The Clinical Utilization of Proton Beam Therapy: Applications in the Head and Neck

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Photons for Chordoma

Author	Years of treatment	No. of pts	Median age (range)	Surgery (resection entity)	TD range in Gray (median)	% OS in years		% LC in years		F/U in months (median)	Remarks
						5	10	5	10		
Catton et al. 1996 [12]	1958–1992	20	60 (23–79)[a]	Two total, 18 biopsy or incomplete	25–60 (50)	54	20	23	15	1–240 (62)	Some pts treated with an HF regime; better results (not ss) with >50 Gy and in resected pts
Fuller et al. 1986 [24]	1952–1981	13	45 (28–63)	Two biopsy, nine partial, two none	47–65 (55)	44	17	23	16	2–144 (31)	Doses higher than 55 Gy or a TD of 90 associated with an ss improvement in LC duration
Forsyth et al. 1993 [23]	1960–1984	39	46[a]	29 subtotal, ten biopsy	22.93–67.42 (50)	51	35	39	31	66–353 (99)	51 pts treated (39 with XRT)
Zorlu et al. 2000 [77]	1979–1997	18	32 (9–54)	11 subtotal, seven biopsy	50–64 (60)	35	–	23	–	12–96 (42)	
Cummings et al. 1983 [19]	1958–1979	10	53 (2–73)	Six subtotal, four biopsy	25–60 (50)	62	28	41 (3.5)		14–120 (40)	Five pts treated with Co^{60}
Amendola et al. 1986 [2]	1962–1982	11	46 (11–70)	10 subtotal, one biopsy	53.20–66.30 (60)	30	–	40 (3)		24–168 (48)	
Chetiyawardana 1984 [14]	1932–1980	14	na	13 total, one subtotal	30–40	45	23	na		12–240	
Raffel et al. 1985 [56]	1940–1984	17	31 (19–75)	All surgically treated	36–69.36 (54.54)	70	–	47	–	12–252 (60)	Three pts treated with an interstitial boost
Watkins et al. 1993 [75]	1958–1988	38	44 (7–78)	Ten total, 25 subtotal, three biopsy	50–60	63	59	34	–	84	12 pts lost at follow-up
Cho et al. 2008 [15]	1991–2005	11	34 (3–69)	One total, nine subtotal, one partial	50.4–69.3 (59.4)	72	–	40	–	10–172 (55)	Four pts treated with GKS (three as a boost)
Average		191	43.9		52.70	53.5	36	33.5	23.8	65.6	

Avg 5yr LC: ***33.5%***

Avg 5yr Surv: ***53.5%***

Amichetti et al., Neurosurg Rev; 2009

Protons For Chordoma

Table 1 Studies and patient characteristics in series of skull base chordoma treated with protons or protons + photons

Reference	Years of treatment	No. of pts	Median age in year (range)	Surgery	Histology	Volume	Gender	% LC	% Survival	Median F/U in months (range)
Hug et al. 1999 [31]	1992–1998	33	48.7 (10–85)	Two total One surgery 70% Two surgeries 25%	Ch of low histological grade	Tumor size after surgery: 3 (9%): 0 to ≤15 mL; 4 (12%): >15 to ≤25 mL; 26 (79%): >25 mL	M 15, F 18	3-year 67 5-year 59	3-year 87 5-year 79	33.2 (7–75)
Munzenrider et al. 1999 [48]	1975–1998	290 pts treated (169 evaluated)	39 (1–80)	na	Ch 200 chondroid C 90	na	M 159, F 131	5-year 73 10-year 54	5-year: 80 10-year 54	41 (1–254) for the 169 evaluated pts
Hug et al. 2002 [32]	1992–1999	Ten (pediatric)	11 (mean)	All underwent surgery (not specified) or biopsy	Ch nos	na	M 5, F 5	LC 60	OS 60	30 (13–86)[b]
Igaki et al. 2004 [33]	1989–2000	13	61 (14–74)	Two subtotal Five partial	Ch nos	33.7 mL (mean; 3.3–88.4)	M 5, F 8	3-year 67.1	3-year 84.6	69.3 (14.6–123.4)
				Six biopsy				5-year 46	5-year 66.7	
Weber et al. 2005 [76]	1998–2003	18	40 (15–77)	One total 17 subtotal (eight after second surgery)	Ch 16 chondroid C 2	Median GTV 16.4 mL (1.8–48.1)	M 8, F 10	3-year 87.5	3-year 93.8[a]	29 (6–68)
Noël et al. 2005 [52]	1993–2002	100	53 (8–85)	16 total 75 subtotal	Ch nos	Median volume 23 cm^3 (1–125)	M 60, F 40	2-year 86.3	2-year 94.3	31 (0–87)
				Nine biopsy						
				One resection 64 Two to four resections 35				4-year 53.8	5-year 80.5	
Hoch et al. 2006 [29]	1981–2003	73 (pediatric)	9.7 (1–18)	All pts treated with partial or subtotal resection	Conventional 42 (58%); chondroid 17 (23%); cellular eight (11%); poorly differentiated six (8%)	na	M 31, F 42	na	81 DOD according to histotype: conventional 14%, chondroid 18%, poorly differentiated 83%	86.5 (12–252)
Average		416	38				M 283, F 254	5-year 69.2	5-year 79.8	46

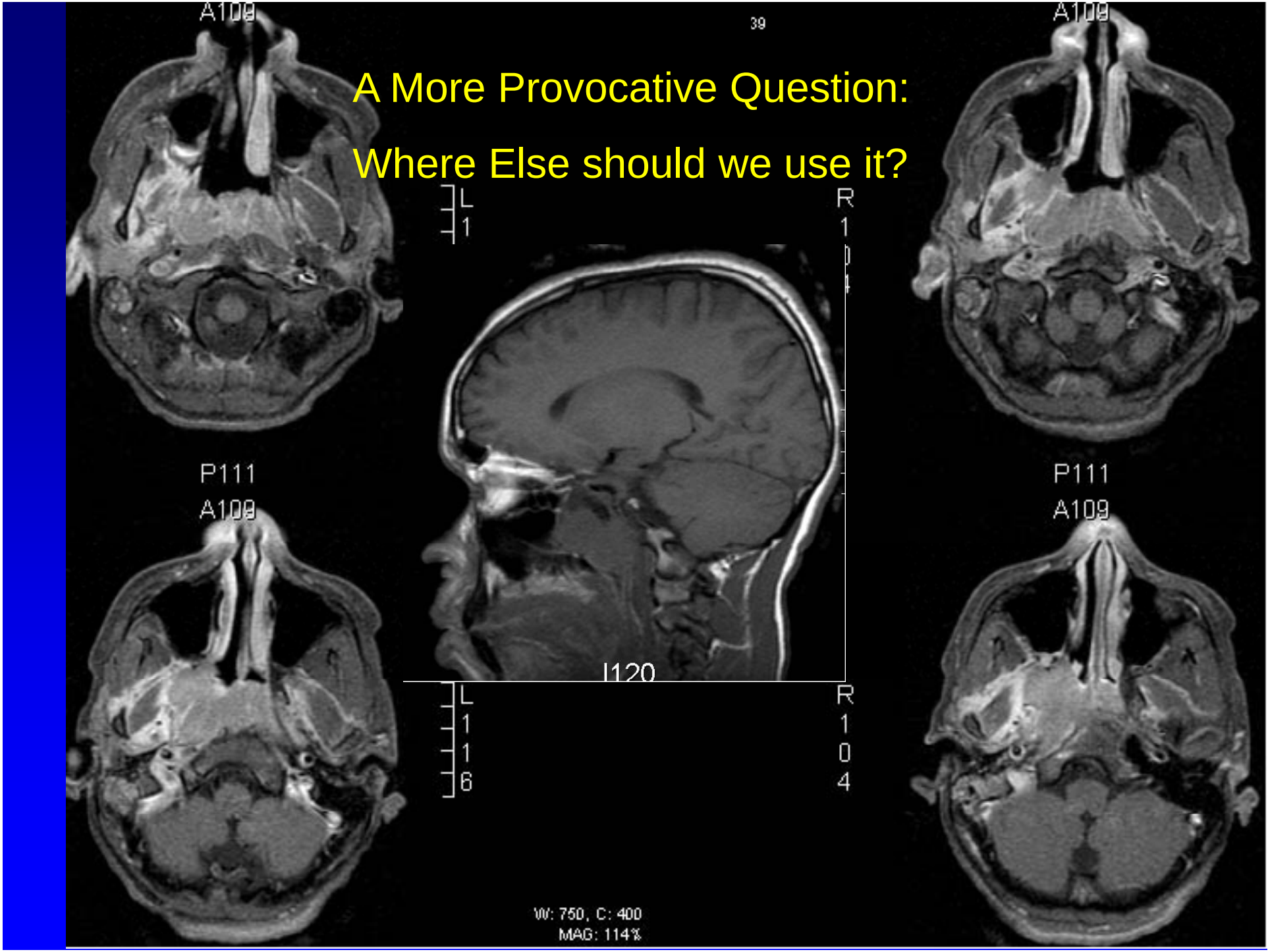
Avg 5yr LC ***69.2%***
Avg 5yr survival ***79.8%***

Amichetti et al., Neurosurg Rev; 2009

IMRT
Application in the Head and Neck

- Complicated anatomy with many avoidance structures

  Salivary glands, optic nerves, optic chiasm, retina, lacrimal glands spinal cord, brainstem, mandible, etc.
- predictable pattern of disease spread
- Easy to immobilize
- Opportunity to improve cure rates and simultaneously improve quality of life
  - Significant toxicity associated with combined modality therapy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39
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A More Provocative Question:
Where Else should we use it?
L
1
R
1
P111
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I120
L
1
1
6
R
1
0
4
W: 750, C: 400
MAG: 114%

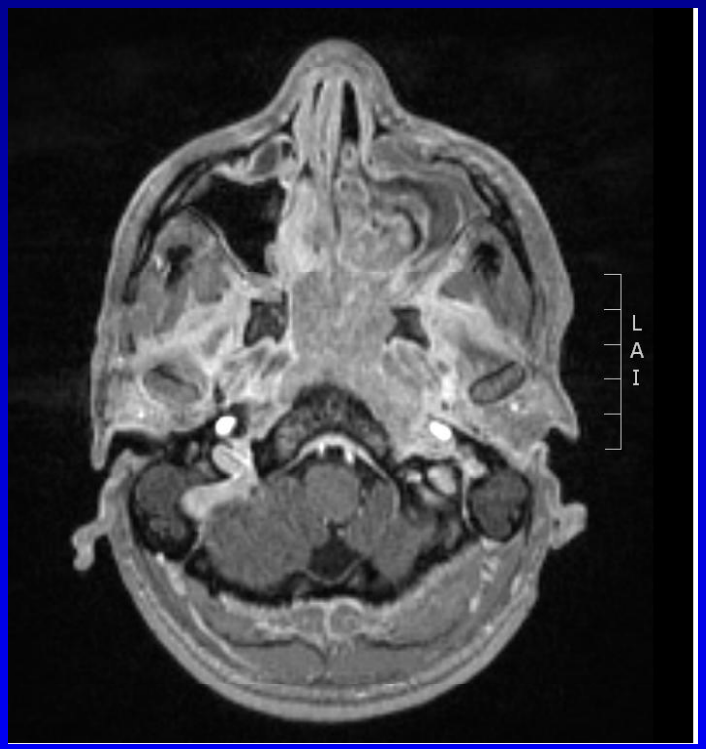
IMRT NPC (Single Institutions)

Center Year	***N***	***Stage***	***F/U Mo***	***Local Control (3-year)***
Lee et al **IJROBP, 53:1:12-21**	87	T3/4 45% N+ 80%	30	97%
Kwong Cancer 2004	33	T1	24	100%
Kam IJROBP, 2004	63	51% T3/4	29	92%
Wolden IJROBP, 2005	74	T1-T4	35	91%

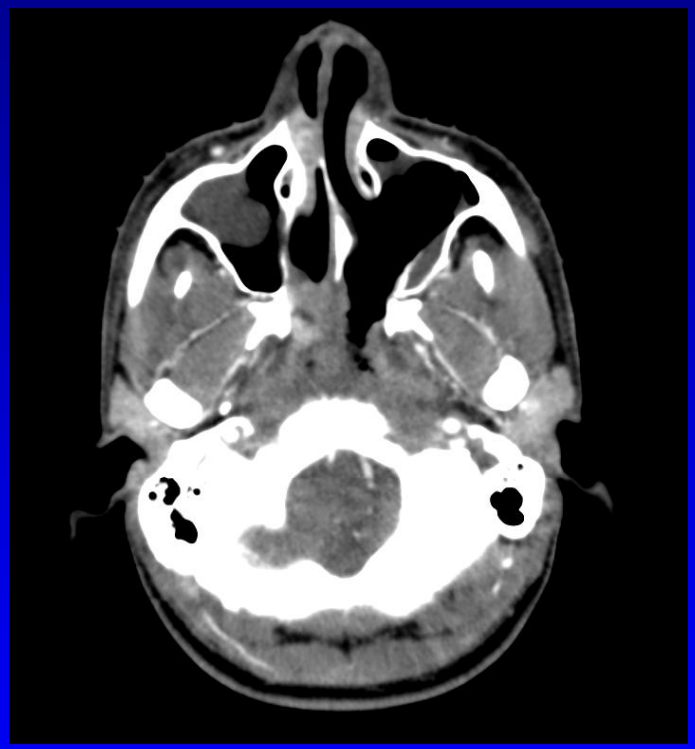
Late complications from RT for NPC

- Xerostomia
- Hearing Loss
- Temporal Lobe Necrosis
- Oral and dental complications
- Pituitary hypofunction
- Neural complications
- Soft and hard tissue cx

Changes of GTV During Tx: Nasopharyngeal Carcinoma



Pre-therapy



During Tx

Issues to consider: Range Uncertainty Due to Daily Setup, Air-tissue interface/ Reconstruction Artifacts impact in Planning? Is Replanning Feasible?

- "Those Who Fail to Study History are Doomed to Repeat It"

Lessons Learned from the IMRT Experience

Identifying Opportunities and Challenges

1) Challenges With Target Delineation

2) Recurrences due to inadequate coverage compared to conventional techniques

3) Unexpected Consequences

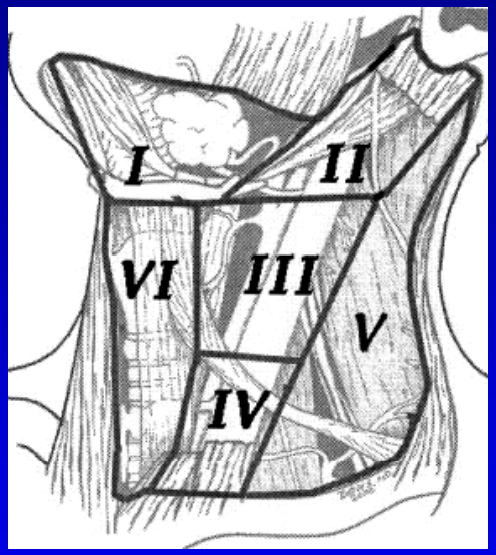
Target Delineation
Nodal Stations of the Head and Neck

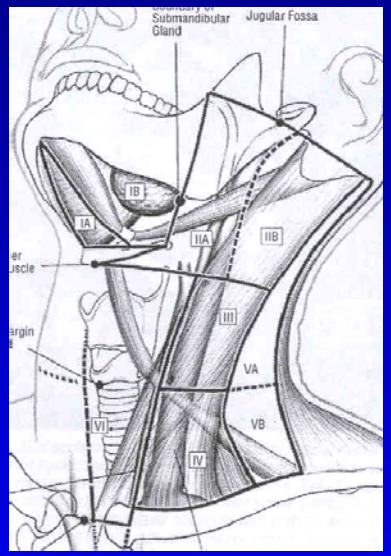
Surgical

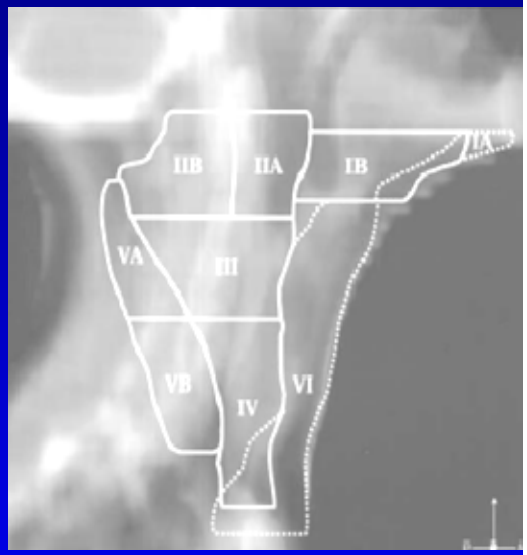
Diagnostic Radiologist

Radiation Oncologist

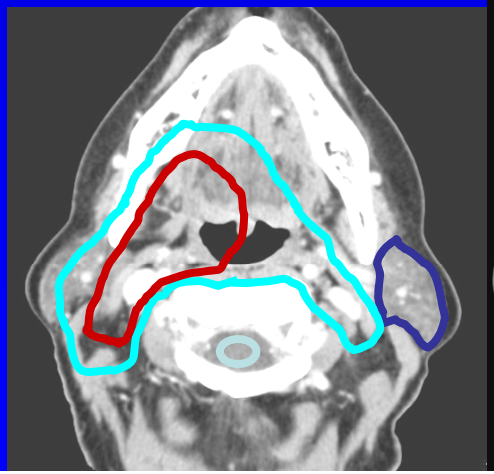
Treat a nodal station in an "all or none" fashion

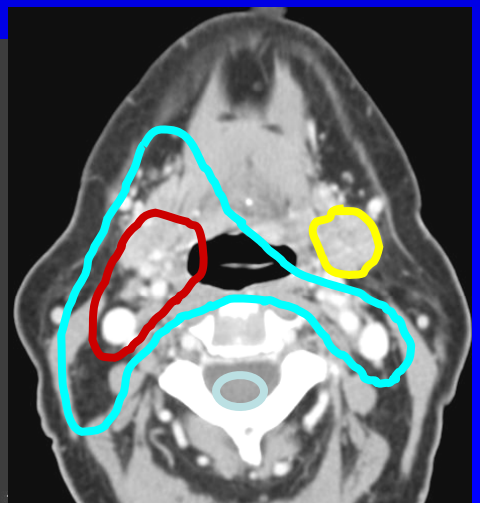


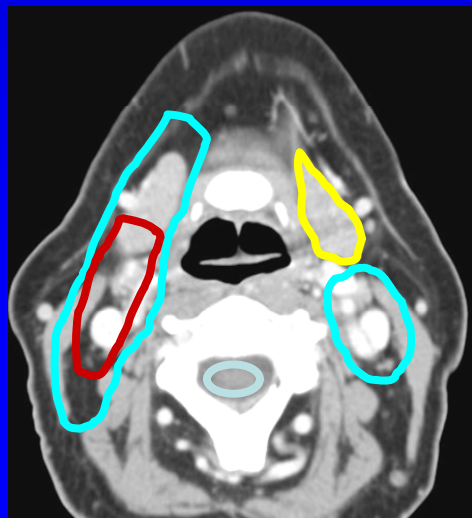




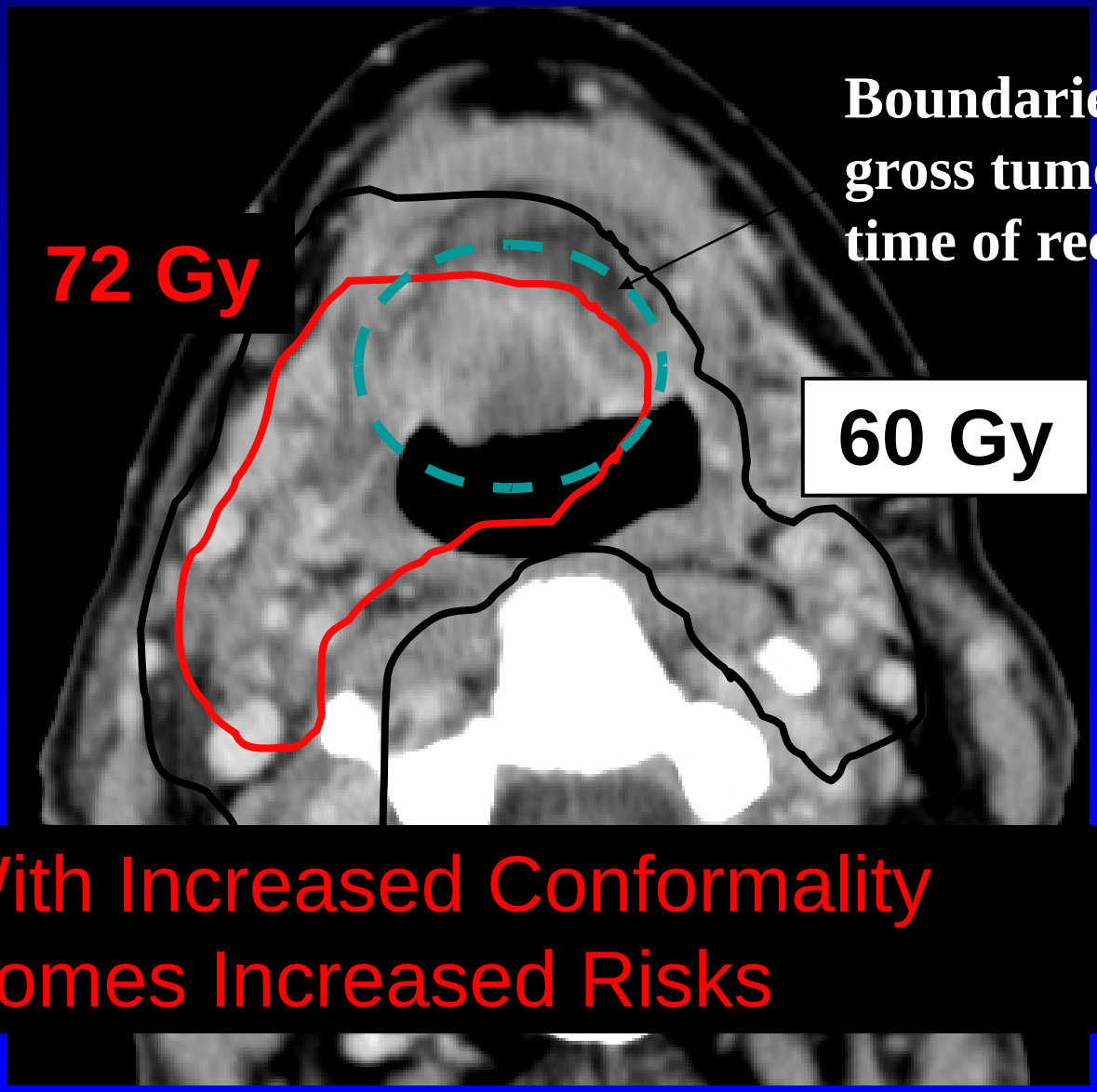
Implications for IMRT







T1N1 BOT with Marginal Failure



With Increased Conformality
Comes Increased Risks

RECURRENCES NEAR BASE OF SKULL AFTER IMRT FOR HEAD-AND-NECK CANCER: IMPLICATIONS FOR TARGET DELINEATION IN HIGH NECK AND FOR PAROTID GLAND SPARING

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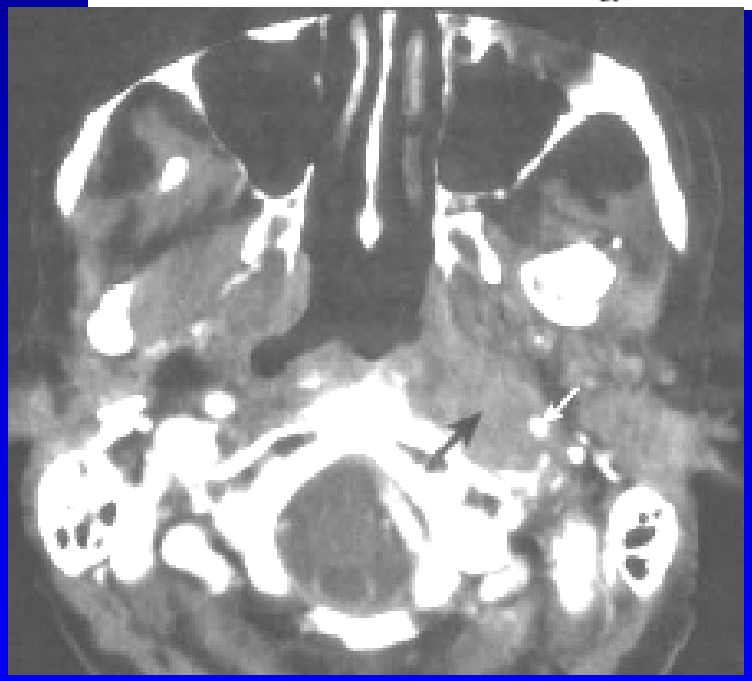


3 RP node recurrence

All oropharynx

2 of 3 in N-0 necks!

2 ipsalateral, 1 contralat RP

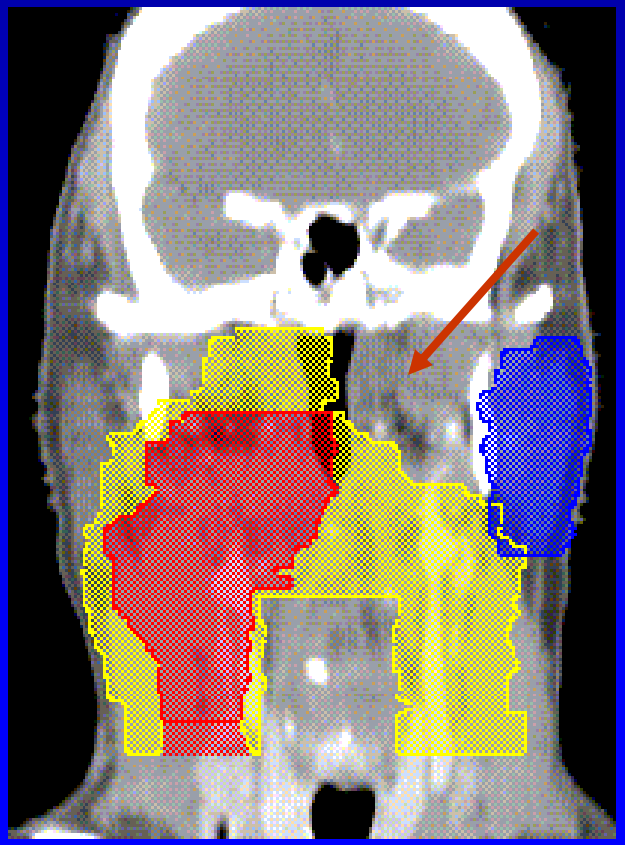
Conclusions:

- Cover RP nodes bilaterally in all (N+ and -) “locally advanced” orophx
- Top of C-1 is not high enough. Cover RP to base of skull

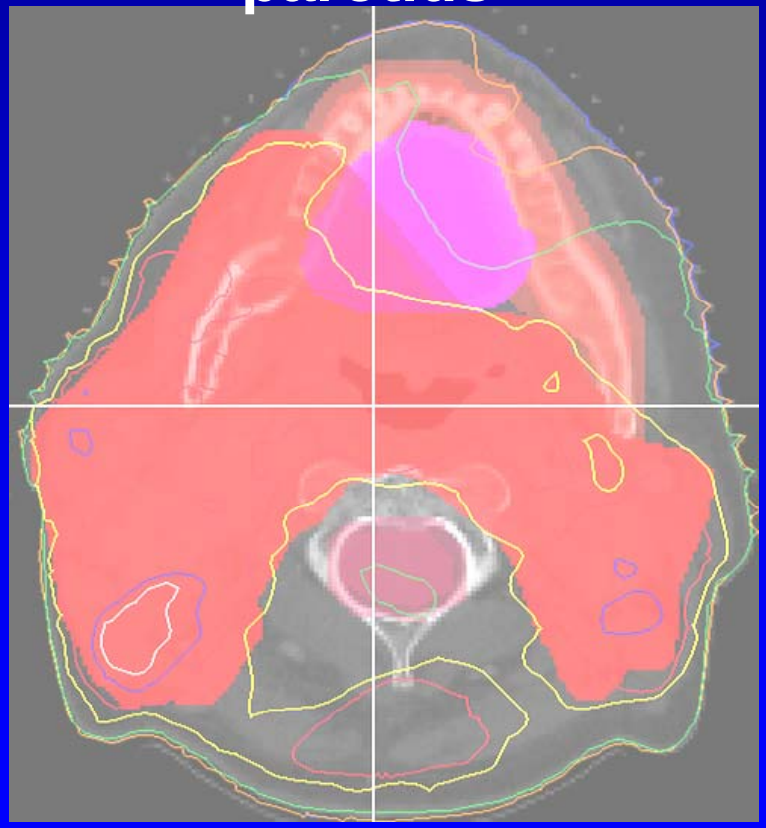
Don’t use IMRT with bilateral level 2 adenopathy

Treat the retrostyloid space on a side with positive cerivcal nodes

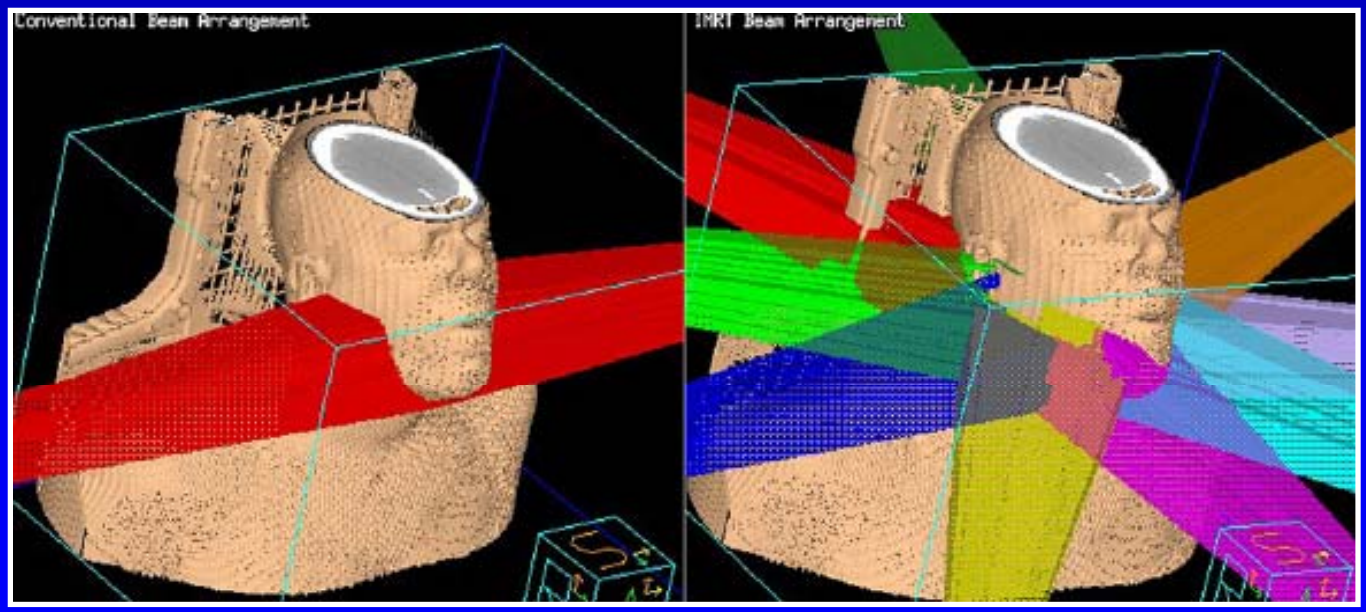
(Gregoire abst 2004)



50 Gy to both retrostyloid spaces means >30 Gy to both parotids



"Dose reduction to specified structures during IMRT implies an increased beam path dose to alternate non-target structures that may result in clinical toxicities that were uncommon with previous, less conformal approaches."



Rosenthal et al., IMRT non-target beam path toxicity, IJROBP 72(3), 2008.

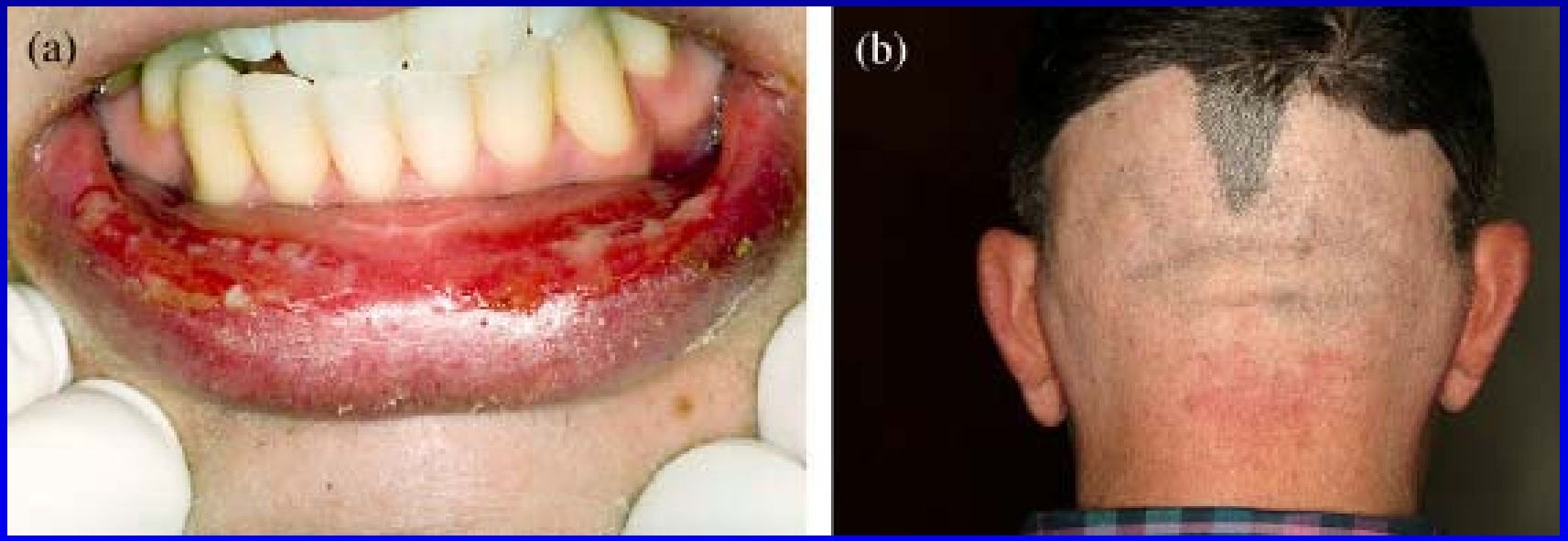
IMRT pushed dose into unexpected regions…

Table 6. Average of maximum voxel dose (in cGy) to noncontoured structures per patient, by treatment technique

Structure	Conventional	IMRT
Brain stem	3741.6	4590.4
Cochlea, left	426.4	3467.1
Cochlea, right	433.5	3372.3
Lower lip	226.7	3587.1
Mandible, anterior	752.4	3871.1
Mandible, middle	1124.3	4954.3
Mandible, posterior	4886.1	6149.3
Maxilla, anterior	264.7	3070.8
Maxilla, posterior	2894.0	4206.8
Middle ear, left	574.6	3557.3
Middle ear, right	642.3	3584.4
Occipital scalp	118.6	3453.6

Rosenthal et al., IMRT non-target beam path toxicity, IJROBP 72(3), 2008.

…and caused unexpected problems… "The Dose Bath Effect"



Does Proton Therapy offer chance to deal with this issue?

Rosenthal et al., IMRT non-target beam path toxicity, IJROBP 72(3), 2008.

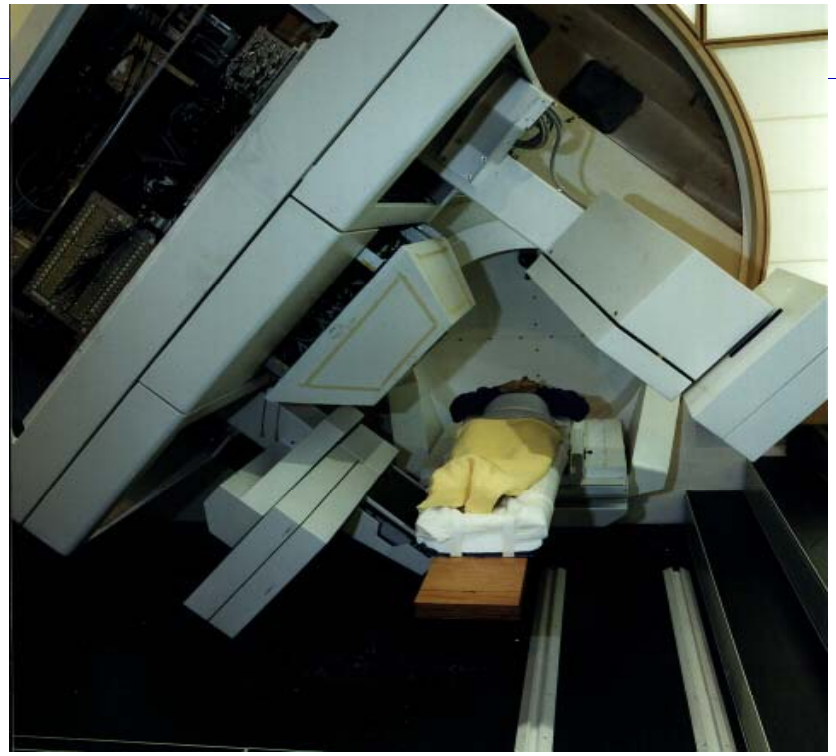
The Timeline For Data

- IMRT –clinical data first appears in the mid-late 90's
- NCI sponsored clinical trials –Phase II
  - H-0022 (oropharyngeal cancer)
  - H-0225 (nasopharyngeal cancer)
- Published phase III trial that defined a clinical benefit for SCCHN
  - Kam et al JCO Benefits to Parotid Sparing
- Current Phase III trial to allow routine use of IMRT
  - H-0522

Proton Beam Delivery

Accelerator and Gantry

Cyclotron



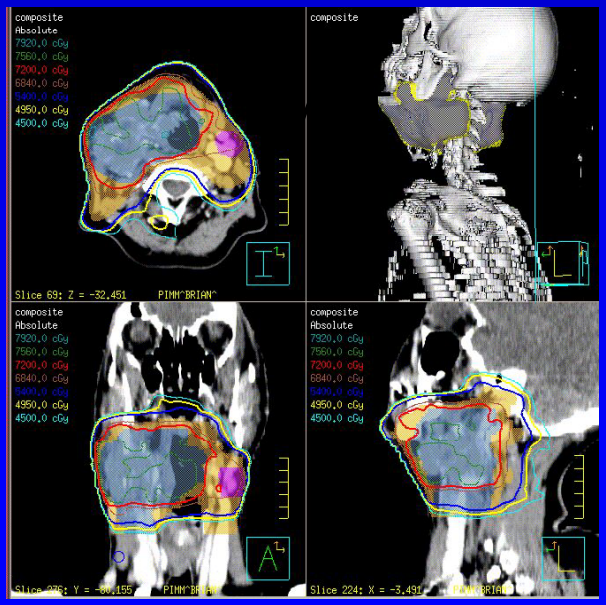
Gantry

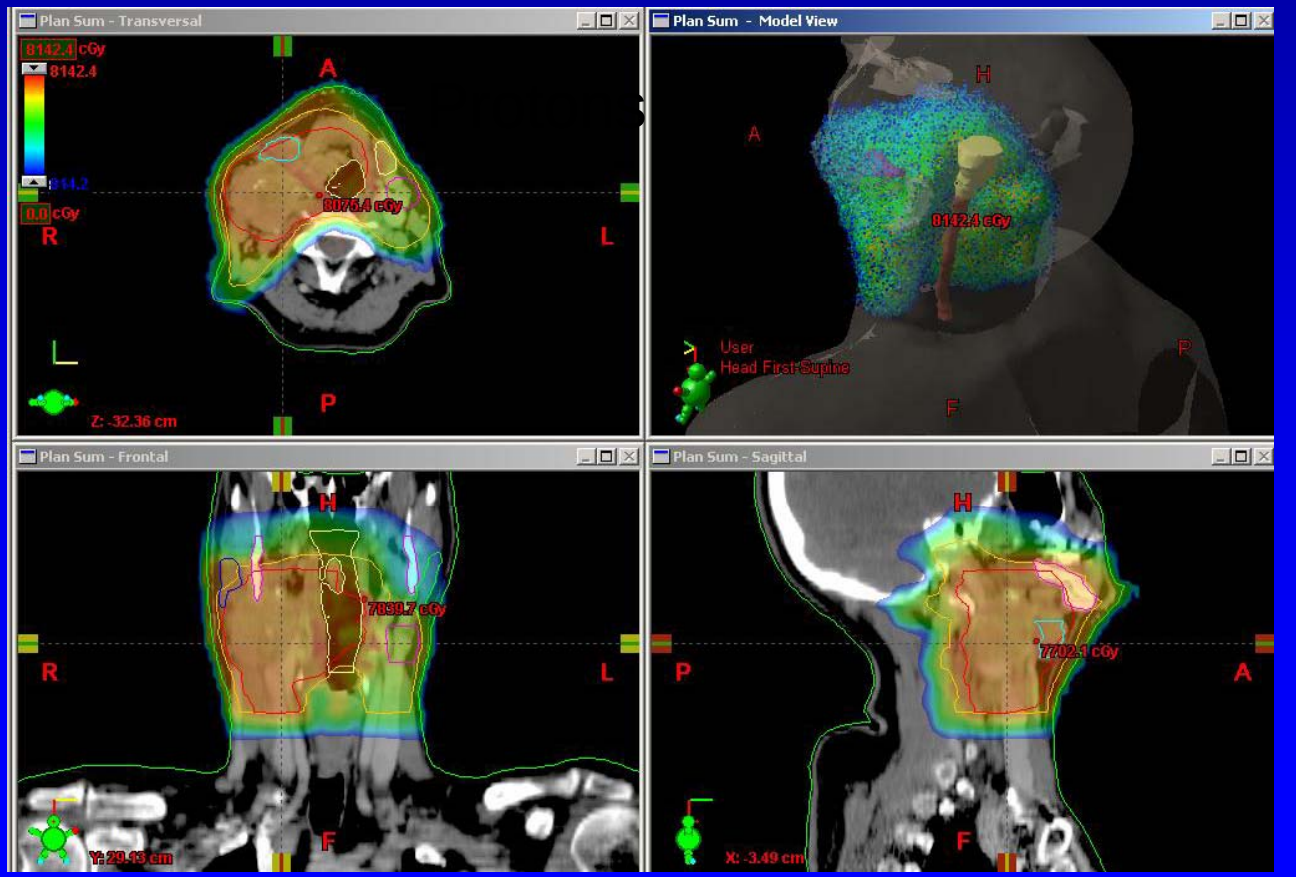
Ca Oropharynx:

Concomitant Boost (7200 cGy)

(95% PTV receives prescription dose, 99% PTV receives 93% of prescription dose and 20% PTV receives <110% of prescription dose)

•Brain stem (0.1 c.c.)	•5020	•2685
•**Spinal cord (0.1 c.c.)**	•4400	•546
•Contralateral parotid •(mean dose ≤ 2600)	•2529	•1482
•Contralateral submandibular gland (mean dose ≤ 2600)	•6928	•6148





Summary

- Proton Therapy is an exciting new technology with potential to improve clinical results and toxicity
- Must respect anatomy/lymphatics and basic oncologic principles
- Institutions that have defined standards of care in Head and Neck are leading the way with protons
- Must understand contours, margins, and dosing constraints IMRT vs Protons
- Must deal with uncertainties unique to protons