

Particle Therapy for Chordomas and Chondrosarcoma of the Skull Base

Eugen B. Hug, MD
Medical Director,
ProCure Proton Therapy
Centers, NY

ProCure

Particle Radiation Therapy for Tumors of the Skull Base

- Primary skull base tumors:
 - Chordoma, Chondrosarcoma
- Primary SB or Secondary infiltration from intracranial tumors:
 - Meningioma
 - Acoustic Neuromas
- Secondary infiltration from primary H&N tumors:
 - Nasopharynx CA,
 - Paranasal Sinus CA,
 - Adenoid-cystic CA

Skull base tumors

Chordomas:

Midline, soft, gelatinous

Developed from remnants of embryonal Notochord.

Only located Skull base and axial skeleton including sacrococcygeal

Incidence: 300 new patient per year in the USA

(0.02/100,000)

Proton Therapy: approx. 150-200 per year = > 60%

Chondrosarcomas:

Midline or lateral, can calcify

Can arise from any cartilage. Majority in extremities

Incidence in USA:

Approx. 1,200 new cases / year

Approx. 600 / year along paraspinal/trunk/skull base

Approx. 40-50% will receive protons

Example of a rare disease with high acceptance of particles by referring surgeons

Why do we need Particle Therapy for Skull base Chordomas and Chondrosarcomas?

....because the majority of photon-based local control data are unsatisfactory?

Management of intracranial and extracranial chordomas with CyberKnife stereotactic radiosurgery.

Jiang B, Harsh GR, Adler JR, Chang SD. J Clin Neurosc, 2012 19(8):1101
Department of Neurosurgery, Stanford

- **20** patients treated between 1994 and 2010
- Average tumor volume **16.1cm³** (2.4-45.9 cm³)
- Mean marginal dose of **32.5 Gy** (18-50 Gy).

- Median follow-up was **34 months** (2-131 months).
- Local Control: in 11 patients (**LC = 55% - crude rate**)
- Overall Kaplan-Meyer survival at five years **OS = 52.5%**.

Note: Local failure precedes death by average 2-3 years. Thus 5-yr actuarial LC rate likely < 40%)

Note: mean volume 16 cc small

.....what about 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)

- Kaiser Permanente, Los Angeles, CA
- FSRT between 2002 - 2009,
- 12 patients with skull base chordomas.
- **Median dose of 66.6 Gy** (range, 48.6 to 68.4 Gy), at 1.8 Gy.
- Median follow-up 42 months.
- 5-year Overall 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 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 local failure

...but what about high dose photons
by very experienced skull base team?

Image-guided intensity modulated radiation therapy (IG-IMRT) for skull base chordoma and chondrosarcoma: preliminary outcomes.

Sahgal A¹, C Catton C¹, O'Sullivan B¹, Gentili F¹, Laperriere NJ¹. Et al.

Toronto Hospitals, including Princess Margaret, Canada

Neuro Oncol. 2014 Dec 27.

42 consecutive IG-IMRT patients, with either skull base chordoma (n = 24) or chondrosarcoma (n = 18)

Median follow-up 36 months (range, 3-90 mo) Chordomas, 67 months (range, 15-125) Chondrosarcomas

Median IG-IMRT doses 70 Gy chondrosarcomas and 76 Gy Chordomas at 2 Gy/fraction.

RESULTS:

5-year Overall Survival	85% Chordoma	88% Chondrosarcoma
5-year Local control	65% Chordoma	88% Chondrosarcoma
Late Effects: 8/42 (actuarial > 10%?)		

Particle Therapy for Skull Base Chordomas and Chondrosarcomas:

Treatment concepts Target Contouring

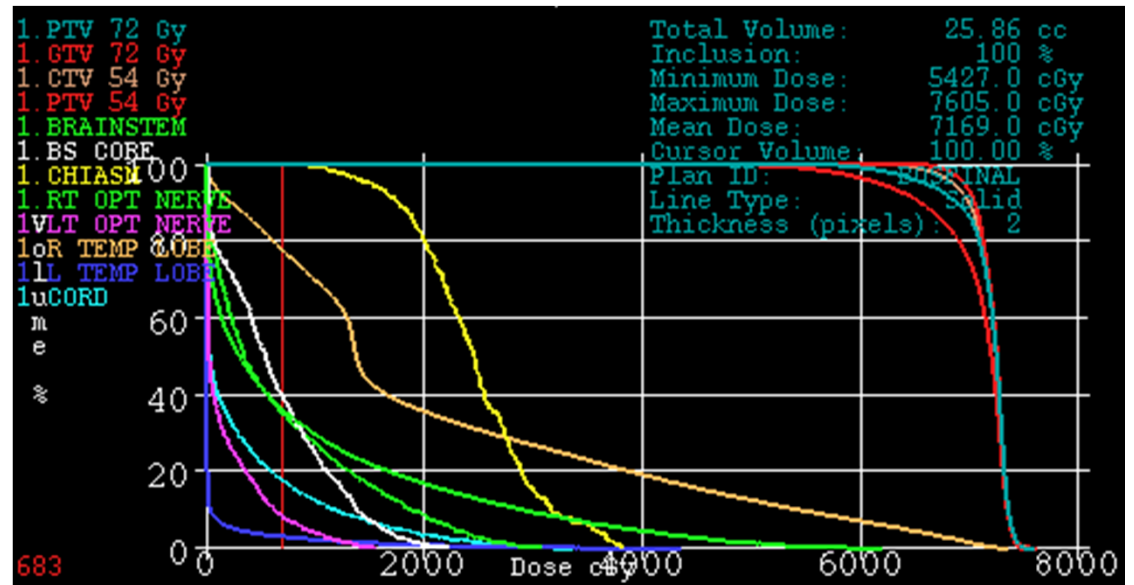
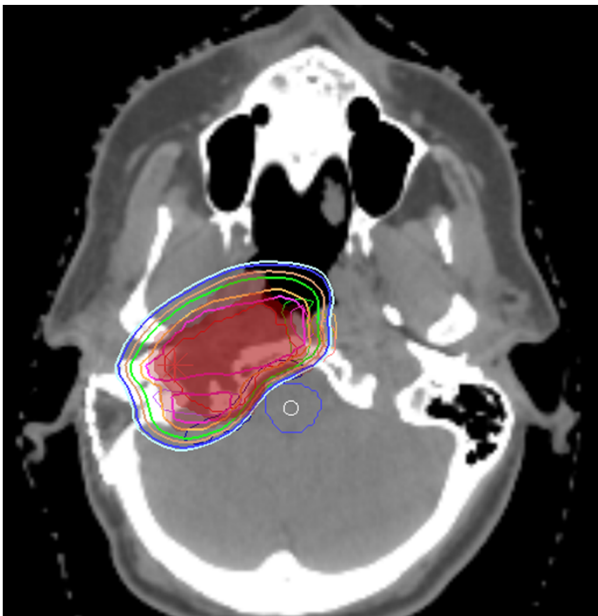
.....common treatment regimen for fractionated Proton Therapy for chordomas and chondrosarcomas

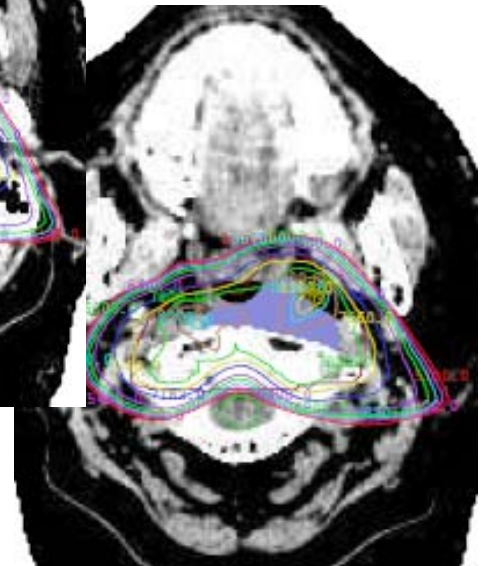
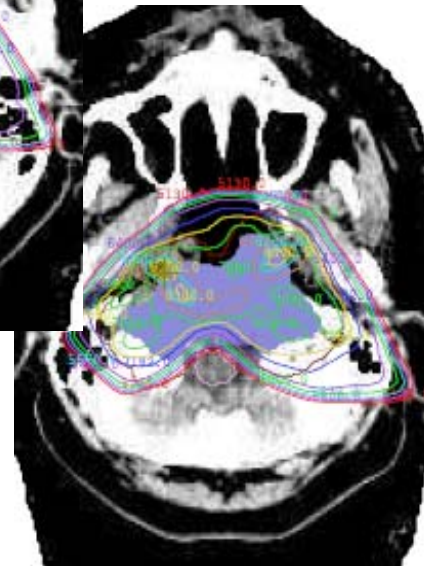
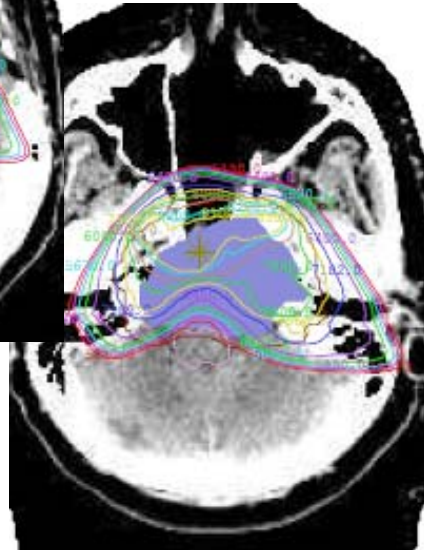
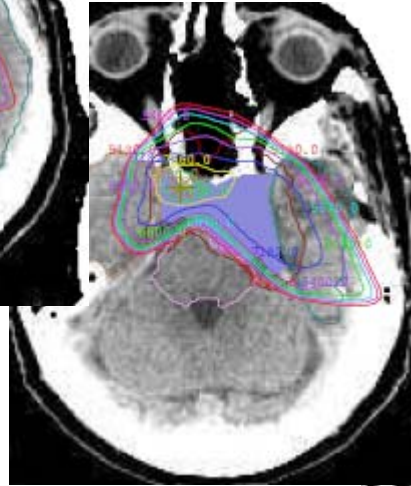
Fraction Dose: 1.8-2.0 Gy (RBE), 5 frcts. per week

CTV = 54 – 60 Gy (RBE)

Chordomas GTV = CH: 74-79 Gy (RBE) Chondrosarcomas: 68-72

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.





... combination of high target dose
and high OAR dose constraints
essential

Skull Base Target Contouring

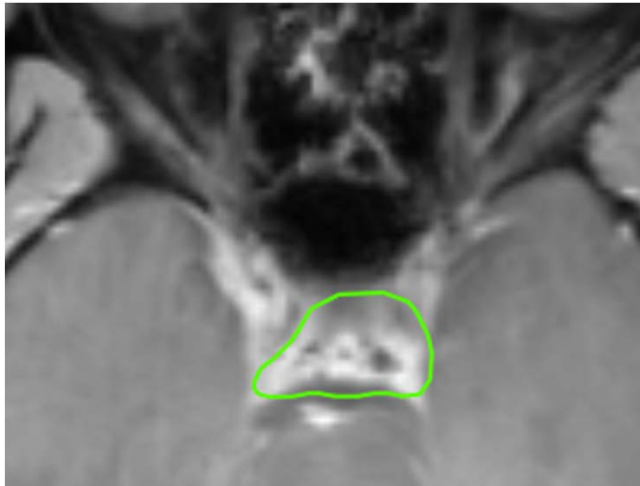
... compartmental CTV
and GTV definition,
.... postoperative bed
coverage
....typically no coverage
of surgical access
(although seeding rate
<5%)



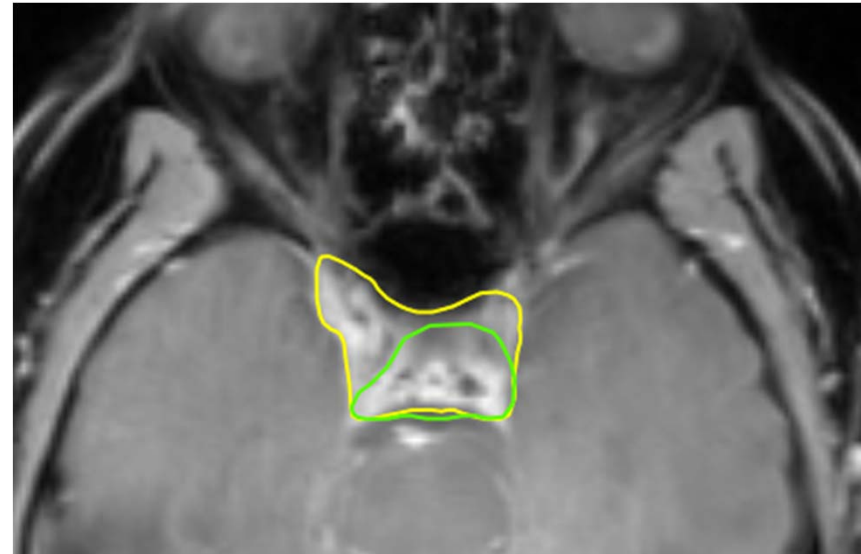
Skull Base Tumor Contouring: The Cavernous Sinus

Example:

“Preop. Tumor Contour”



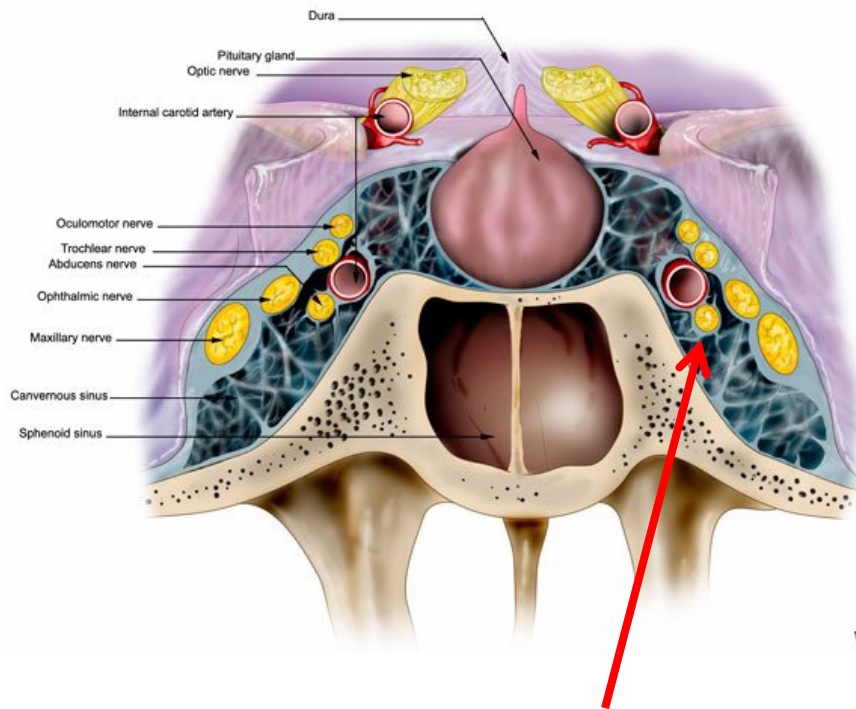
Edited Version:



- 1) Once CS is involved ENTIRE Sinus needs to be contoured*
- 2) Loss of Concavity or “fullness” suggests involvement*
- 3) Include contralateral sinus at least in CTV*

Skull Base Tumor Contouring: The Cavernous sinus

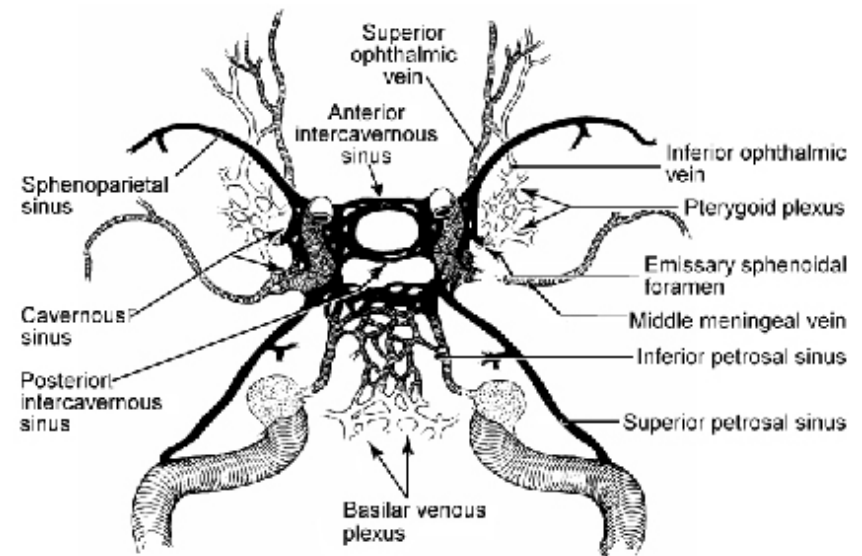
Cavernous Sinus = “Space” between Dura and Bone



wp

1) 6th CN palsy most frequent Sx

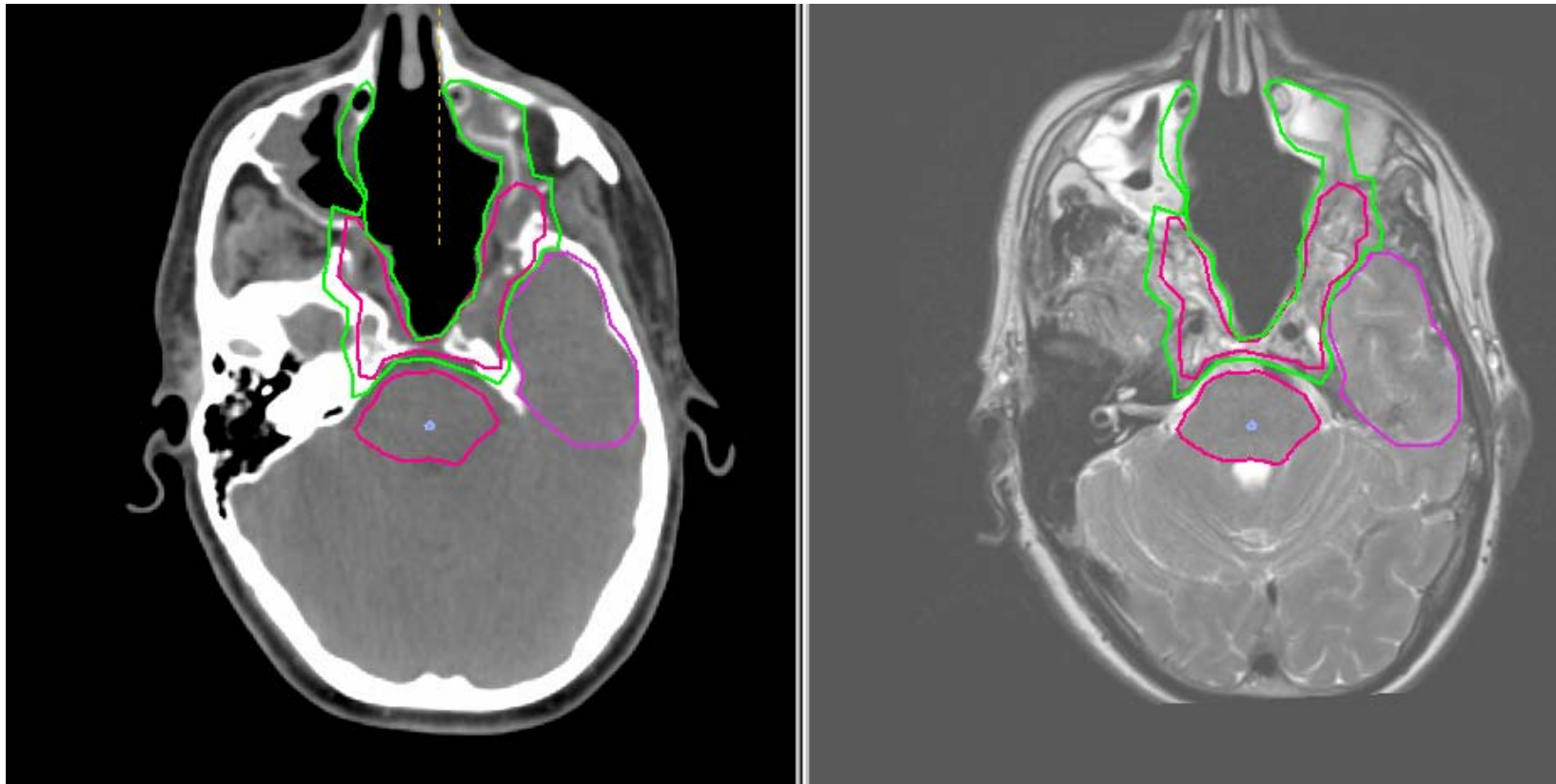
2) No internal septations. Once involved, contour ENTIRE CS



Cavernous sinuses connected via venous complex at posterior wall of clivus

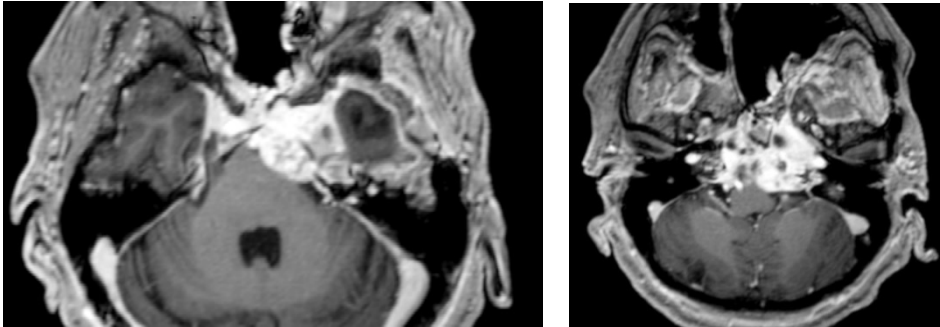
Chordoma Extension into nasal cavity / infratemp. fossa

Large chordoma – High dose volume includes gross disease plus high risk / radiographically undetermined. CTV: NOT with automatic expansion, but risk-determined



Target Contouring – Skull Base Chordoma inferior and extracranial extension

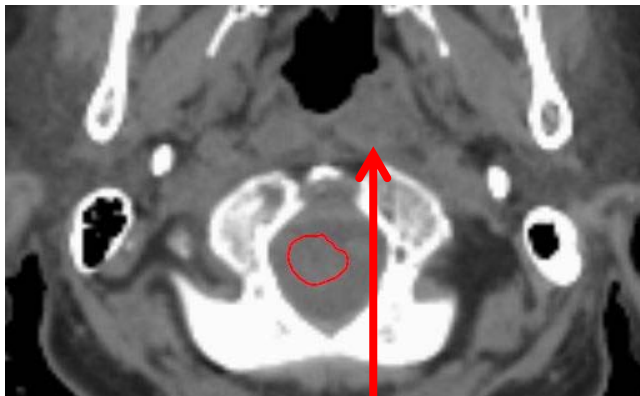
Large Chordoma in 68 y.o. female.



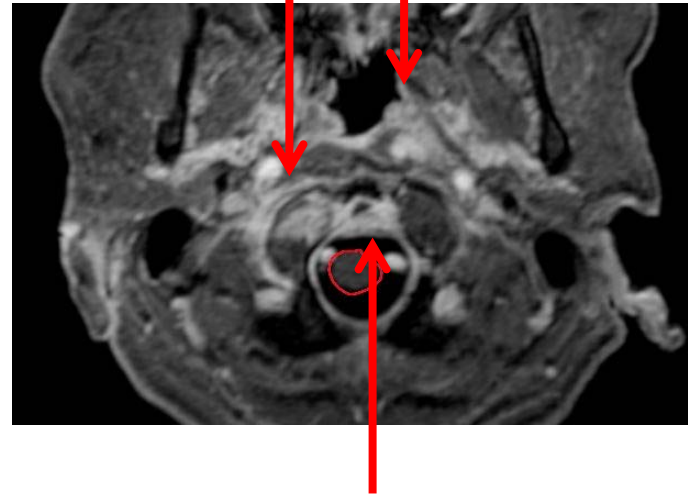
Note: Inferior Extension

- *Frequently non-contiguous extensions*
- *CAVEAT: extracranial extension in posterior pharyngeal tissues*
- *(longus capitis musculature)*

Inferior extension:



*Longus capitis involvement on CT
small asymmetry only*



Skull Base Tumor Contouring

Rules of contouring in skull base tumors:

- If in doubt, include in GTV. Patient can't afford that you are wrong. There is no cure after failure.
- Surgical report: "I accomplished complete tumor resection" means I accomplished complete resection of all tumor visible at time of surgery".
- Know surgical techniques and their limitations.
- An area suspicious for tumor preop. that remains with unchanged MR signal postop. is tumor until proven otherwise and needs to be included as GTV
- When contouring: think "compartment"
- Use CTV to generously include preop. tumor extension, compartments, and uncertain areas.

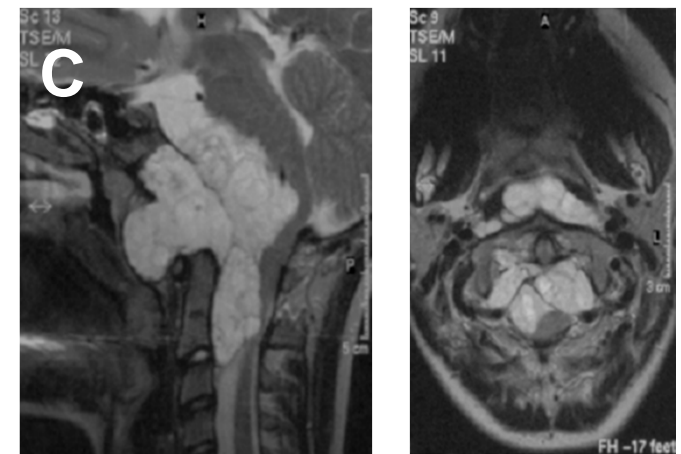
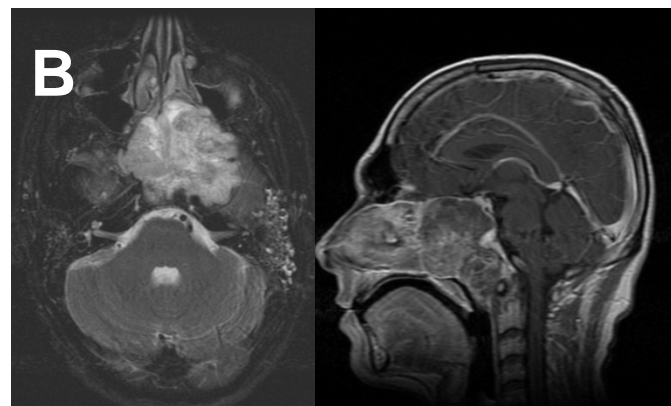
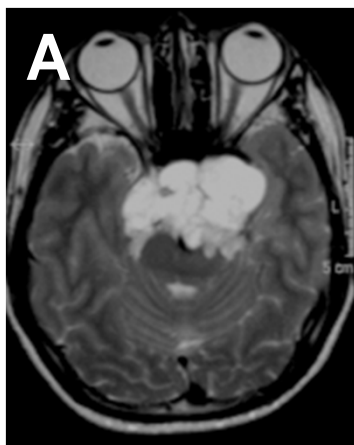
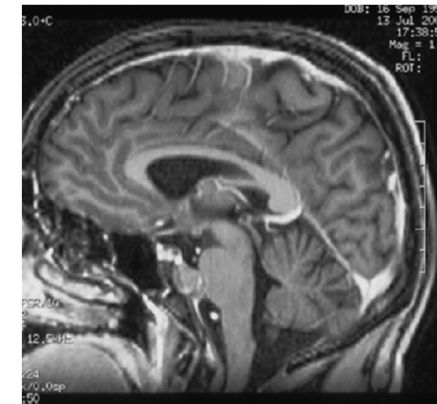
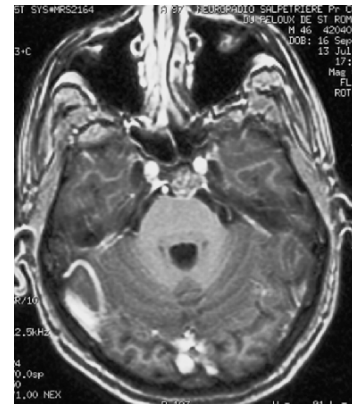
Particle Therapy for Skull Base Chordomas and Chondrosarcomas:

Results

Chordomas of the Skull Base and Occipito-Cervical Junction

Range of tumor sizes / Patient Selection

- Rarely: small lesions (< 15-20 cc)
- Frequently: Large lesions (>100 cc) with significant postop. residual
 - Pre-pontine extension, bilat. middle cranial fossa (A)
 - Extracranial (B)
 - Occipito-cervical junction with large bony destruction, BS and SC compression (C)



Preop. Extensions, large residual GTV's postoperatively

Proton Therapy at PSI for Chordomas and Chondrosarcomas of the Skull base

Ares, Lomax, Hug, Goitein et al. 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., 4 fractions per week).

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)

Ares et al. cont.

Actuarial Local Control

Chordomas

3 years

87 %

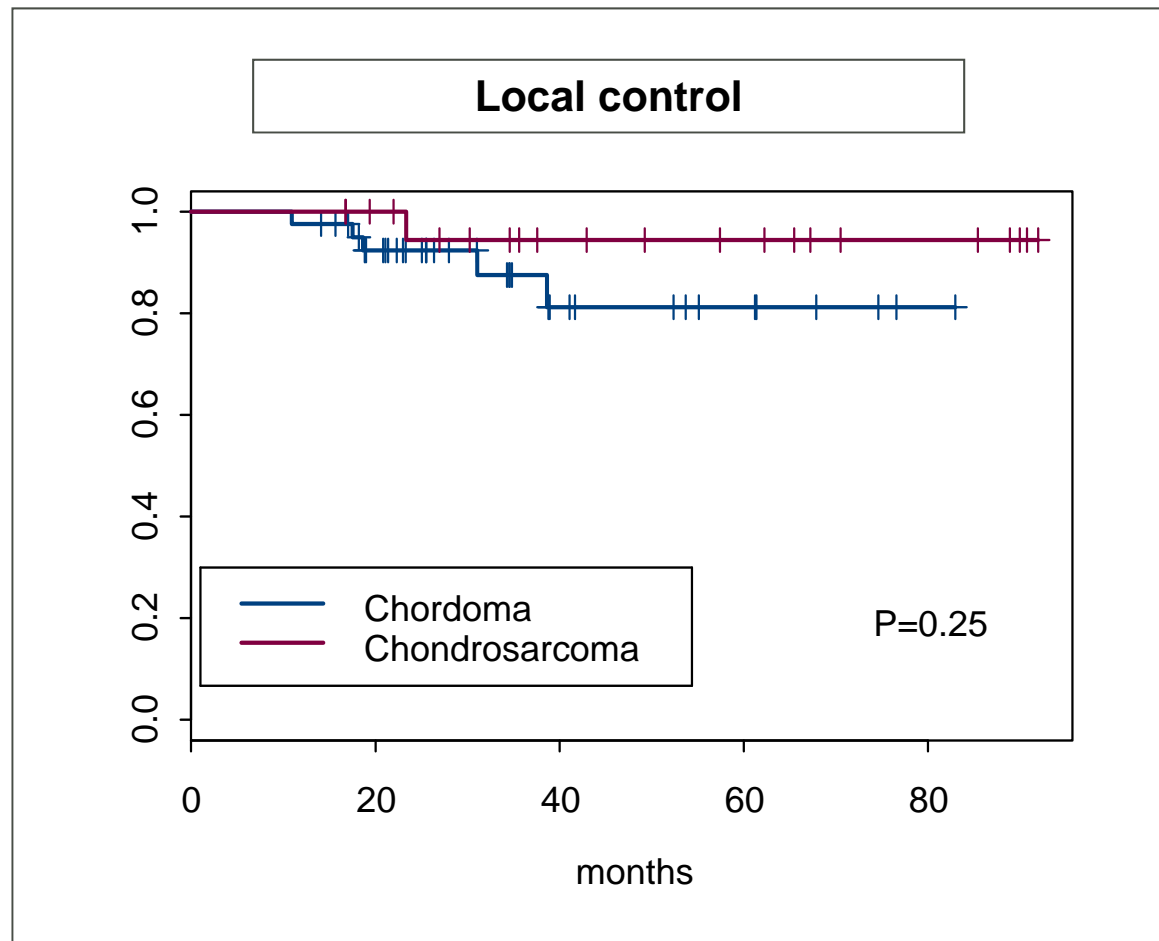
5 years

81 %

Chondrosarcomas

94 %

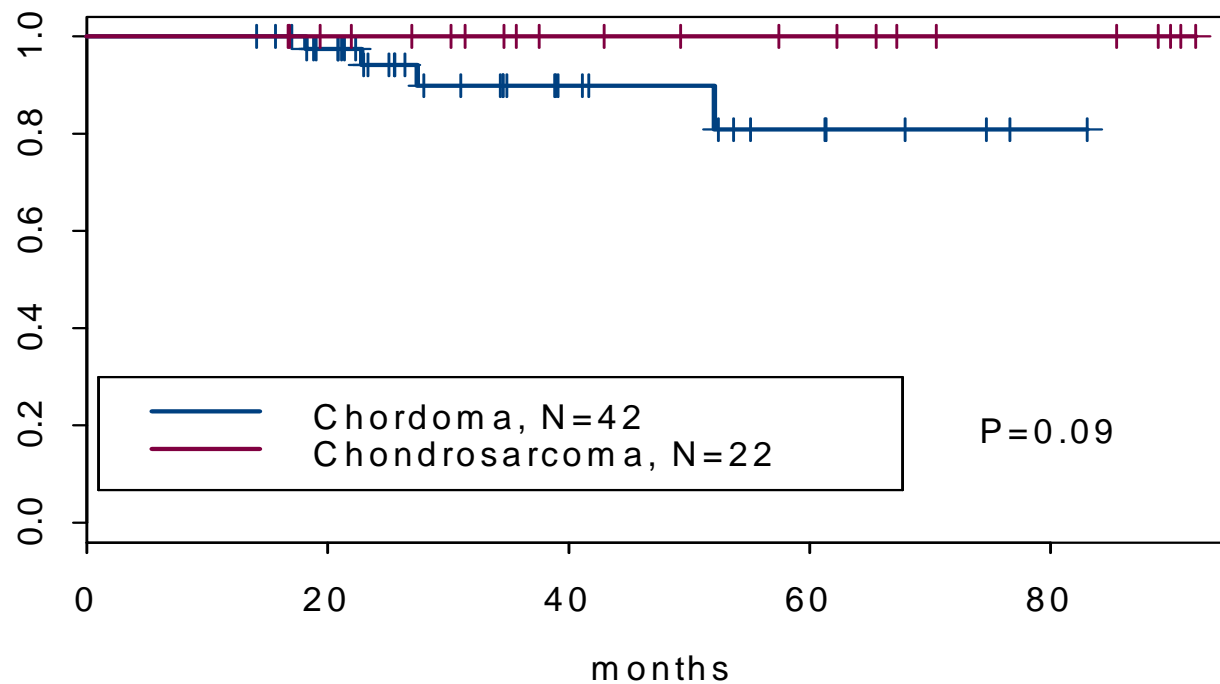
94 %



Ares et al. cont.

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

Disease Specific Survival



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)

≥ Grade 3 Actuarial Toxicity-Free Survival: 94%

Highly Effective Treatment of Skull Base Chordoma With Carbon Ion Irradiation Using a Raster Scan Technique in 155 Patients: Long-Term Results

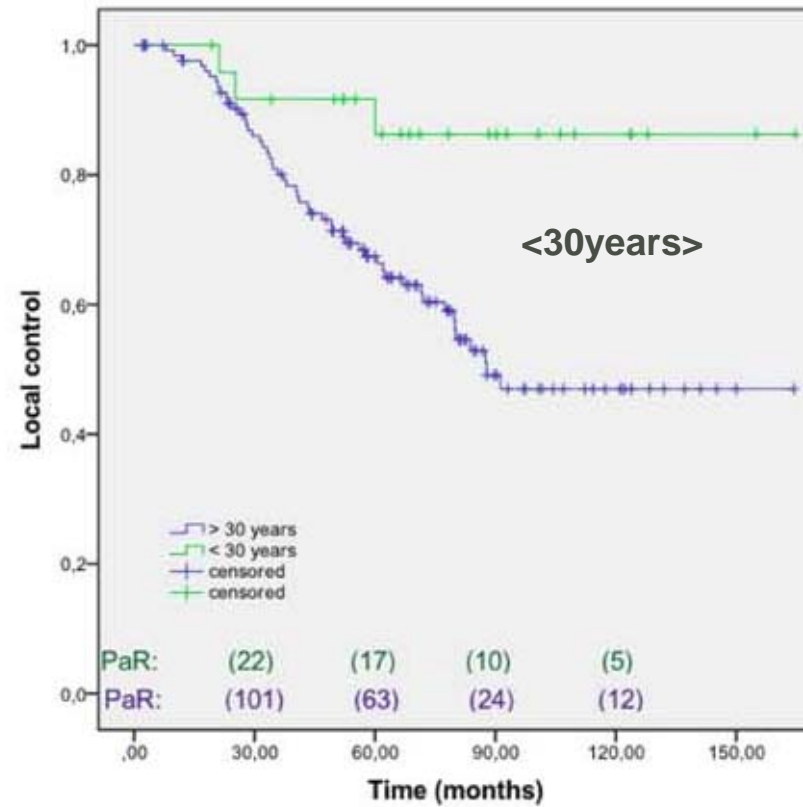
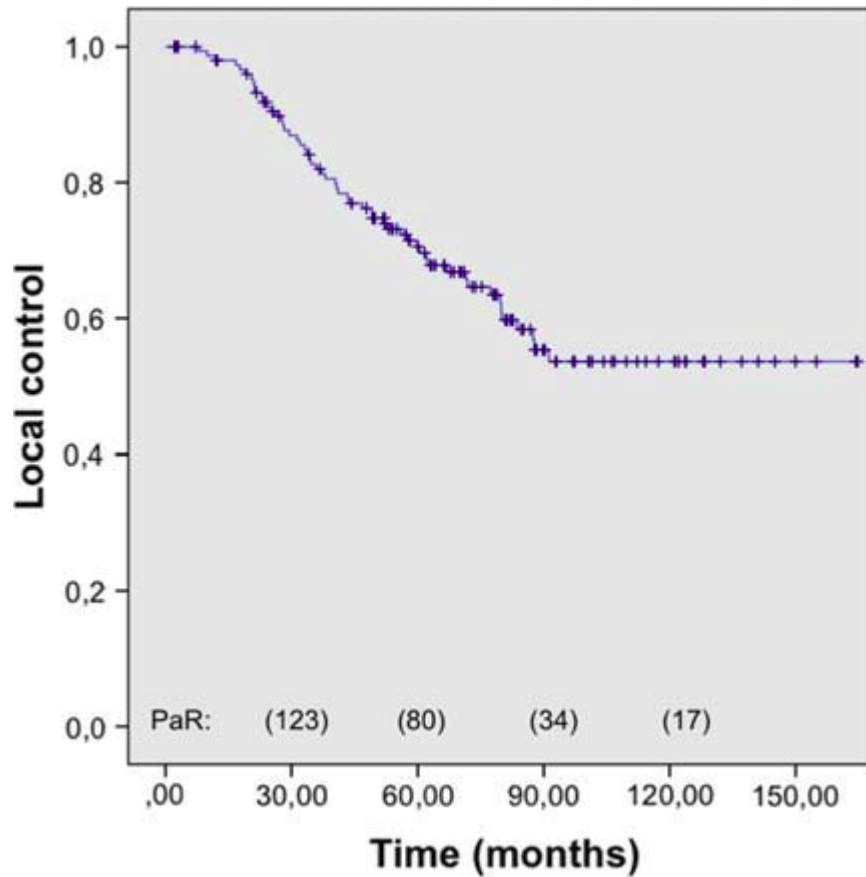
Uhl M., Debus J et al. – Heidelberg, Darmstadt, CANCEC, Nov. 14, 2014

- 155 patients, median age 48
- 1998-2008 treated at GSI

- Median Total Dose 60 Gy(RBE) at 3 Gy(RBE)
- Median Boost PTV 70 ml, all with residual gross disease
- Median F/U 72 months (12-165)

- **5 yr Local Control: 72%** **10-yr LC: 54%**
- 5-yr Overall survival: 85% 10-yr OS 75%

- Age < 48 years (even higher significance: < 30 years)
with > LC and >OS
- Boost Volume < 70 ml with > LC and >OS



Skull Base *Chondrosarcomas*: Particle Series

	n	Radiation	Mean Dose	LC 3-yr	LC 5-yr	LC 10-yr
Munzenrider, MGH 1999	229	PT, RT	72		98	95
Hug, LLUMC 1999	25	PT, RT	71		79	
Johnson, LLU 2002	58	PT, RT	71		91	
Noel, CPO 2004	26	PT, RT	67	91		
Ares, PSI 2009	22	PT	68.4		94	
Uhl, Heidelberg,"14 (update Schulz-E 2007)	79	Carbon	60	95.9	88	88

Skull Base Chordomas: Proton Series

Protons: No large scale prospective studies available

			Pts	Tx	Mean Dose	Local Control 3 yr	Local Control 5 yr
Munzenrider	MGH	1999	290	PT, RT	76	87	73
Terahara	MGH	1999	115	PT, RT	69		59
Hug	LLUMC	1999	33	PT, RT	71	67	59
Yasuda	CPO	2012	40	PT	68.9		70
Ares	PSI	2009	42	PT	74		81
Rombi	PSI Peds	2011	26	PT	75		81
Deraniyagala	UFPTI	2014	33	PT	78	86% 2 yrs	
Protons for Re-irradiation: McDonald MW (IJROBP 2013)	IU	2013	16	PT	75.6	85% 2 yrs	

Skull Base Chordomas: Carbon Ions

Institution/ Publication	Particle	# Pts.	Follow-up	Local control	Comments
GSI / Heidelberg Uhl, Debus et al Cancer 2014 120(21)	Carbon 60 GyE median	155	72 median 12-165	5- yrs. 72% LC 10-year 54%	No «higher grade» late toxicity
NIRS Mizoe Skull Base 2009	Carbon 48-60.8 GyE	36	4.6 yrs	5-yr 81%	
	60.8 GyE	27	3.8 yr	5-yr 94%	

Skull Base Chordomas and Chondrosarcomas: SRS and CyberKnife LC Data

	Chordomas		Chondrosarcomas	
	n	LC 5 - yr	n	LC 5 - yr
Krishan, 2005	25	32%	4	100%
Martin, 2007 [#]	18	63%	4	80%
Hasegawa, 2007	30	72%	7	2/7 failed
Henderson, 2009	18	59%		
Liu, 2008	28	21%		
Kano, Pittsburg, 2012	71	66%		
Koga, U. Tokyo, 2010	14	Combined Ch + ChS 43% 5-yr LC		
Iyer, Pittsburg, 2012			22	75%
Jiang, Adler, Stanford, 2014			20	41%*

Note: Median target volumes significantly smaller compared to particle series

Review: Kano H et al. *Clinical Neurosurgery* 2014; 61:155



Prognostic Factors

Skull Base Chordoma and Chondrosarcoma: Influence of Clinical and Demographic Factors on Prognosis: A SEER Analysis

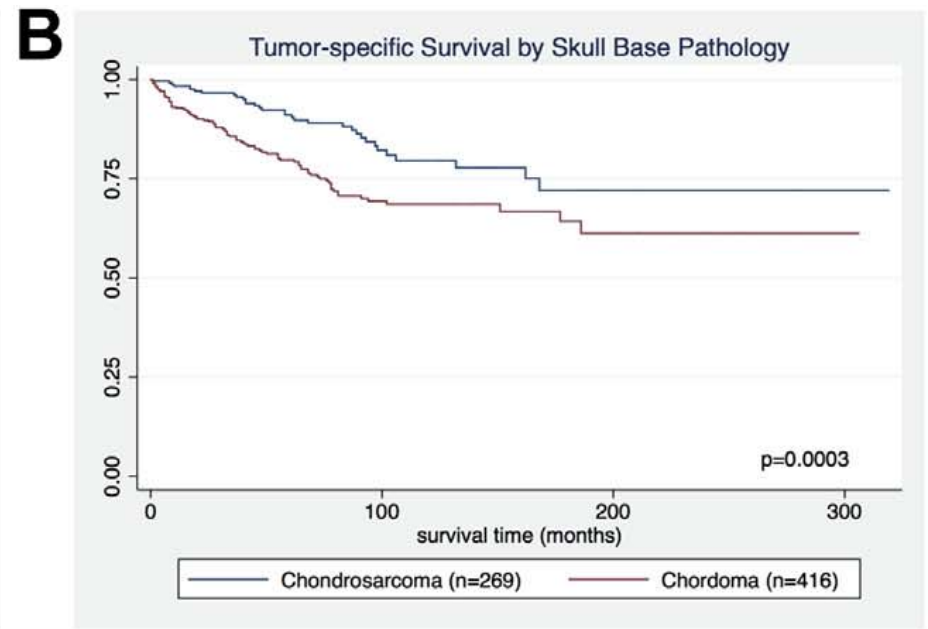
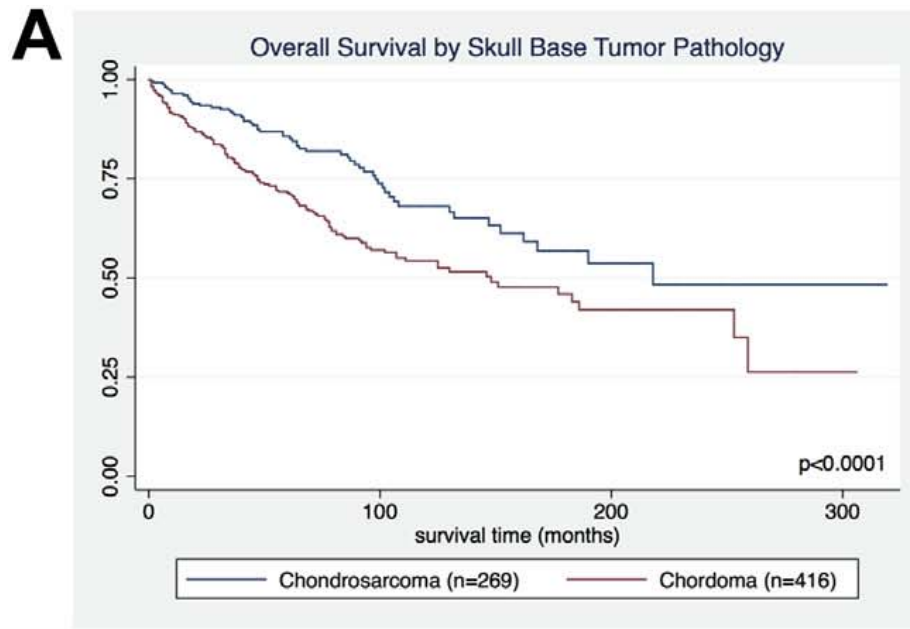
*Leif-Erik Bohman, Matthew Koch, Robert L. Bailey, Michelle Alonso-Basanta, John Y. K. Lee, Depts. Neurosurgery and Rad. Onc., Univ. Pennsylvania
World Neurosurg. (2014) 82, 5:806-814.*

- SEER database from the 1983e-988, 1988-2003, and 2004-2009 data sets
- 685 patients (416 patients with chordomas, 269 chondrosarcomas)

- “The SEER database does not include data on the type of radiation treatment (e.g., photons, protons, other particles/techniques, or combinations).”
- “Postoperative radiation in 42% and 41% of patients with chordomas and chondrosarcomas, respectively.

- “The addition of radiation did not improve survival
- Consistent with previous case series, skull base chordomas have significantly worse prognosis than chondrosarcomas.
- “Patients in the SEER database had worse survival overall compared with existing case series for both chordomas and chondrosarcomas, suggesting selection bias in the existing literature.

Leif-Erik Bohman et al. *World Neurosurg.* (2014) 82, 5:806-814.



Leif-Erik Bohman et al. *World Neurosurg.* (2014) 82, 5:806-814.

Prognostic Factors: Histology , Age, Tumor Size

Table 8. Skull Base Chordoma Survival Subgroups				
	Group 1 (n = 62): Age <50 years and Tumor Size <4 cm	Group 2 (n = 57): Age <50 years and Tumor Size ≥4 cm	Group 3 (n = 68): Age ≥50 years and Tumor Size <4 cm	Group 4 (n = 34): Age ≥50 years and Tumor Size ≥4 cm
5-year survival	91%	63%	53%	35%
10-year survival	57%	28%	23%	9%

Table 5. Skull Base Chondrosarcoma Survival Subgroups			
	Group 1 (n = 191): Age <60 years and Nonmesenchymal Subtype	Group 2 (n = 19): Age <60 years and Mesenchymal Subtype	Group 3 (n = 59): Age ≥60 years
5-year survival	91%	62%	64%
10-year survival	68%	22%	25%

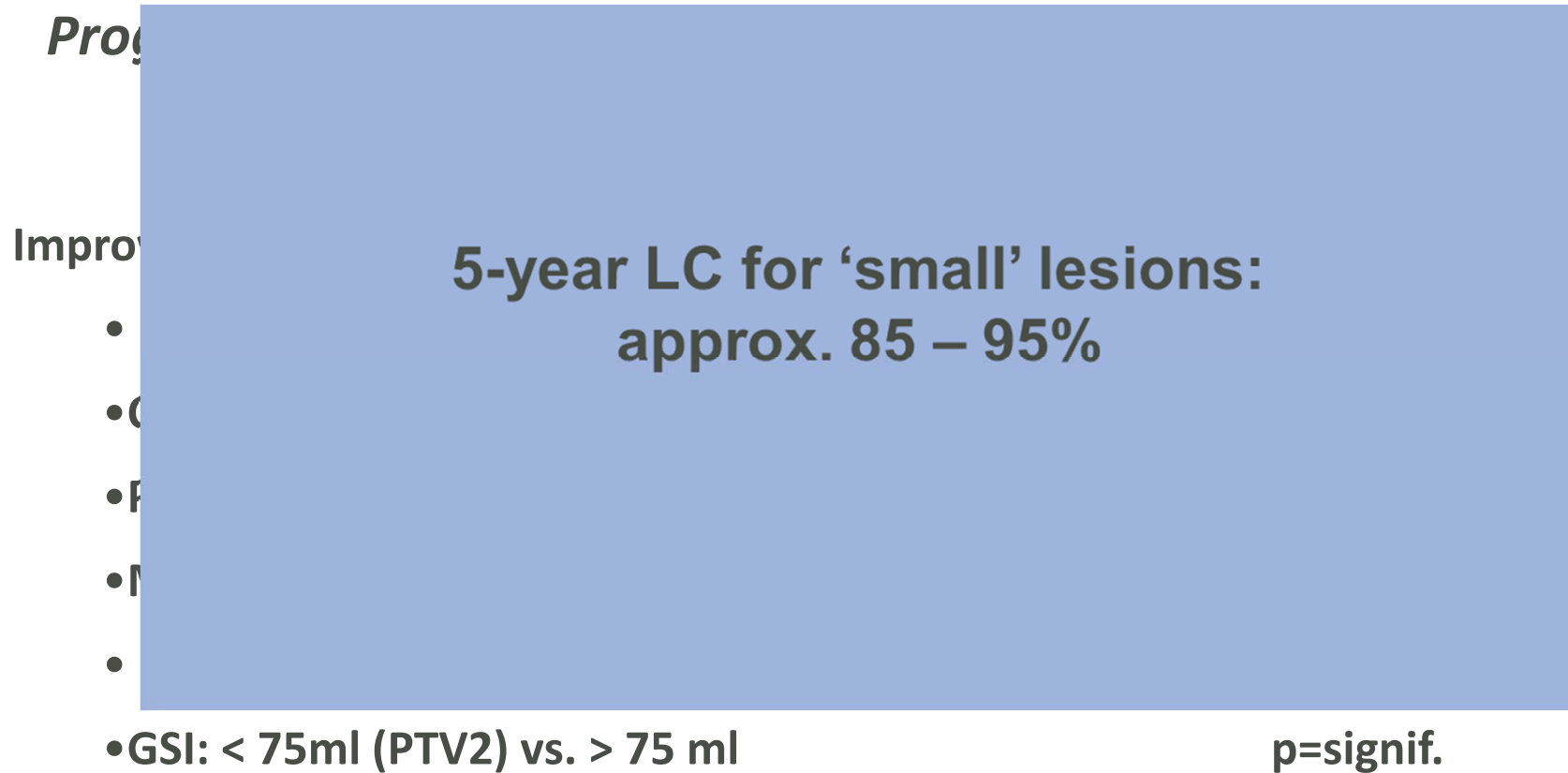
Proton-RT for Skull Base Chordomas

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.
- GSI: < 75ml (PTV2) vs. > 75 ml p=signif.

Proton-RT for Skull Base Chordomas

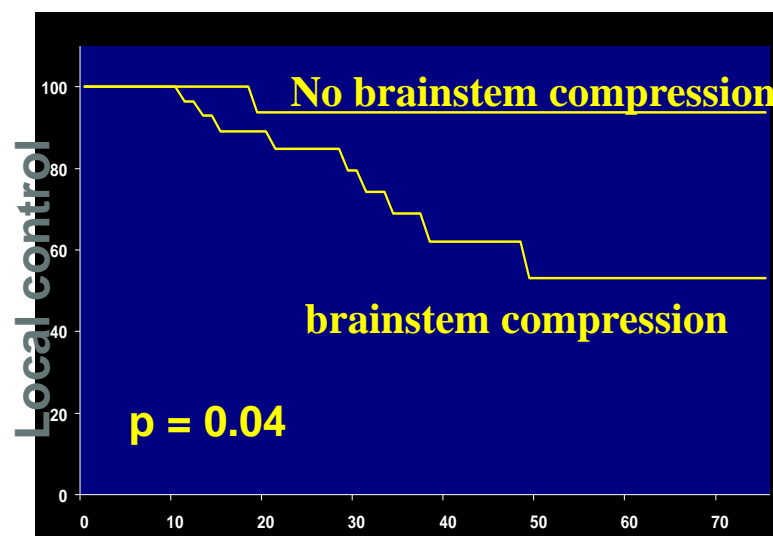


Skull Base Chordomas: Importance of high-dose

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.

OAR compression = underdosage of GTV portion causing compression

Skull Base Chordomas: Importance of high-dose

- The majority of skull base tumors require 70-78 Gy(RBE) GTV-dose
- This exceeds 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

Other prognostic factors?

Gender ?

**Primary vs. Recurrent? i.e.
immediate postop RT vs. RT for
recurrence?**

Biologic Markers?

Conclusion

- Proton and Carbon Ion Therapy for skull base chordomas and chondrosarcomas consistently demonstrate lasting local tumor control with acceptable late toxicity profile
- Chondrosarcomas are highly curable with particle therapy – even in cases of unresectability / large residual disease
- Chordomas consist of subgroups with varying risk profiles:
 - Small chordomas and chordomas without OAR compression have 80-90% LC at 5 years after protons.

Conclusion

- Development of pathologic/biologic prognostic markers emerging: EGFR, c-MET, PDGF, PDGFRa
- SRS and FSRT photon-based data appear inferior – however, no comparative study has been performed.
- Comparison of protons and carbon ions for chordomas in a randomized clinical trial of great interest. Possibly “matched cohort” trial with particle therapy vs. photons depending on institutional technology.
- Given the relative homogeneity of treatment approaches in skull base proton therapy, multi-institutional clinical trials should be feasible.

