



REDISCOVERING RADIATION MEDICINE AND EXPLORING NEW INDICATIONS

**Long-term Failure Patterns and Prognostic Factors in a
Randomized Dose-Escalation Trial for Skull Base Chordomas:
a Secondary Analysis from PROG 85-26.**

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Disclosure

Employer: Mass General Brigham


PROG 85-26: Background

- Chordomas are rare primary malignant bone tumors that are highly recurrent.
- Distinct histology from grade I-II chondrosarcoma (better prognosis).
- Management includes maximal safe resection and adjuvant RT > 70 Gy.
- Proximity of critical structures such as the brainstem, optic nerves, and spinal cord make dose delivery challenging with conventional photon radiotherapy.
- No randomized trials or large prospective series to explore prognostic factors and failure patterns .

PROG 85-26: Study Design

- **Study Period:** 1987 – 2007
- **Patient Population:** Chordomas and Chondrosarcomas of Base of Skull and C-Spine (n=379)
- **Phase I/II Randomized Trial** with **3** dose arms:
 - 70 Gy (RBE)/ 37 fxs
 - 76 Gy (RBE)/ 40 fxs
 - 83 Gy (RBE)/ 44 fxs

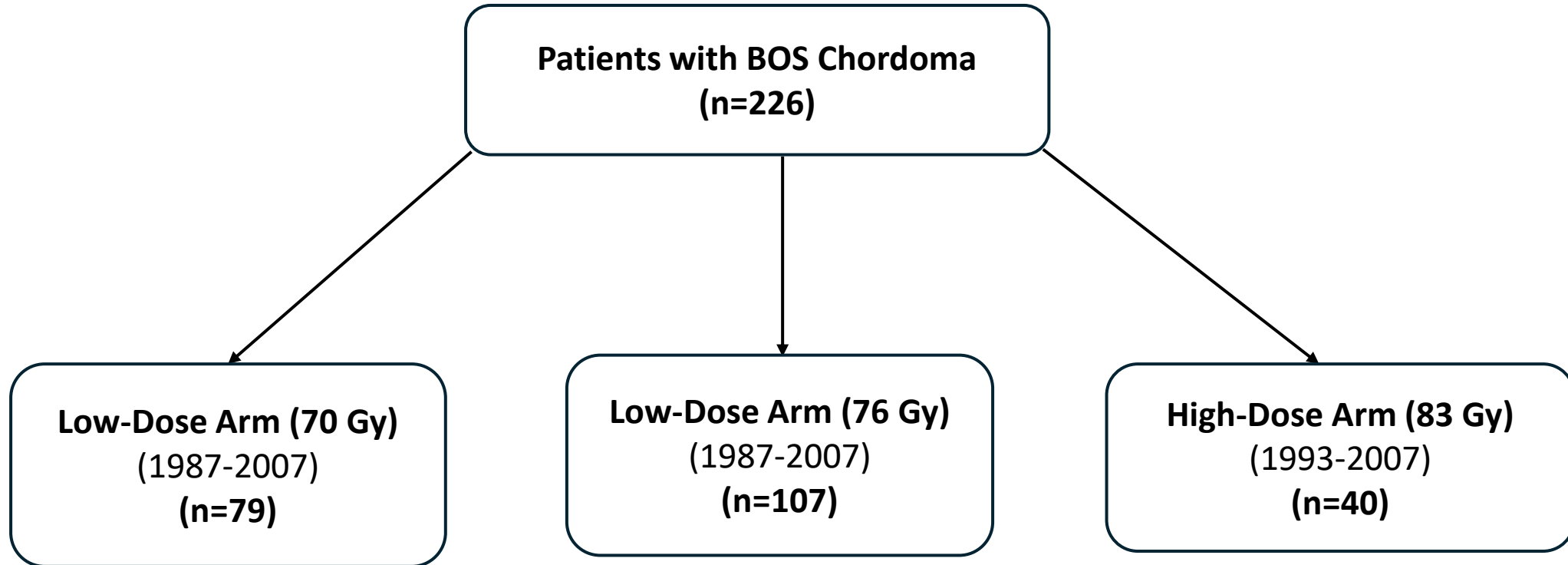
with combined proton/photon radiotherapy (RT) with >70% of the dose delivered with protons.

- **Primary endpoint:** To test the hypothesis that dose escalation improves local control → **ASTRO 2024**
**manuscript under review*
- **Secondary endpoints:**
 - To establish OS, CSS, PFS, LC & DC rates.
 - To explore patterns of relapse and prognostic factors. → 
 - To assess for acute & late toxicities.

PROG 85-26: Study Design

- Eligibility Criteria:
 - Age > 18 years at the time of registration
 - Biopsy proven chordoma of the base of skull.
 - No evidence of metastases
 - KPS > 50
- Exclusion Criteria:
 - Any prior radiotherapy to the head and neck
 - Other active malignancy within 5 years
 - Diabetes Mellitus
- Patient Follow-up:
 - MRI/CT Brain and clinical follow up submitted every 6 months for the first 3 years, then annually.
 - Continued follow up through progression, additional treatment, significant toxicity or death.

PROG 85-26 - BOS Chordoma



OAR Dose Constraints

Organ at Risk	OAR Dose Constraint [Gy(RBE)]	Median D _{max} [Gy(RBE)]
Brainstem / Spinal Cord *	Surface D < 67 Center D < 55	67 (range, 34.3-89)
Optic Structures *	D < 62	Optic Nerve: 61.7 (range, 5.9-76) Optic Chiasm: 62.3 (range, 11-78.7)
Temporal Lobe	--	74 (range, 65-90)
Cochlea	--	51.9 (range, 14-83.2)

*Normal tissue dose constraints were increased by 5% for patients randomized to the 83 Gy (RBE) arm

PROG 85-26 proton/photon plan

TD = 75.5 Gy (RBE)/40 fxs in 1993

PBS plan

VMAT plan

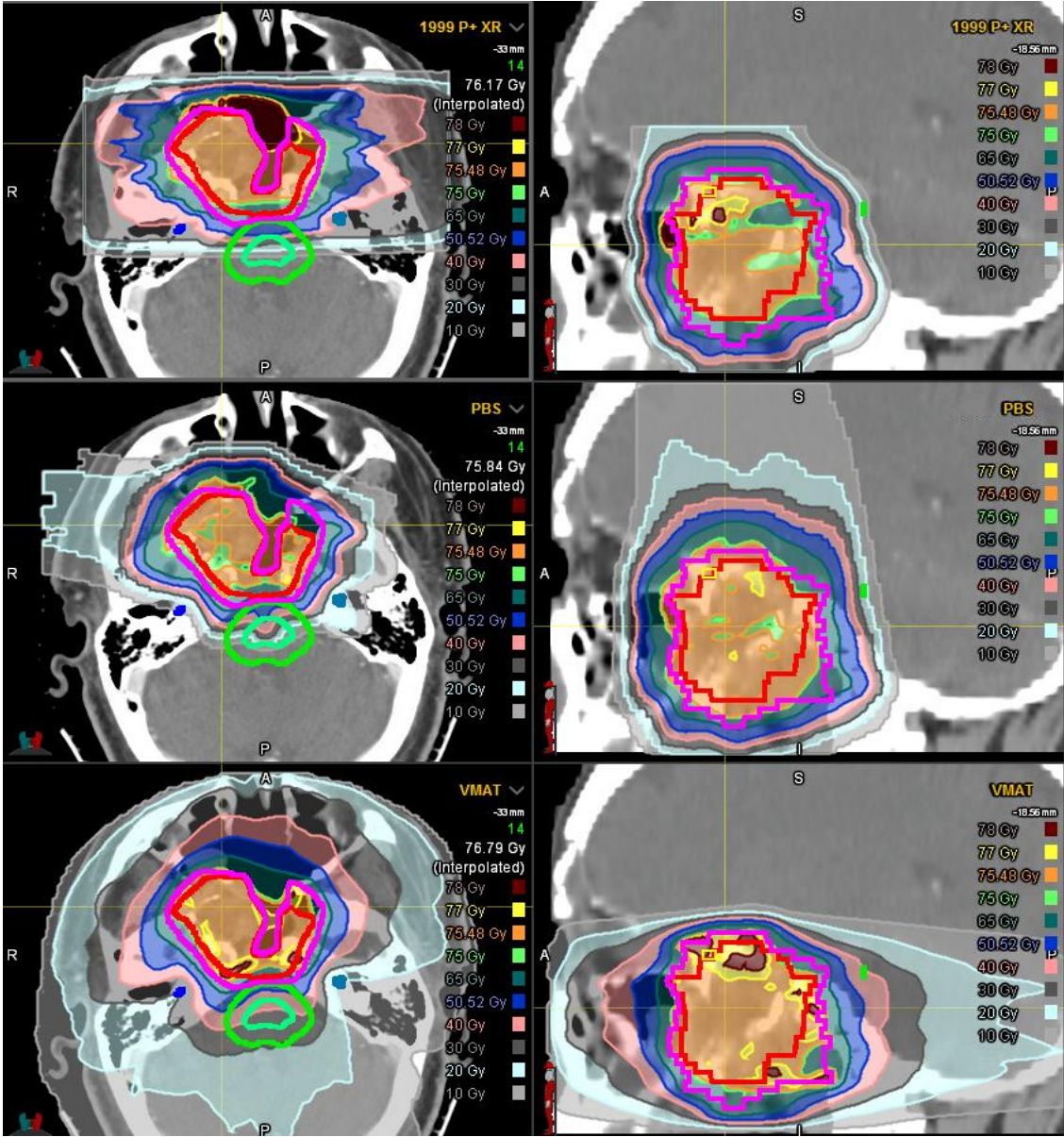


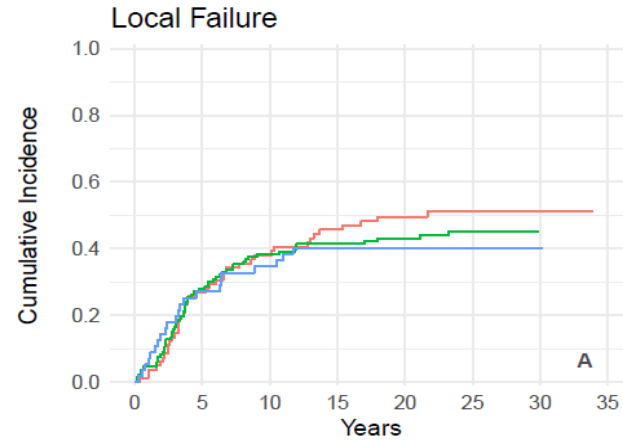
Table 1. Patient and Tumor Characteristics

11	All Patients (n=226)	70 Gy (RBE) (n=79)	76 Gy (RBE) (n=107)	83 Gy (RBE) (n=40)
Age at Tx, years				
Median (range)	43 (18-87)	45 (18-76)	43 (18-87)	38 (20-72)
Gender				
Male	127 (56%)	67 (85%)	57 (53%)	3 (7.5%)
Female	99 (44%)	12 (15%)	50 (47%)	37 (92.5%)
Location				
Upper/Middle Clivus	133 (59%)	52 (63%)	60 (45%)	21 (37%)
Lower Clivus/CCJ	55 (24%)	15 (18%)	23 (17%)	17 (30%)
Whole Clivus	38 (17%)	12 (15%)	24 (18%)	2 (3.5%)
Extent of Resection				
Biopsy only	8 (3%)	5 (6%)	2 (2%)	1 (2.5%)
STR/NTR	193 (85%)	67 (85%)	93 (87%)	33 (82.5%)
GTR	25 (12%)	7 (9%)	12 (11%)	6 (15%)
GTV, cc				
Median (range)	30 (0.2-197.6)	29.3 (0.2-104.7)	30 (2.4-197.6)	25.7 (4.2-134)
Pre-RT Progression				
No	155 (69%)	55 (70%)	73 (68%)	27 (68%)
Yes	71 (31%)	24 (30%)	34 (32%)	13 (32%)

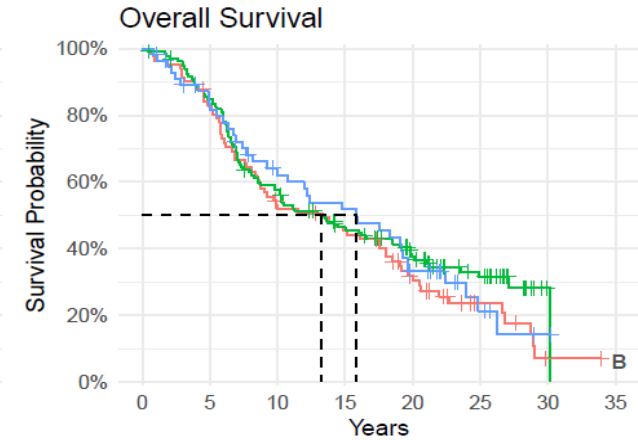
Results

Median Follow-up
= **24.1** years (IQR, 21.1 – 27.6)

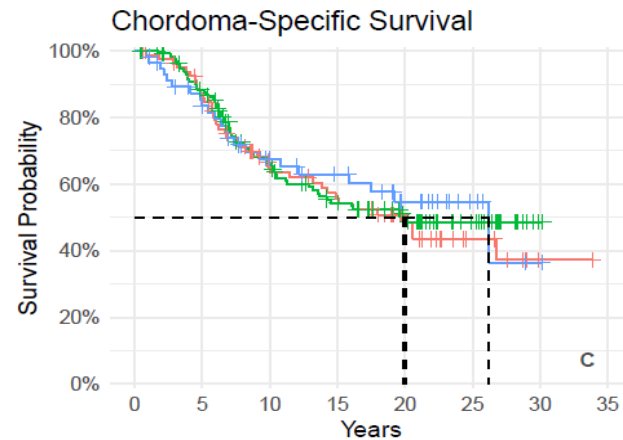
★ No benefit in dose escalation



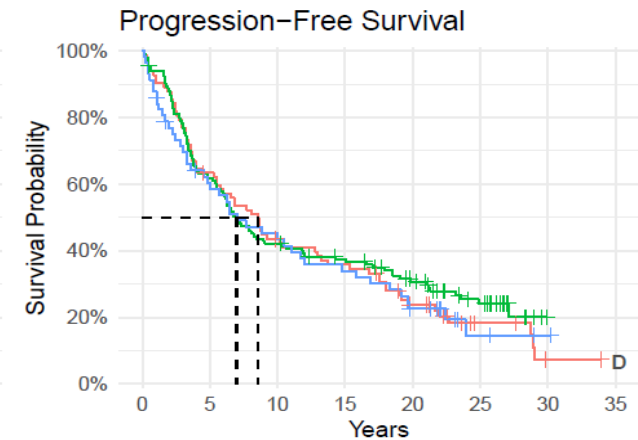
— 70 Gy (RBE) — 76 Gy (RBE) — 83 Gy (RBE)



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— 70 Gy (RBE) — 76 Gy (RBE) — 83 Gy (RBE)

Results - Prognostic Factors

On UVA for OS/PFS:

Older age

Older treatment era

Larger GTV

STR vs GTR

Multiple surgeries

Pre-RT progression/RT avoidance

Results

	All Patients (n=226)	70 Gy (RBE) (n=79)	76 Gy (RBE) (n=107)	83 Gy (RBE) (n=40)
Relapses	126 (56%)	45 (56%)	58 (54%)	23 (57.5%)
Median time to relapse, yrs	3.6 (0.2 – 21.1)	3.6 (0.2 – 21.7)	3.5 (0.2 – 21)	3.1 (0.2 – 16.7)

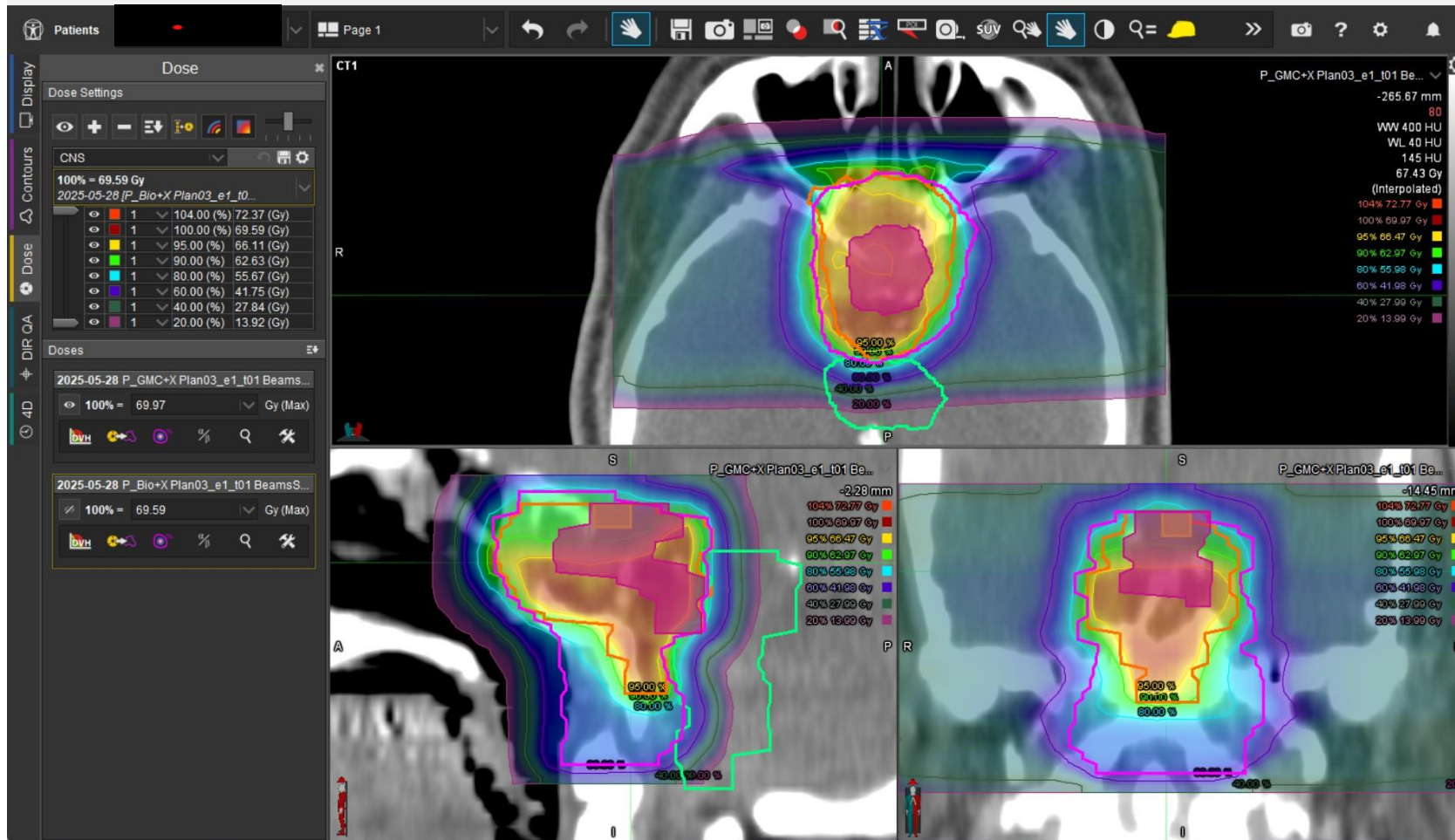
Type of 1st Relapse:

➤ 117 local/locoregional (**93%**)

! 15 (11.5%) iatrogenic relapses along surgical path

➤ 14 distant relapses (11%): lung, spine/sacrum, pelvis

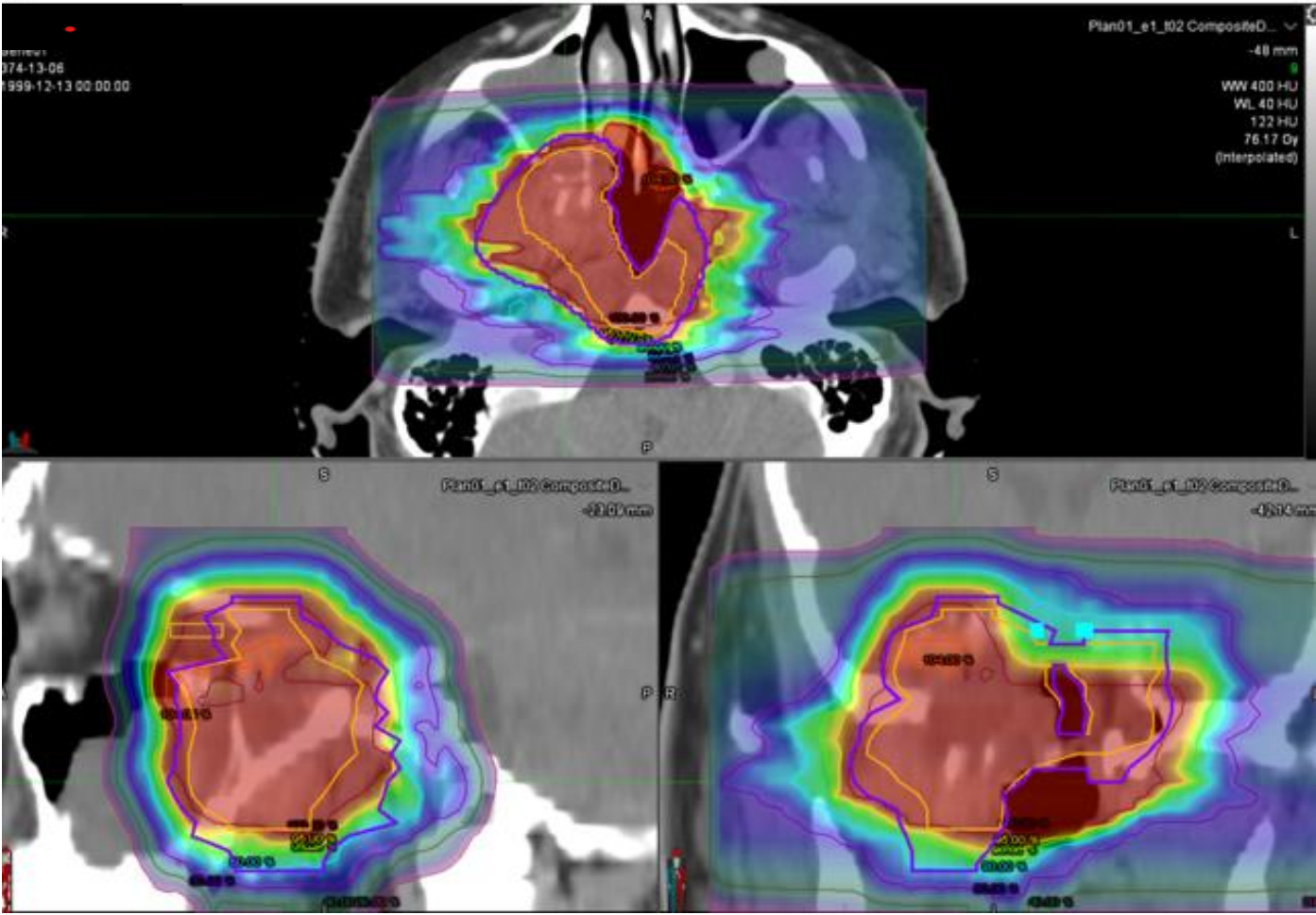
Pattern of Relapse #1



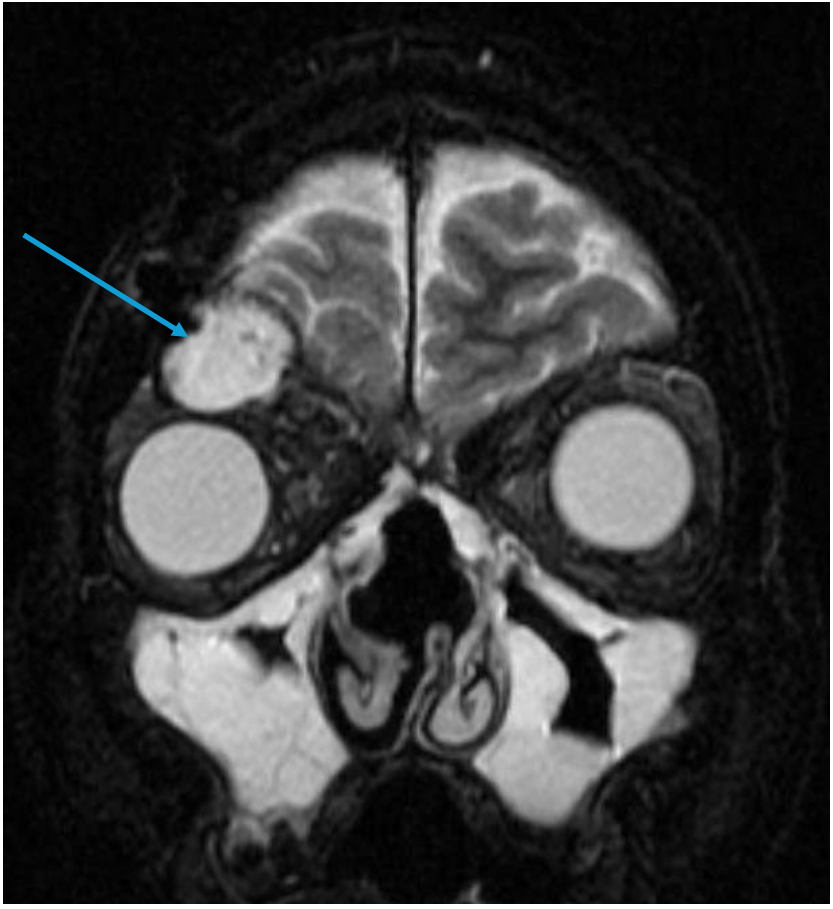
TD = 70.2 Gy (RBE)

Local relapse
at 1.5 y post-RT

Pattern of Relapse #2

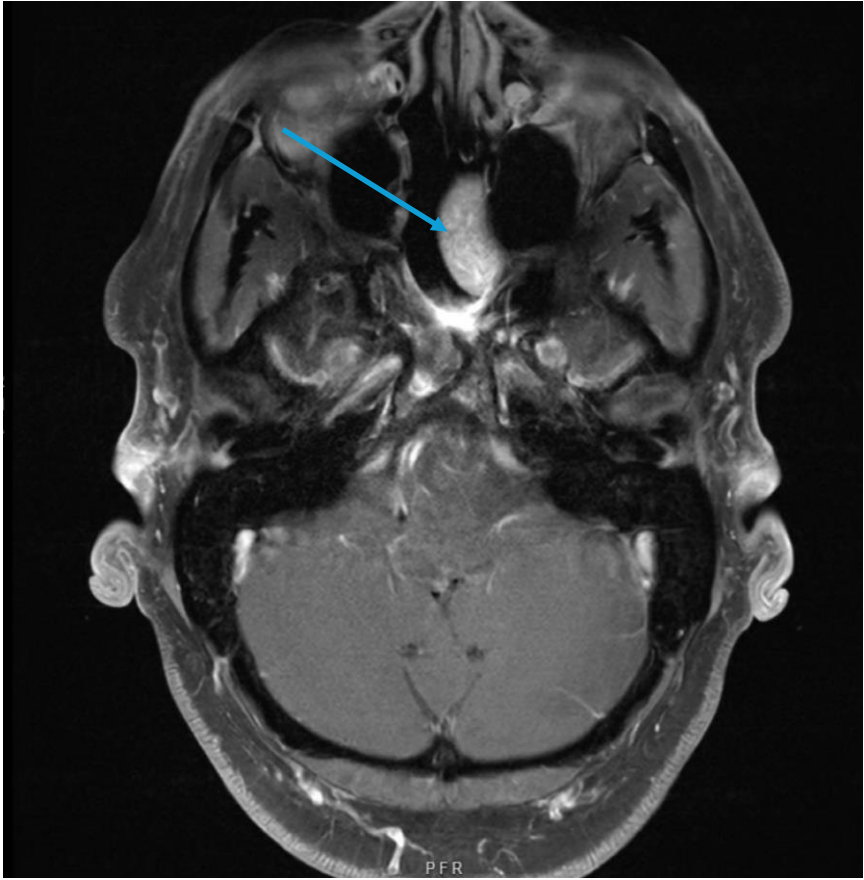
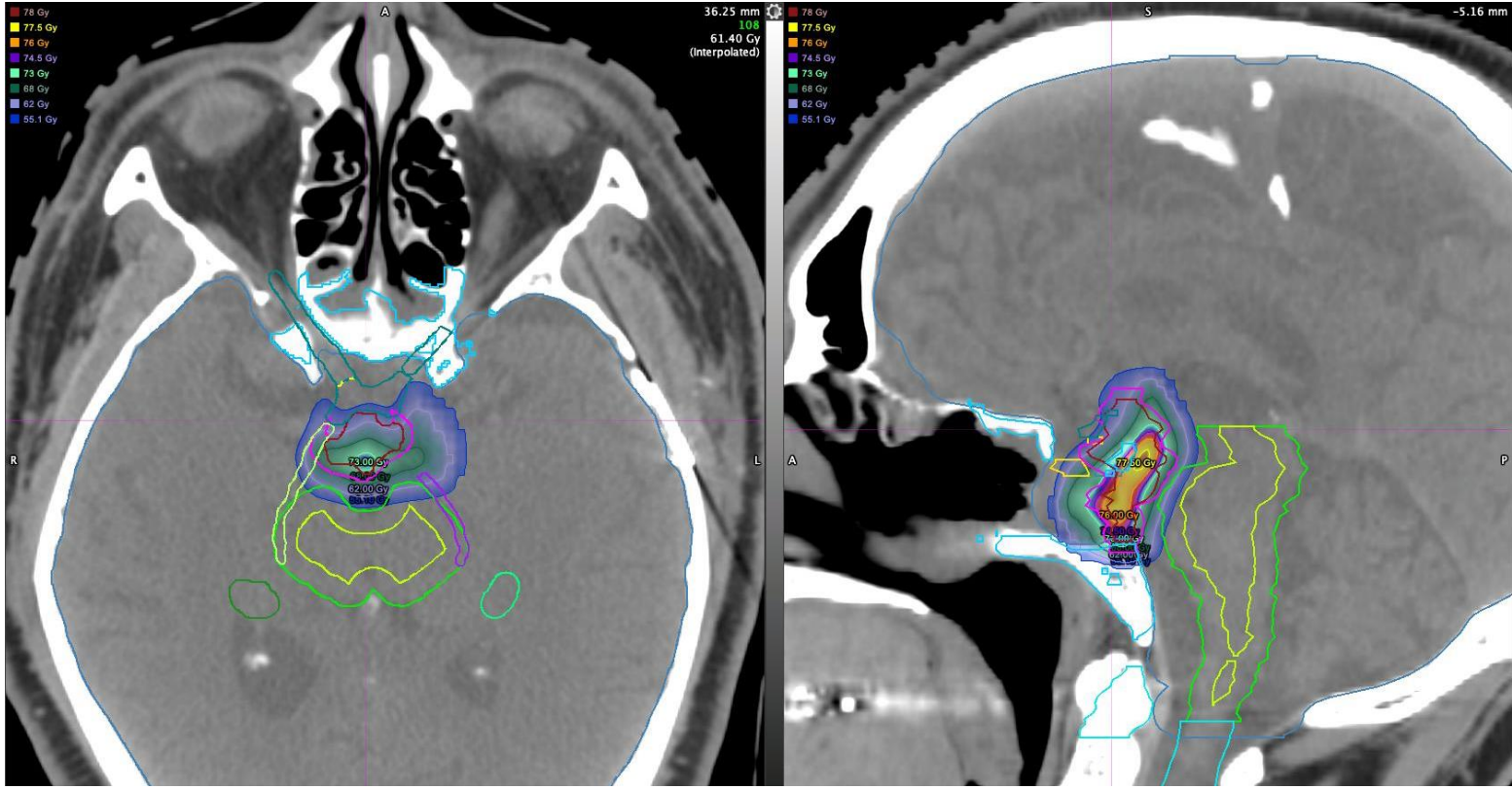


TD = 75.5 Gy (RBE)



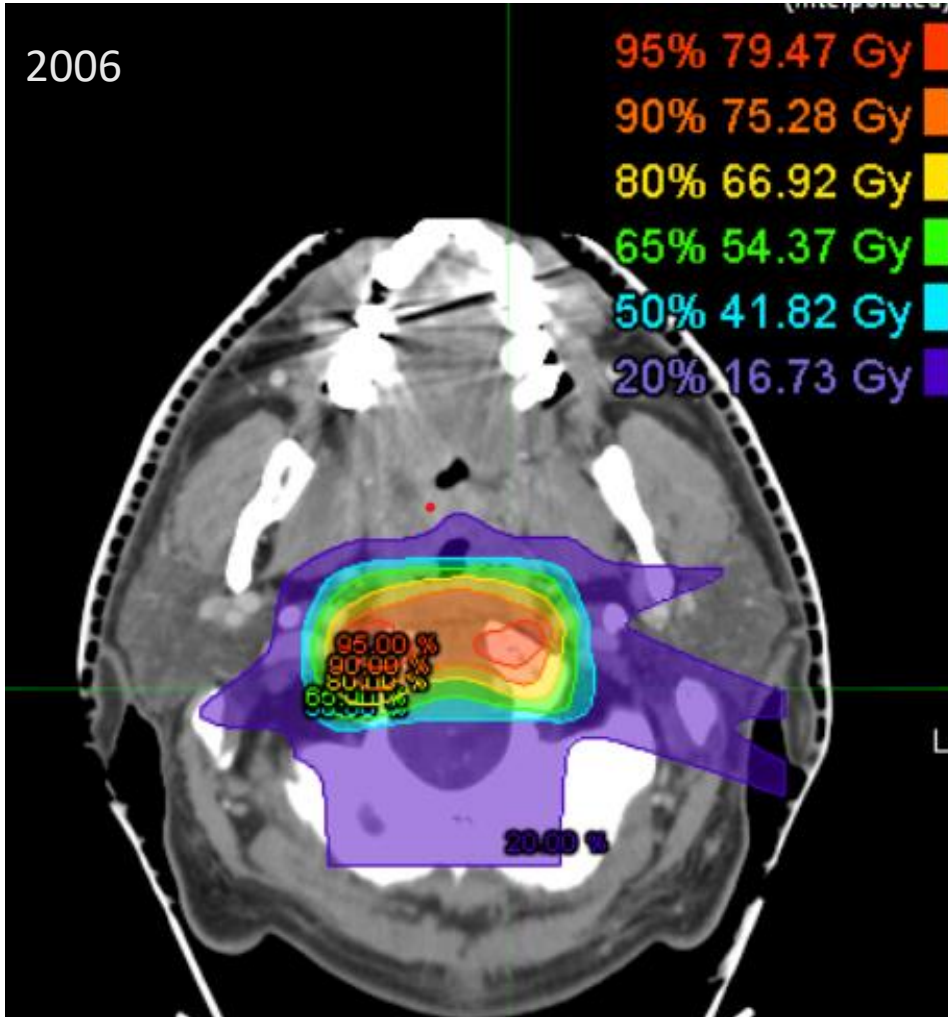
Iatrogenic R eyelid met at 2y post-RT

Pattern of Relapse #2

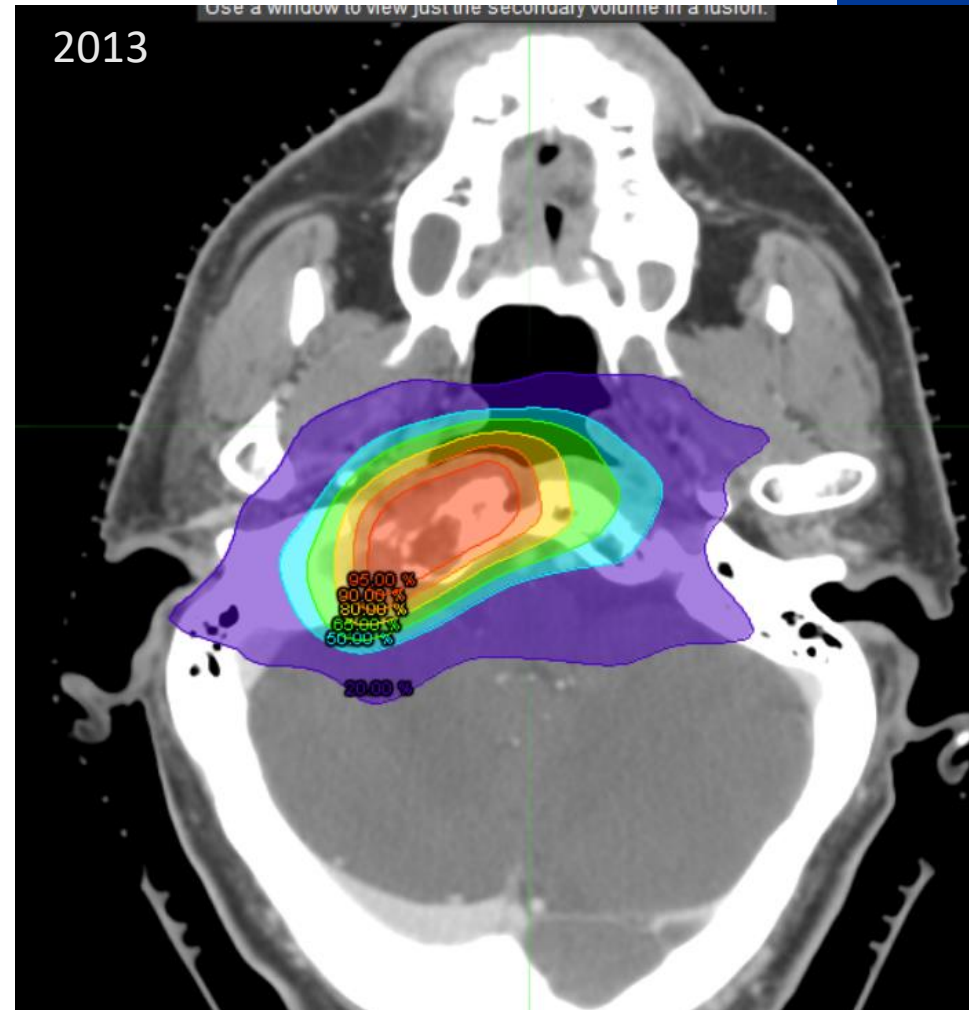


TD = 76 Gy (RBE), PBS

Pattern of Relapse #3



TD = 76.8 Gy (RBE) 2006



TD = 72.0 Gy(RBE)/60 fxs, 1.2 Gy(RBE)/ fx BID in 2013

Conclusions

➤ Strengths:

- Largest dose escalation trial of BOS chordomas (n=226)
- Long median follow-up of 24 years

➤ Conclusions:

- Local/locoregional failure was found to be the most common (93%) pattern of failure.
- Local failure may reflect underdosing in tumor regions near critical organs.
- Evaluate for prior surgical seeding before initiating radiation and at follow-up.
- Large GTVs, STR, and pre-RT progression are associated with poor outcomes.
- Advances in surgical techniques and adjusted radiotherapy target volumes might improve (recurrence-free) survival.

Thank you!!

