Proton Therapy in Neuro-Oncology

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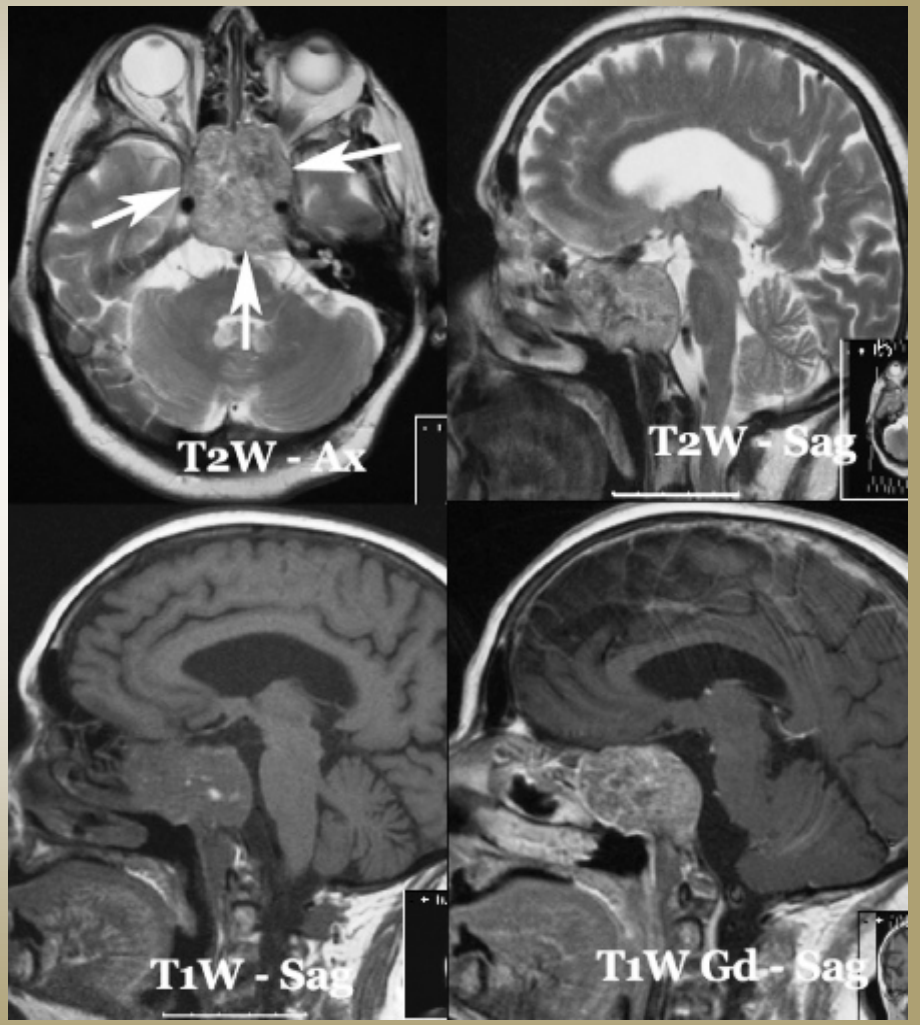
Tumors of the Skull Base

- **Primary-Tumors:**
  - **•Chordomas, Chondrosarcomas**
- **•Primary / secondary infiltration via intracranial tumors:**
  - **•Meningiomas**
- **•Secondary infiltration from H&N tumors:**
  - **•Nasopharynx Ca,**
  - **• Paranasal Sinus Ca,**
  - **•Adenoid-cystic Ca (ACC) Karzinom**
  - **•Rhabdomyosarcomas - a.o.**



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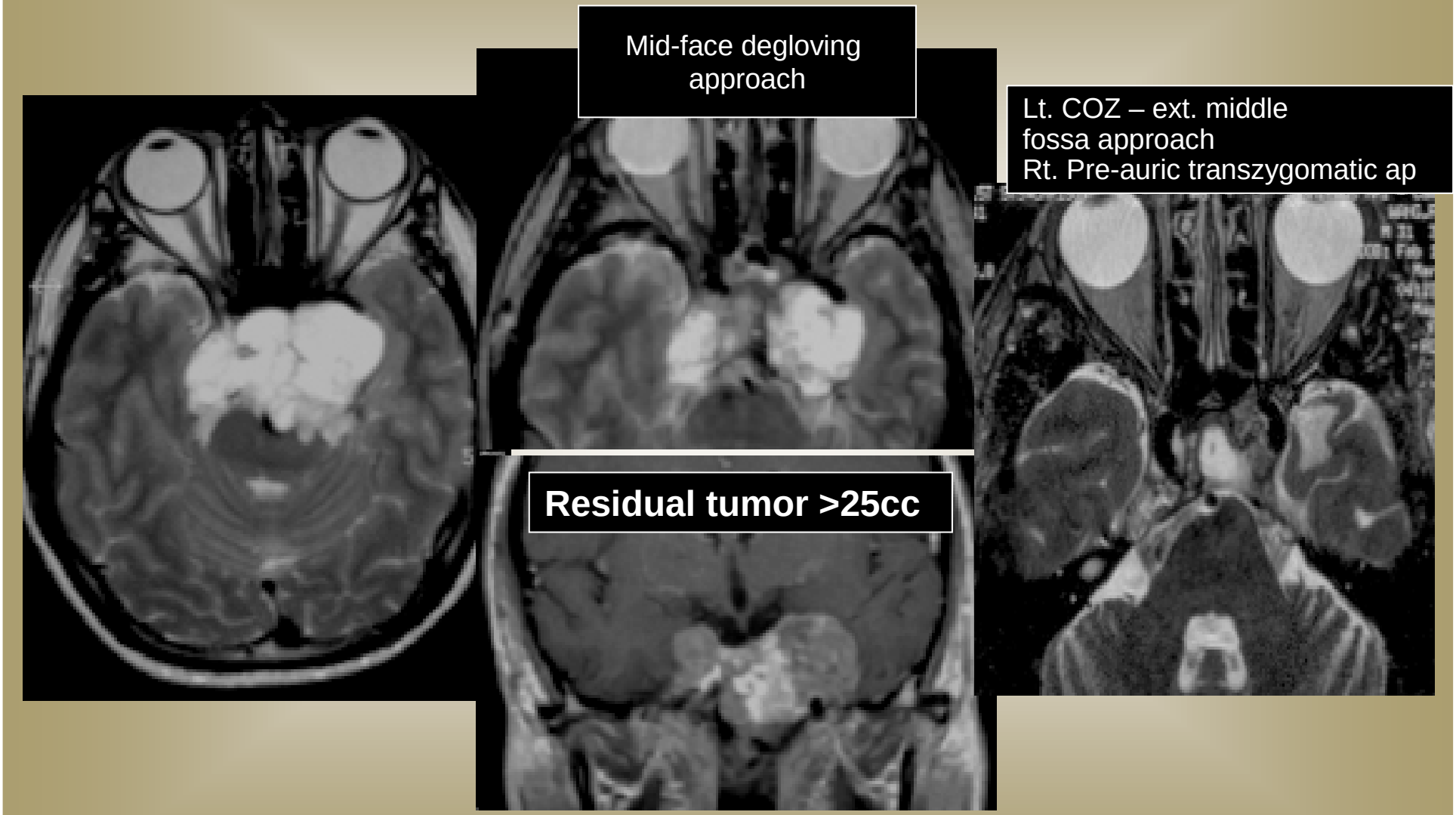
Long Term Results of Proton Radiation Therapy for *Chordomas and Chondrosarcomas* of the Skull Base

Skull Base Chordoma



In Proton Therapy we typically recommend more surgery in case of compression of critical OAR's prior to PTx

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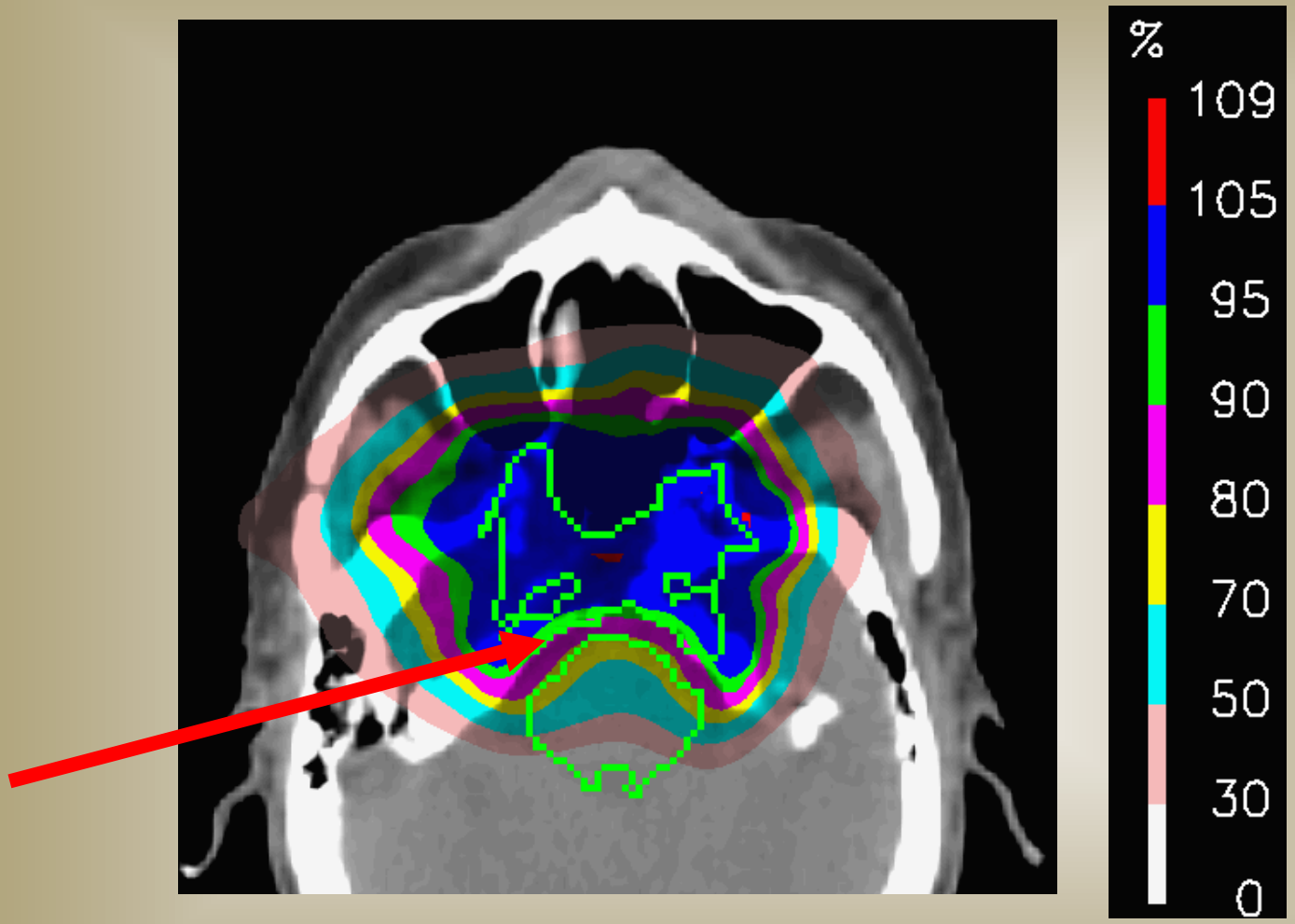

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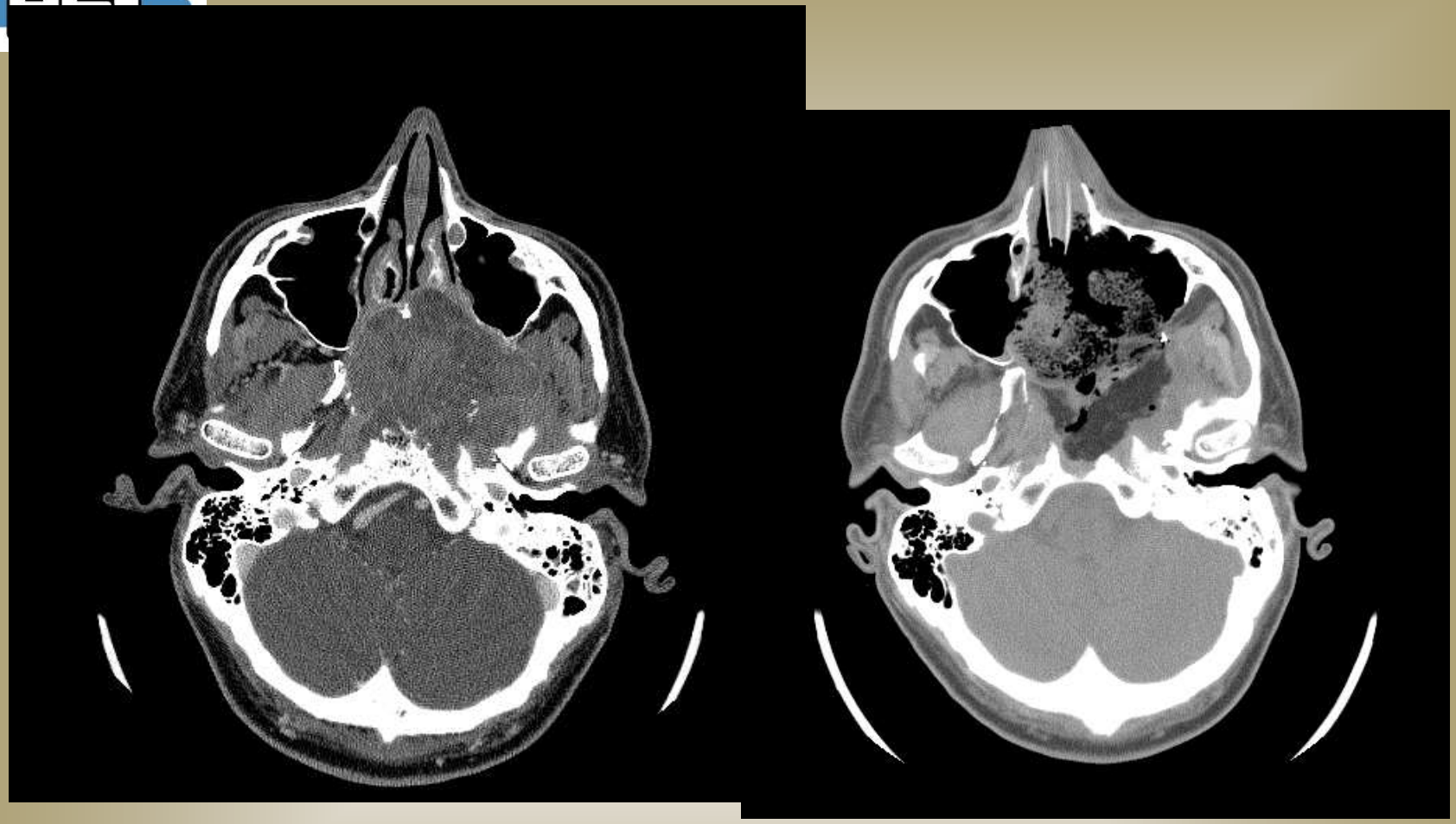
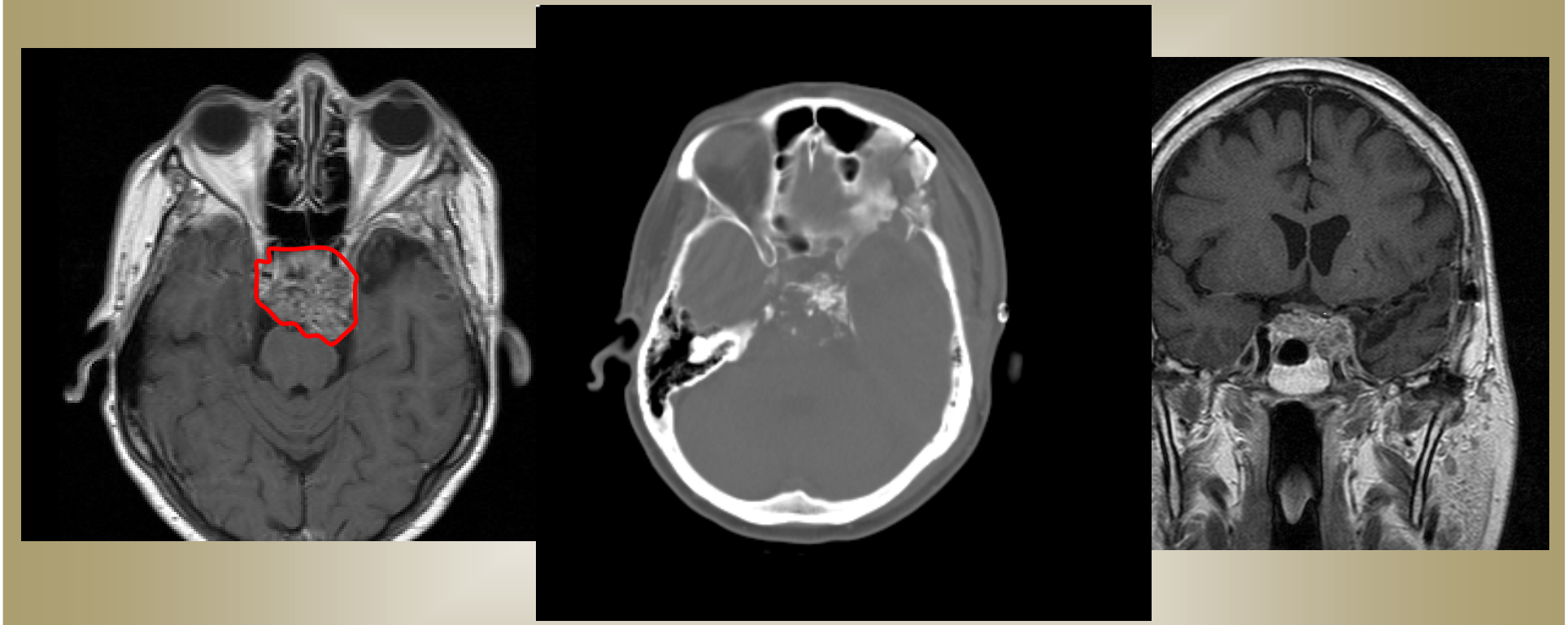


CT preop

CT postop

…reduce tumor bulk……

Low grade Chondrosarcoma



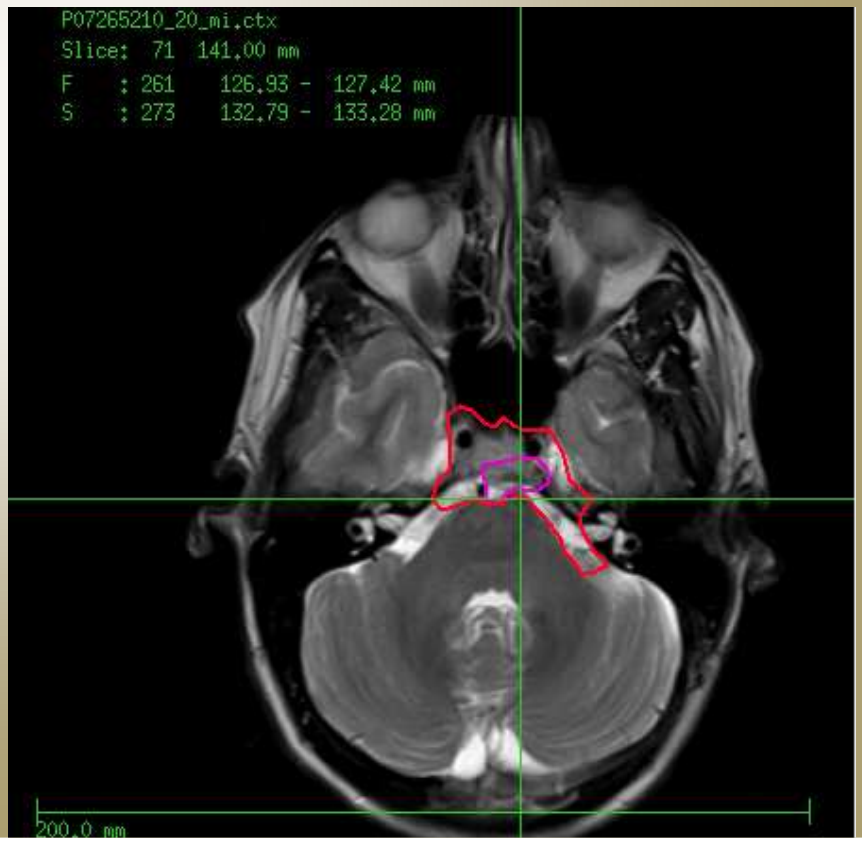
…in case of calcified tumors (“rock hard”), additional surgery might be too risky… treat with PTx as is…

Current treatment concepts at PSI

Skull Base Chordoma – Proton RT Volume Definitions

GTV = Gross Tumor Volume = residual macroscopic tumor

CTV = Clinical Target Volume = preop. Volume plus anatomic areas at risk for microscopic disease

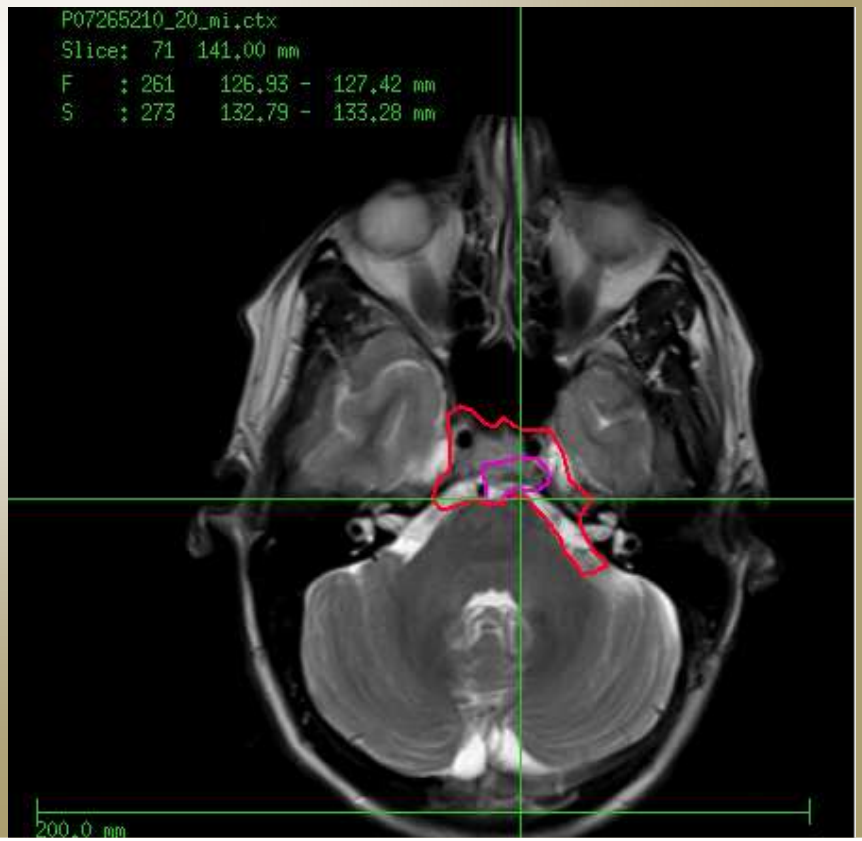


Fractionated Proton Therapy at *Paul Scherrer Institute*

Fraction Dose: 2.0 Gy (RBE), 5 frcts. per week

CTV = 54 Gy (RBE) ***GTV = 74-76 Gy (RBE) (Chordoma)***

OAR constraints: OPTIC Chiasm and Nerves: 60 Gy(RBE); Brainstem surface 64 Gy(RBE), BS-Center: 53 Gy(RBE), BS max. volume: 60 Gy(RBE) < 1.0 cc.



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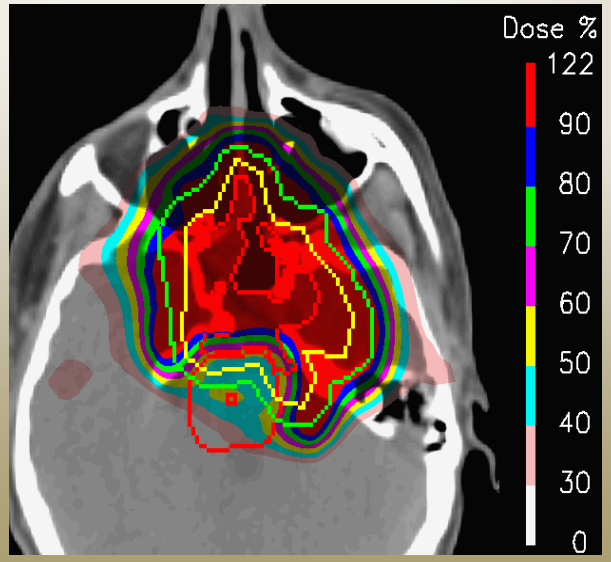
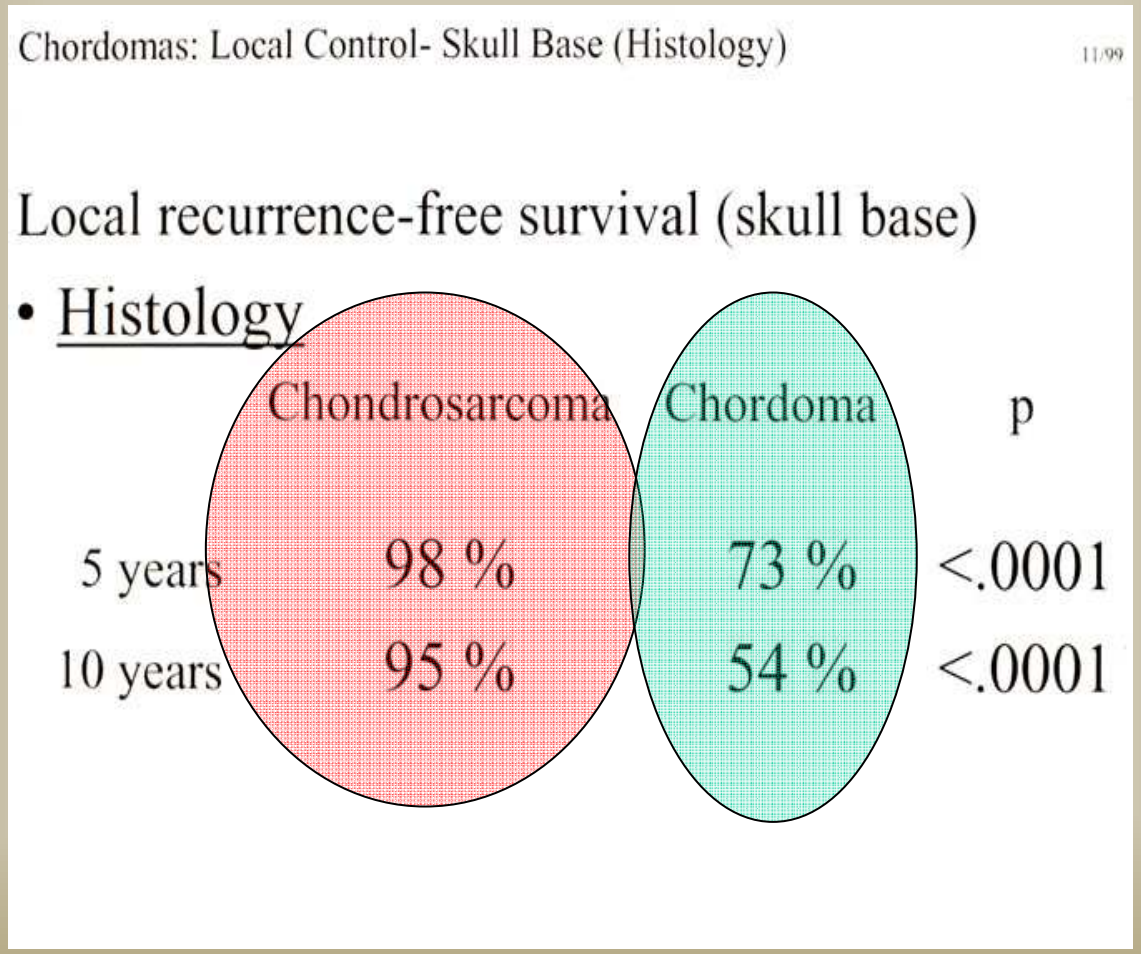
Tumor Control Data
of
fractionated Proton Therapy
for
Skull Base Chordomas and Chondrosarcomas



Chondrosarcoma and Chordoma

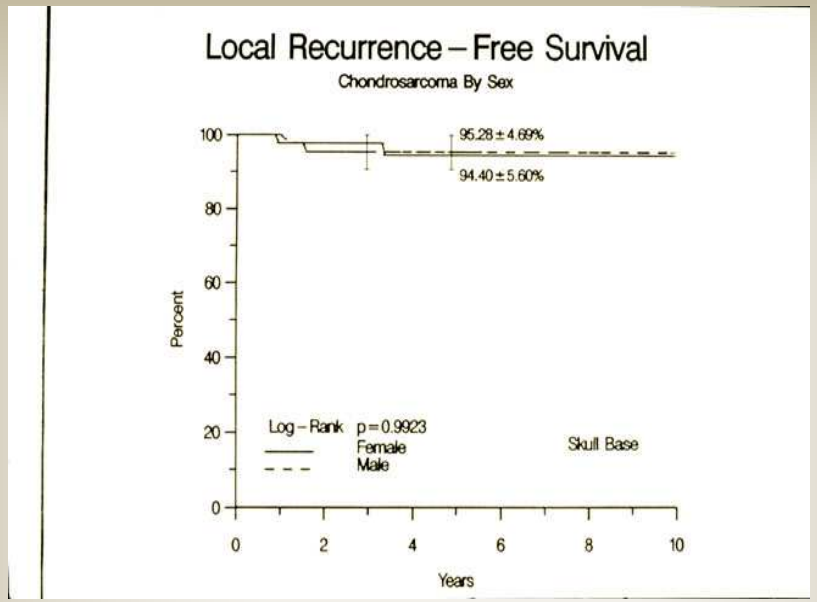
Long term tumor control: MGH data



Courtesy: John Munzenrider, MGH/HCL, 1999

Chondrosarcoma :

Long term tumor control: MGH data



Courtesy: John Munzenrider, MGH/HCL, 1999

ASTRO 2009, J. Munzenrider *(IJROBP 72(1), suppl.)*

•1987 to 1993, either „ 70.2 (LD) vs. 76 CGE (HD)“
F/U: median 16.7 y **(4.5-20 y).**

Results:	**5-yr**	**10-yr**	**15-yr**
LC for CSA (LD – HD)	**94 vs. 85 %**	**89 vs. 67 %**	**89 vs. 58 %**

Skull Base *Chondrosarcomas:* Proton series

	n	Radiation	Mean dose	LC 3 -yr	LC 5 -yr	LC 10 -yr
Munzenrider, 1999	229	PT, RT	72		98	95
Hug, 1999	25	PT, RT	71		79	
Johnson, 2002	58	PT, RT	71		91	
Noel, 2004	26	PT, RT	67	91		
Schulz-Ertner, 2007	54	*Carbon, RT*	60*	96	*89 @4y*	
Ares, 2008	22	PT	68.4		94	

**at 3.0 CGE per fraction*

Review: Amichetti et al., Neurosurg Rev., 32:403, 2009 !

Skull Base *Chordomas:*
Proton series

	n	Radiation	Mean dose	LC 3 -yr	LC 5 -yr	LC 10 -yr
Munzenrider, 1999	**290**	**PT, RT**	**76**		**73**	**54**
Terahara, 1999	**115**	**PT, RT**	**69**		**59**	**44**
Hug, 1999	**33**	**PT, RT**	**71**	**67**	**59**	
Noel, 2005	**100**	**PT, RT**	**67**	**86** 2y	**53 4y**	
Schulz-Ertner, 2007	**96**	***Carbon, RT***	**60***	**81**	70	
Igaki, 2004	**13**	**PT, RT**	**72**	**67**	**46**	
Ares 2008	**42**	**PT**	**74**		**81**	

***at 3.0 CGE per fraction**

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Prognostic Factors of Local Control

after

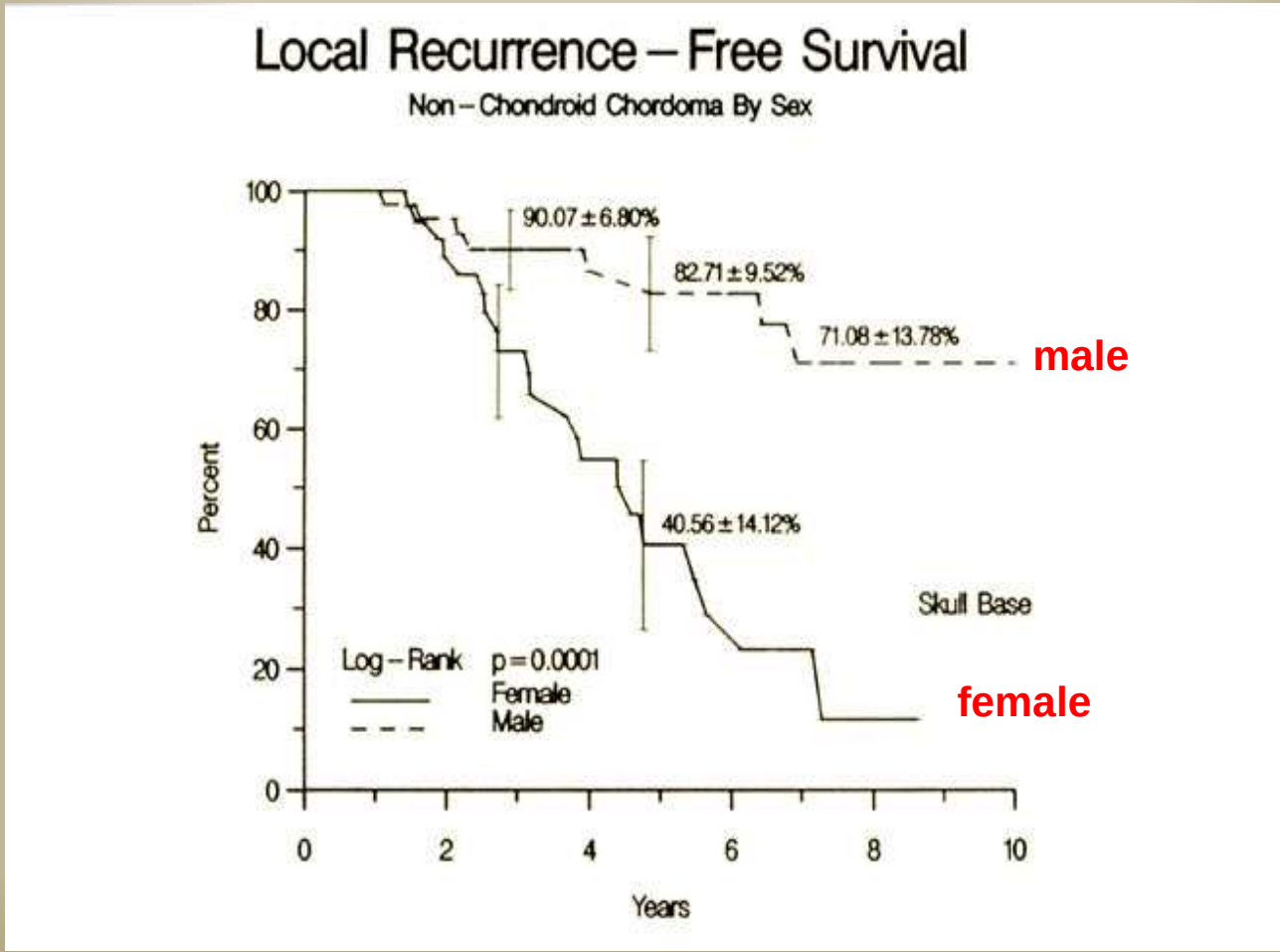
fractionated Proton Therapy

for

Skull Base Chordomas and Chondrosarcomas

Chordomas:

Long Term outcome – the MGH Data



Courtesy: John Munzenrider, MGH/HCL, 1999

Prognostic Factors of Local Control of *fractionated Proton Therapy* for Skull Base Chordomas and Chondrosarcomas

- Tumor Size
- Compression of critical OAR‘s
- Primary versus Recurrent Disease
- Age
- Gender
- Dose

Proton-RT for Skull Base Chordomas

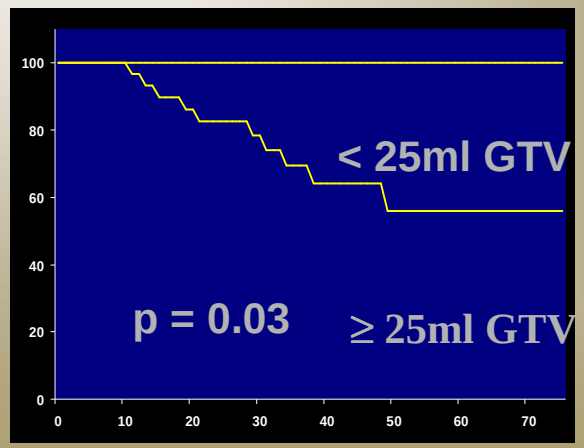
Prognostic Factor: Tumor Size and Local Control

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-freesurvival) 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

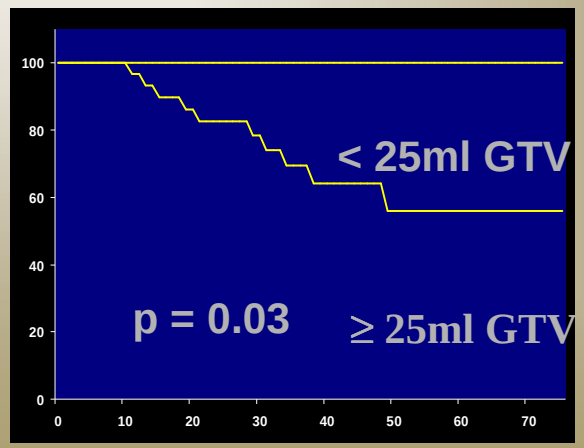
Improved LC for "smaller" size

- **LLUMC: < 25 ml vs. > 25 ml (10[illegible] nif.**
- **CPO: <29 [illegible] 29ml [illegible] nif.**
- **PSI: > [illegible] fa[illegible] p=signif.**
- **MG[illegible] reesurvival) p=signif.**
- **L[illegible] vs. > 35 cc (80% vs. 33%) p=signif.**
-

>90% for small tumors

Loma Linda UMC Analysis

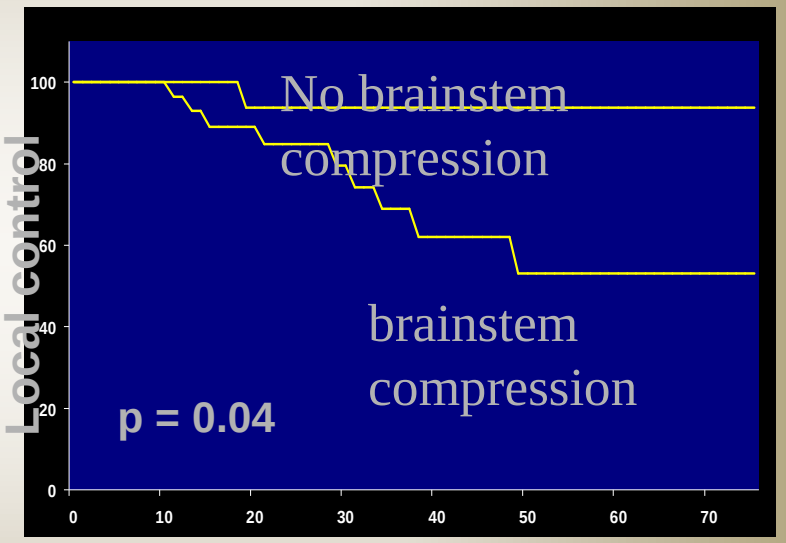
Hug, Laredo, et al.
J Neurosurg. 91:432-439, 1999



Proton-RT for Skull Base Chordomas

Prognostic Factor: Tumor Compression of Critical Structures and Local Control

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



CPO: 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)**

Proton-RT for Skull Base Chordomas

Prognostic Factor: Tumor Compression of Critical Structures and Local Control

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

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

Proton-RT for Skull Base Chordomas

Prognostic Factor: Tumor Compression of Critical Structures and Local Control

PSI: 5/6 failures with bra[illegible]st[illegible] p=signif.

MGH: 15/26 [illegible]s on p=signif.

surgery to decompress

Proton-RT for Skull Base Chordomas

Prognostic factor: primary versus recurrence

MGH	no info	
LLUMC	no difference	
CPO	not significant	
PSI	not significant	
GSI – Carbon Ions	primary vs. recurrence	P= signif.
	92% vs. 62%	
LBL	primary vs. recurrentce	p = signif.
	78% vs. 33%	

MGH = Massachusetts General Hospital

CPO = Centre de Protontherapie d'Orsay

LBL = Lawrence Berkely Laboratory

LLUMC= Loma Linda University Medical Center

PSI = Paul Scherrer Institute

GSI = Gesellschaft für Schwerionenforschung

Proton-RT for Skull Base Chordomas

Prognostic factor: AGE and Local Control

MGH	< 40 years vs. >40 years	trend only
	DFS worse > 40 years	
LLUMC	no info	
CPO	< 52 years vs. > 52 years	P = signif.
	94% vs. 65% (at 3 years)	
PSI	No difference	
GSI – Carbon Ions	No info	
Pediatric vs. adult **	some reports worse	conflicting data
	some reports better	

**** see MGH / N. Liebsch's presentation on Saturday !**

Proton-RT for Skull Base Chordomas

Prognostic factor: GENDER and Local Control

MGH	**male vs. female**	**p = signif.**
	85% vs. 65 % (5 yrs.) 62% vs. 42% (10 yrs.)	
LLUMC	70% vs. 54% (5 yrs.)	trend
CPO	not significant	
PSI	female worse (4/5 failures)	trend
GSI – Carbon Ions	No difference	
E: Hug (pediatric patients)	female worse (4/5 failures)	trend

MGH = Massachusetts General Hospital

LLUMC= Loma Linda University Medical Center

CPO = Centre de Protontherapie d'Orsay

PSI = Paul Scherrer Institute

GSI = Gesellschaft für Schwerionenforschung

Proton-Radiotherapy for Skull Base *Chordomas and (Chondrosarcomas*)

Prognostic factors

(+++)	Skull base: Chondrosarcomas versus Chordomas
(+++)	Tumor Size
(+++)	Tumor Compression of Critical Structures, i.e. OAR-Tumor-Dose-Gradient
(+++)	Radiation Dose
(++)	Gender
(+/-)	Primary versus recurrent disease
(+/-)	Age
(+/-)	Pediatric versus Adult

Proton-Radiotherapy for Skull Base
Chordomas and (Chondrosarcomas)

High-Grade Toxicities:

MGH	5-13%
LLUMC	5%
CPO	6 %
PSI	6%

Risk 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

Low-risk group: < 5%

High-risk group: > 10 % - ?? *

Skull base tumors: Radiosurgery and Cyberknife series

	Chordomas		Chondrosarcomas	
	n	5-y LC	n	5-y LC
Krishan, ´05	25	32%	4	100%
Martin,´07#	18	63%	10	80%
Hasegawa, ´07	30	72%	7	2/7 failed
Henderson, ´09	18	59%		
Liu, ´08	28	21%		

19 patients as a boost after external RT with mean dose 50.4 Gy

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Proton Radiation Therapy for *Meningiomas* of the Skull Base

Meningioma

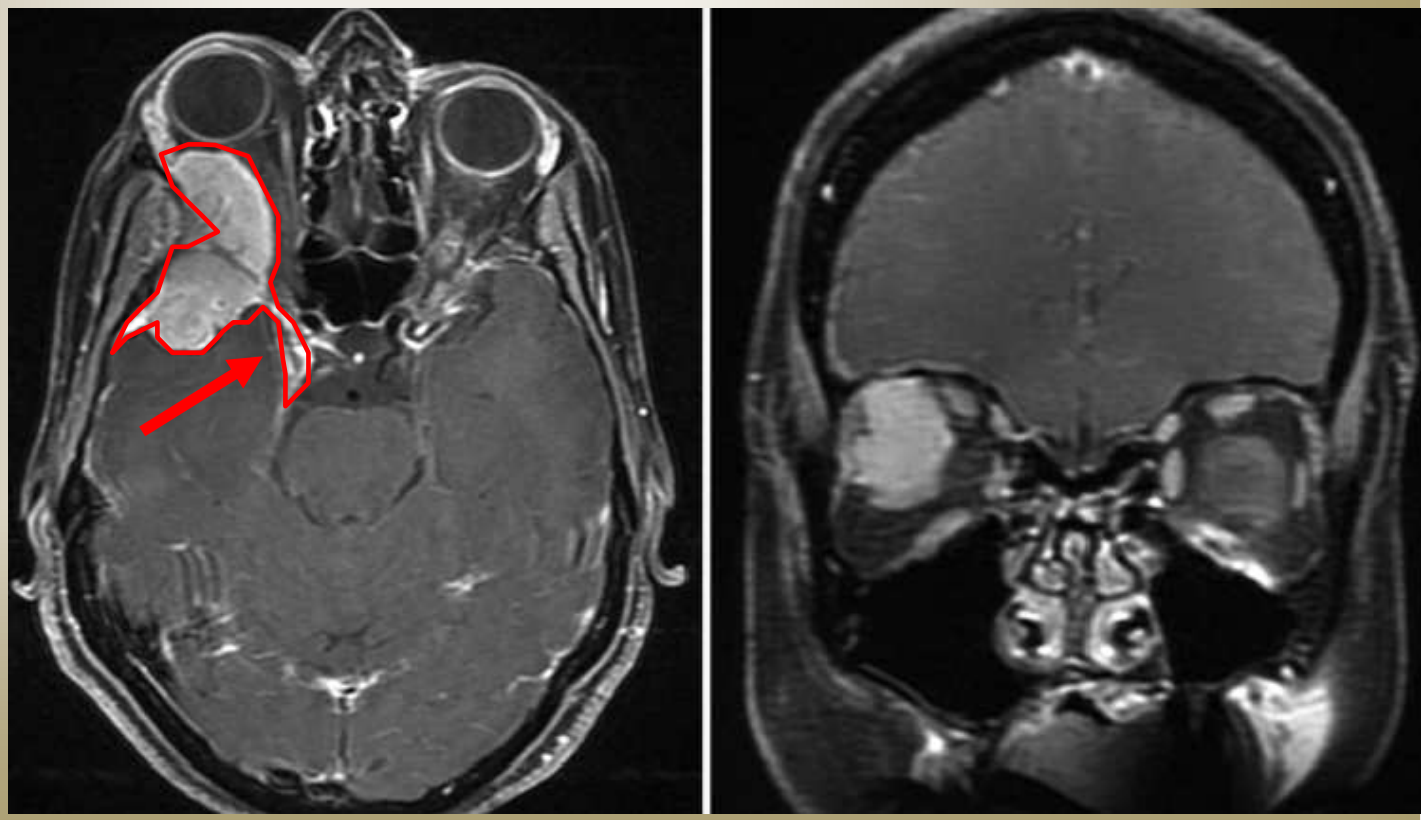
Patients treated at CPT / PSI:

"complex" benign meningiomas
atypical meningiomas
anaplastic / malignant meningiomas

Benign Meningioma

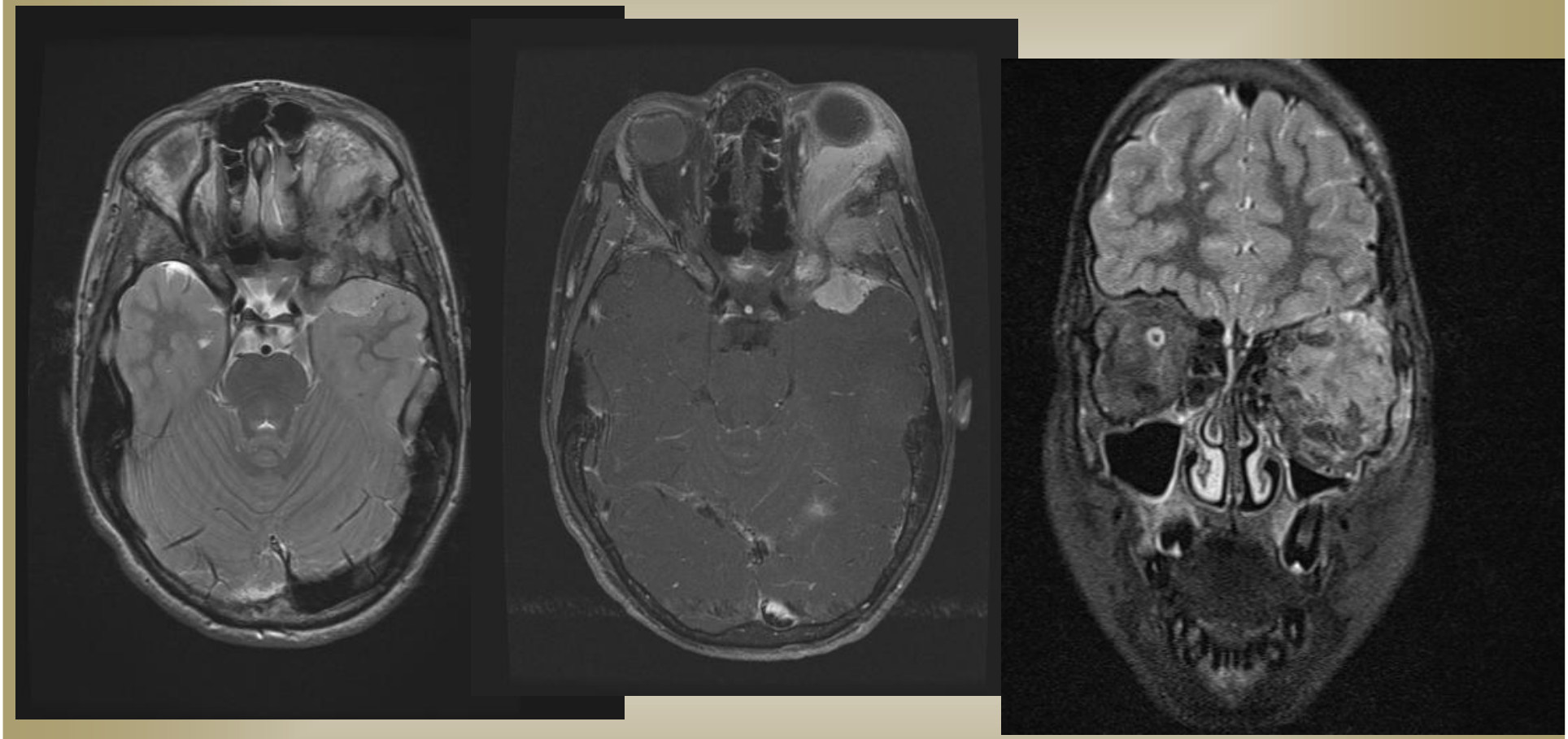
Recurrent (3 surg.)

Reduced vision



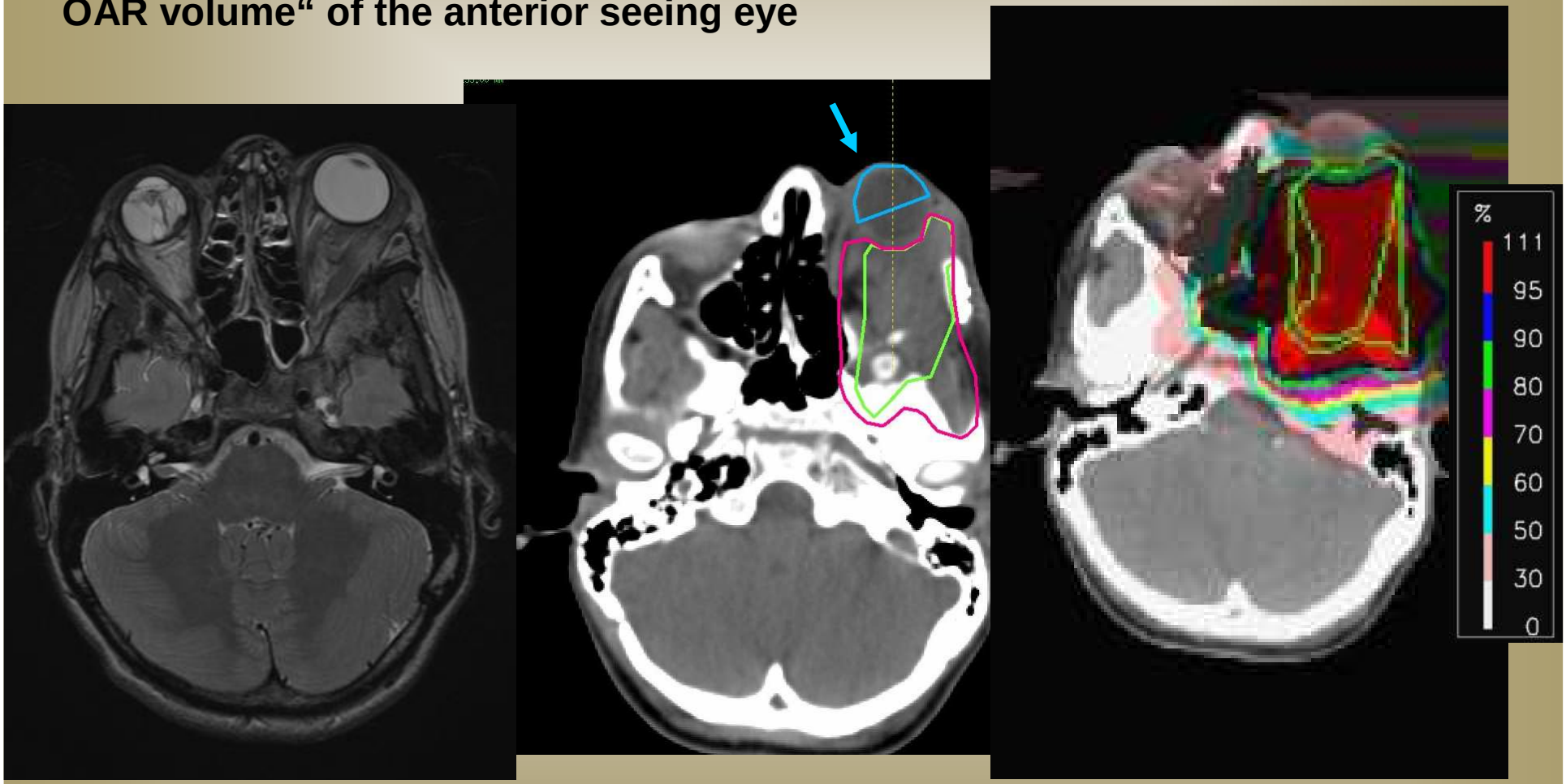
atypical meningioma

13 y.o. male



atypical meningioma

Only 1 seeing eye ipsilaterally. Create a „technical OAR volume“ of the anterior seeing eye



Results of PHOTONS

Atypical and malignant meningioma:
outcome and prognostic factors in 119 irradiated patients. A multicenter, retrospective study of the Rare Cancer Network.

Pasquier D et al. Centre O. Lambret and University Lille,Lille, France.

IJROBP. 2008 Aug 1;71(5):1388-93.

- Ten academic medical centers
- **119** cases of patients with atypical or malignant meningiomas treated with external beam radiotherapy (EBRT) after surgery or for recurrence.
- mean age was 57.6 years.
- Surgery: macroscopically complete (Simpson Grades 1-3) in 71%
- **atypical and malignant histology in 69% and 31%**
- Mean dose of EBRT was **54.6 Gy** (range, 40-66 Gy).
- Median follow-up was 4.1 years.

- **RESULTS:**
- Actuarial overall survival rates: 5-year 65%, 10-year 51%lysis):
- Factors (univariate analysis):age >60 years (p = 0.005), Karnofsky performance status (KPS) (p = 0.01), and high mitotic rate (p = 0.047).
- Factors (multivariate analysis) age >60 years and high mitotic rate.
- **Disease-free survival rates: 5-year 58% and 10-year 48%.**
- Factors: KPS (p = 0.04) and high mitotic rate (p = 0.003) (univariate analysis).
- **Factors: (multivariat a.): only high mitotic rate** (p = 0.003).

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Management of atypical and malignant meningiomas: role of high-dose, 3D-conformal radiation therapy

Hug, De Vries et al. J Neurooncol. 2000, 48(2) 151-154

- 31 patients treated at Massachusetts General Hospital:
- 15 Atypical, 16 Malignant Meningioma
- Primary Dx: 16 pts., Recurrent: 15 pts.
- 8 total, 21 pts. subtotal resection, 2 biopsy
- RT: 15 photons, 16 protons/photons
- mean F/U time 59 months (range: 7-155 months)

- Actuarial local control rates at 5- and 8-years were similar for both histologies:
  - 38% and 19% for Atypical Meningioma
  - 52% and 17% for Malignant Meningioma

Hug, De Vries et al. J Neurooncol. 2000, 48(2) 151-154 ***cont.***

•Improved *Local Control* at 5 years:
•Proton versus Photon RT: *80%* versus 17% (p = 0.003)
•Target doses > or = 60 Gy for both, atypical (p = 0.025) and malignant meningioma (p = 0.0006).

•Actuarial 5- and 8-year survival rates for Malignant Meningioma were significantly improved by use of proton over photon RT and radiation doses > 60 CGE.

Combined Proton and Photon Conformal Radiotherapy for Intracranial Atypical and Malignant Meningioma

Boskos et al., , Centre Protontherapie d'Orsay, France

IJROBP 75:388, 2009.

Patients and Methods

•1999 and October 2006,
•24 patients (12 male, 12 female): atypical 19, malignant 5
• postoperative combined photon / proton RT
•6 patients underwent gross total resection and 18 a subtotal resection.
•Median GTV 44.7 cm3
•Mean total irradiation dose was **65.01 CGE** with a mean proton dose of 34.05 CGE and a mean photon total dose 30.96 Gy **(mean total dose 64 CGE atypical, 68 CGE malignant)**
•.

Results

•Median (range) follow-up 32.2 (1–72) months.
•10 tumors recurred locally.
• **3- and 5- year LC rates for the entire group were 61.3% and 46.7%**
• **> LC rate with doses > 60 Gy**

• 3- and 5- year overall survival rates were 80.4% and 65.3%
•Survival was significantly associated with total dose.
•One patient developed radiation necrosis 16 months after treatment.

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

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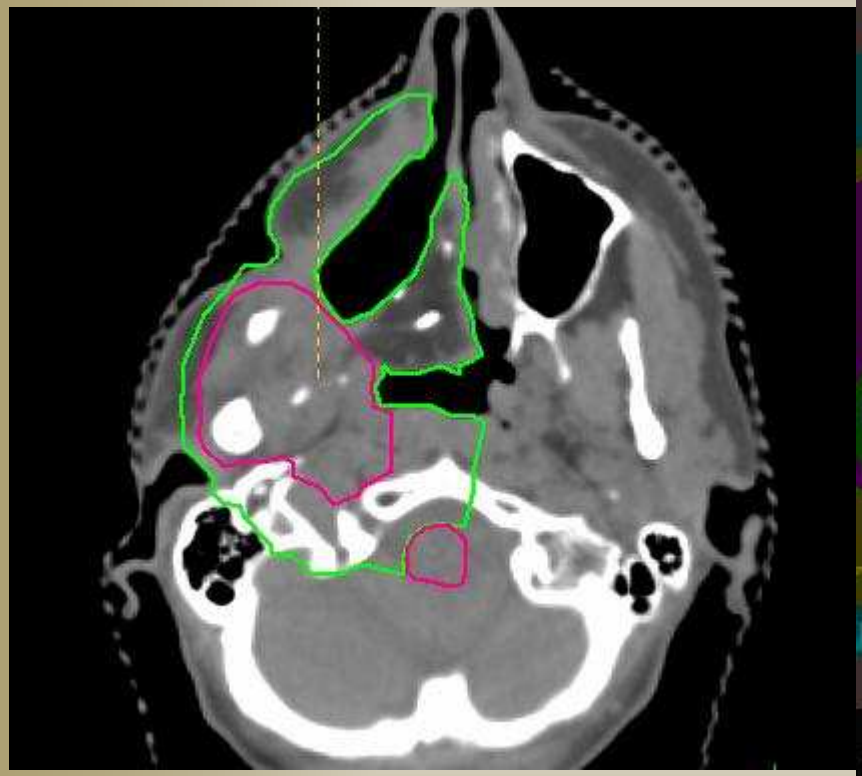

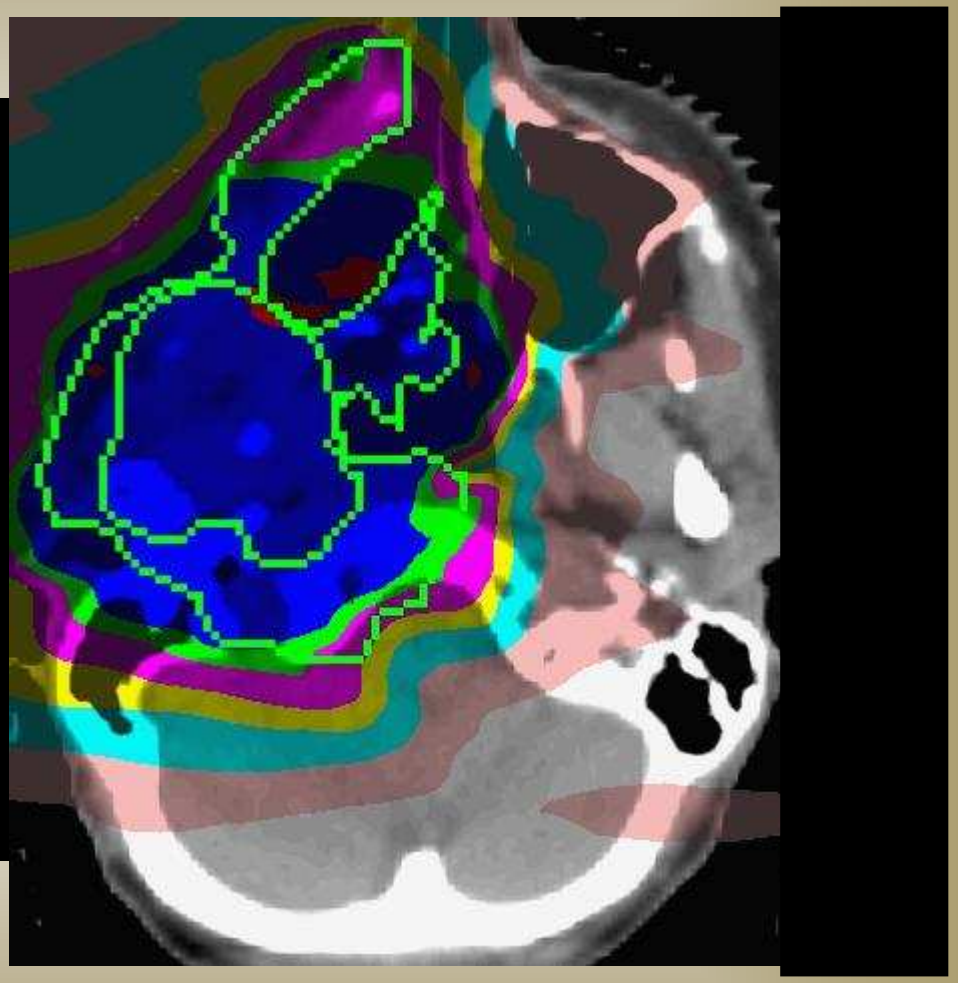

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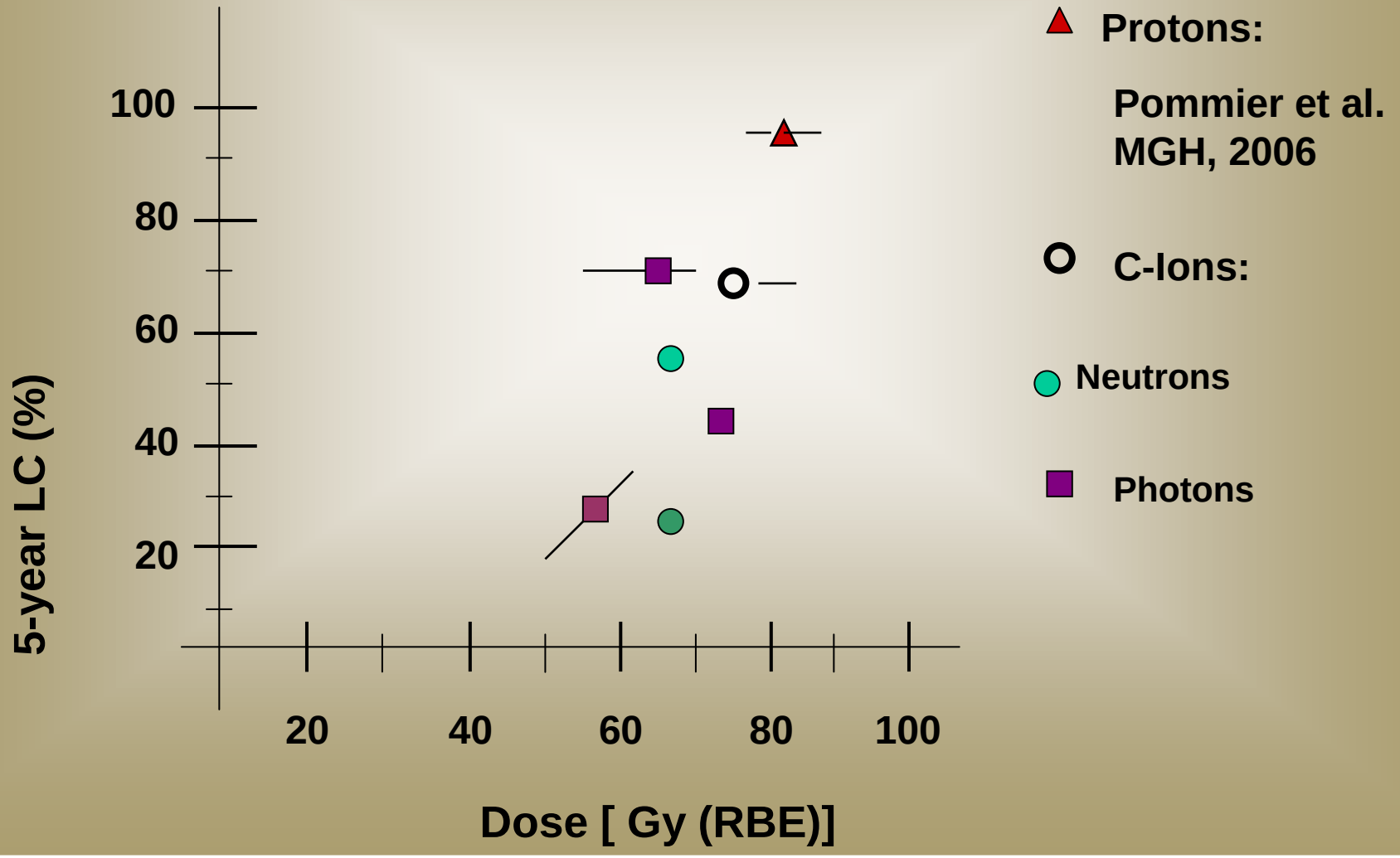
Adenoid-cystic Carcinoma with infiltration of the skull base



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Proton Radiation Therapy for *Pediatric CNS-neoplasms*

…see the following sessions…….


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