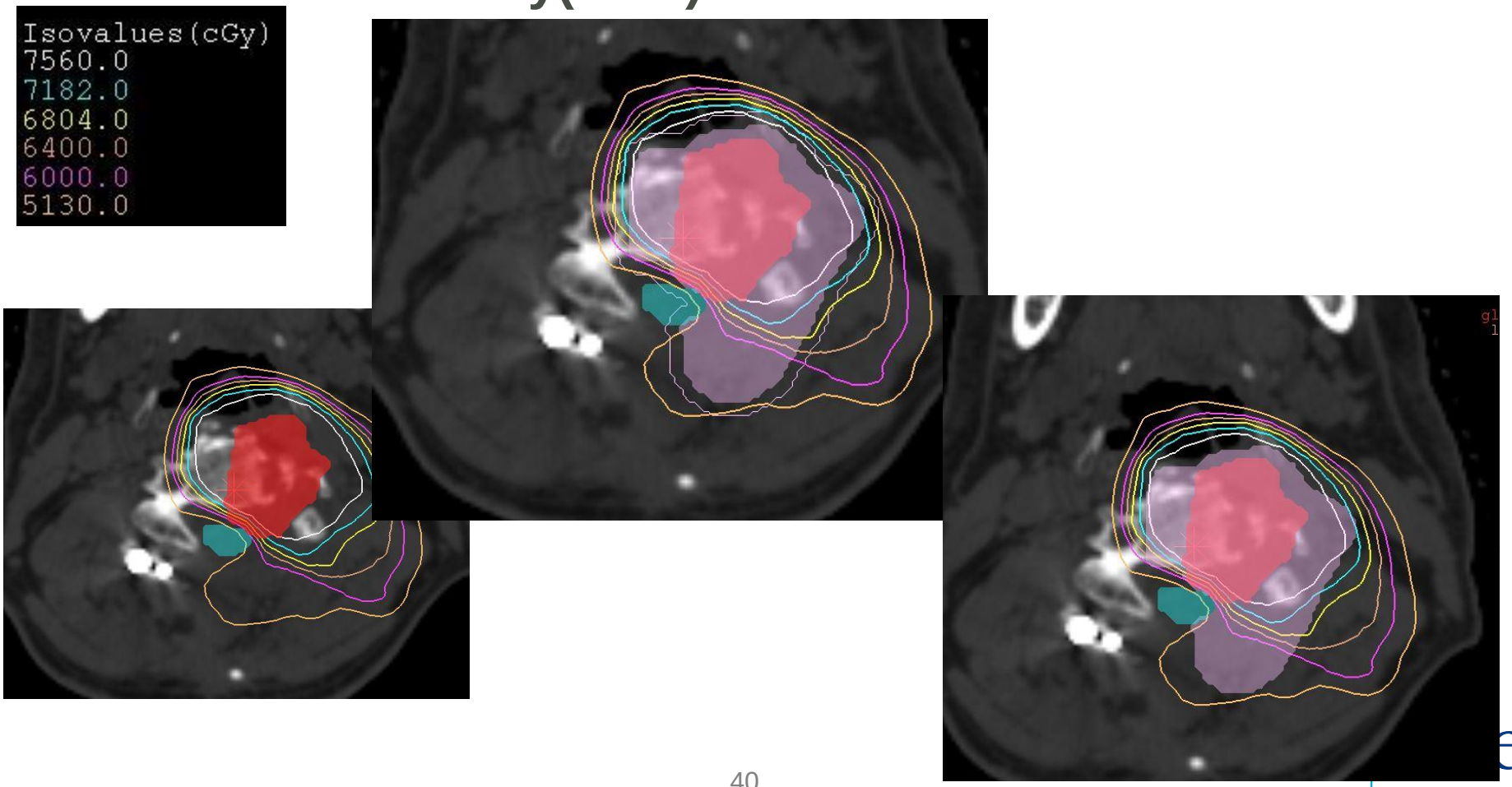




Chordoma of the Cervical Spine

Patient: V.Y. 63 y.o.

Total dose: 75.6 Gy(RBE) at 1.8 / frct.



Chordoma of the Cervical Spine

Patient: V.Y. 63 y.o.

Total dose: 75.6 Gy(RBE) covers 82 %; 71.8 Gy(RBE) = 95% Iso covers 92%