CCRT in Oropharynx and Oral Cavity Cancer

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HEAD AND NECK CANCERS – INDIAN EXPERIENCE

- In the year 2005 at RGCI, Delhi – 1248/6728 patients

  (18.54%) had Head and Neck Cancer.

- Males – 1158/3736 (30.9%)

  Females- 90/2992 (3.01%) M:F - 10:1

- National cancer registry data (New Delhi) shows Head and Neck constitutes 15.4% of all cancers.

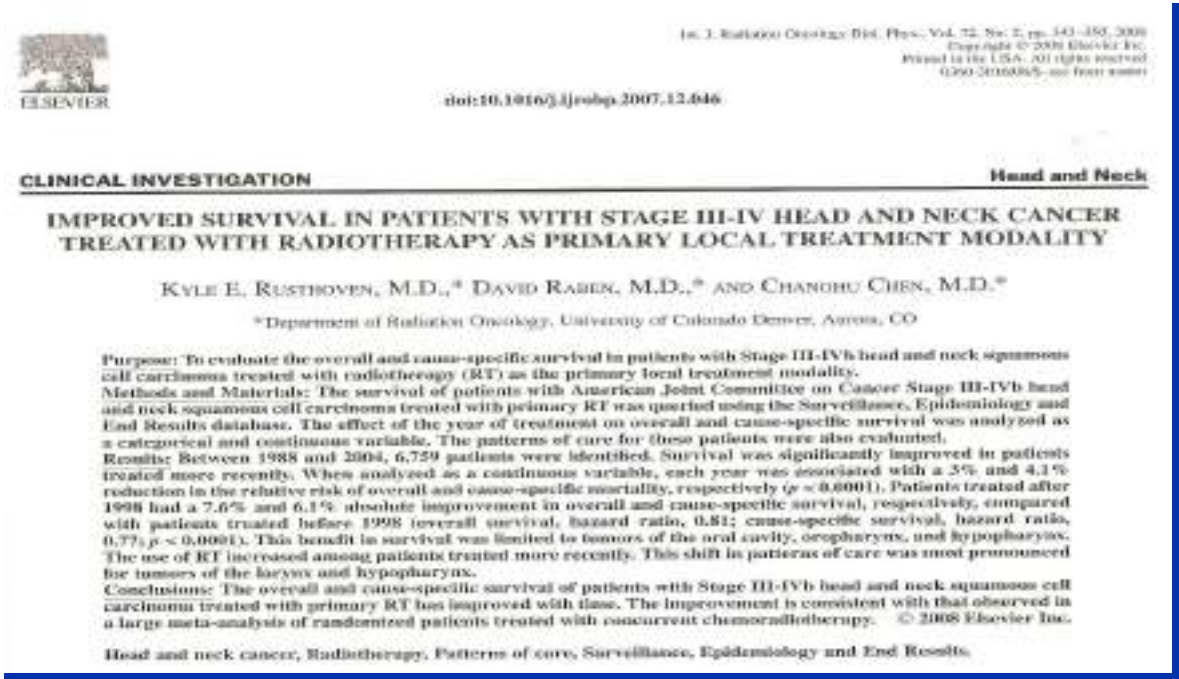
- MAX HOSPITAL,NEW DELHI 2009—HNC 285/1872 (15.3%)

Treatment aims in locally advanced SCCHN

- Overall survival
- Concurrent RT + CT Vs Neo- Adj CT and RT
- Organ-function preservation
- Symptom control
- Quality of life
  - Minimal long-term toxicity
  - Tolerability
  - Patient satisfaction

LOCALLY ADVANCED HEAD AND NECK CANCERS

- Radiation with concurrent chemotherapy is considered to be the standard of care for locally advanced and unresectable Head and Neck Cancers.
- Surgery ± Radiation therapy is reserved for certain sites only
- RT + CT has an important advantage of conservation of organ related to speech and swallowing.



doi:10.1016/j.ijrobp.2007.12.046

CLINICAL INVESTIGATION — Head and Neck

IMPROVED SURVIVAL IN PATIENTS WITH STAGE III-IV HEAD AND NECK CANCER TREATED WITH RADIOTHERAPY AS PRIMARY LOCAL TREATMENT MODALITY

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*Department of Radiation Oncology, University of Colorado Denver, Aurora, CO

Purpose: To evaluate the overall and cause-specific survival in patients with Stage III-IVb head and neck squamous cell carcinoma treated with radiotherapy (RT) as the primary local treatment modality.
Methods and Materials: The survival of patients with American Joint Committee on Cancer Stage III-IVb head and neck squamous cell carcinoma treated with primary RT was queried using the Surveillance, Epidemiology and End Results database. The effect of the year of treatment on overall and cause-specific survival was analyzed as a categorical and continuous variable. The patterns of care for these patients were also evaluated.
Results: Between 1988 and 2004, 6,729 patients were identified. Survival was significantly improved in patients treated more recently. When analyzed as a continuous variable, each year was associated with a 3% and 4.1% reduction in the relative risk of overall and cause-specific mortality, respectively ($p < 0.0001$). Patients treated after 1998 had a 7.6% and 6.1% absolute improvement in overall and cause-specific survival, respectively, compared with patients treated before 1998 (overall survival, hazard ratio, 0.81; cause-specific survival, hazard ratio, 0.77; $p < 0.0001$). This benefit in survival was limited to tumors of the oral cavity, oropharynx, and hypopharynx. The use of RT increased among patients treated more recently. This shift in patterns of care was most pronounced for tumors of the larynx and hypopharynx.
Conclusions: The overall and cause-specific survival of patients with Stage III-IVb head and neck squamous cell carcinoma treated with primary RT has improved with time. The improvement is consistent with that observed in a large meta-analysis of randomized patients treated with concurrent chemoradiotherapy. © 2008 Elsevier Inc.

Head and neck cancer, Radiotherapy, Patterns of care, Surveillance, Epidemiology and End Results.

Improved Survival in H & N Cancers

- Patients treated between 1988-97 and 1998-2004 (SEER Data)
- Patients treated after 1998 had 7.6% & 6.1% absolute improvement in overall and cause specific survival
- The absolute OS benefit observed is likely related to improvement in efficacy of treatment with Concurrent RT+CT
- Proportion of patients treated with RT has also increased over time attributable to improvements in Larynx preservation

IJROBP Vol. 72 (2) pp 343-50, 2008

Improved Survival in H & N Cancers

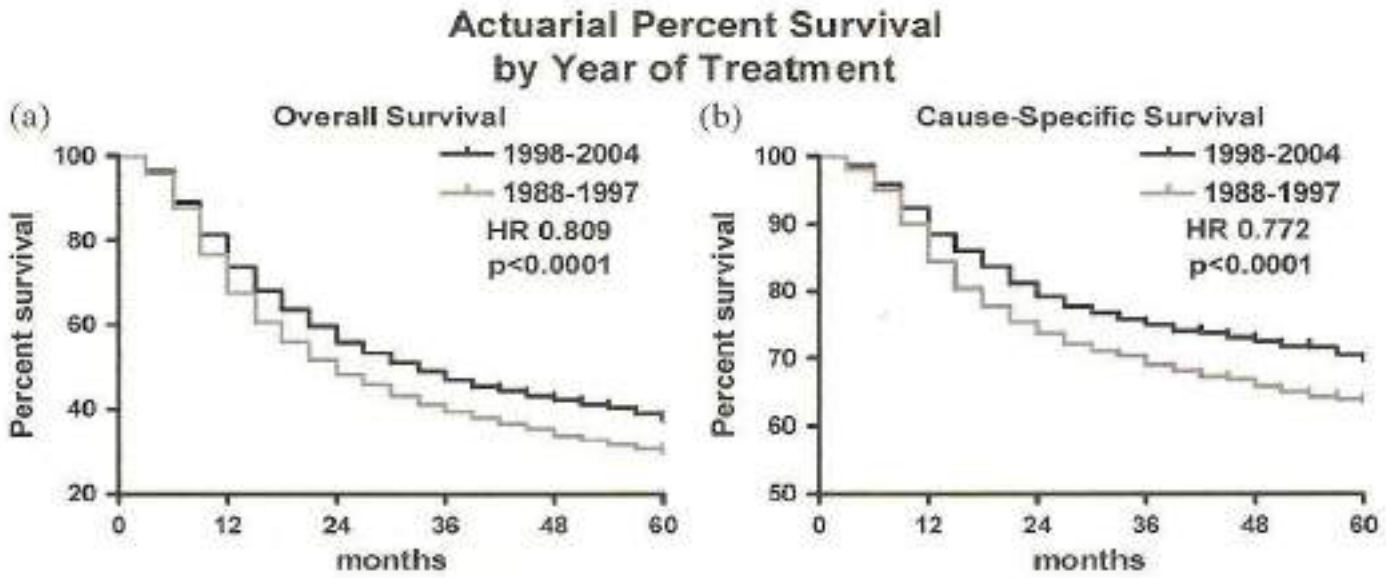


Fig. 1. Actuarial percentage of (a) overall and (b) cause-specific survival of patients treated between 1988 and 1997 vs. 1998 and 2004. Hazard ratio (HR) <1.0 indicates improved survival in patients treated between 1998 and 2004. Statistical comparisons done using log–rank method.

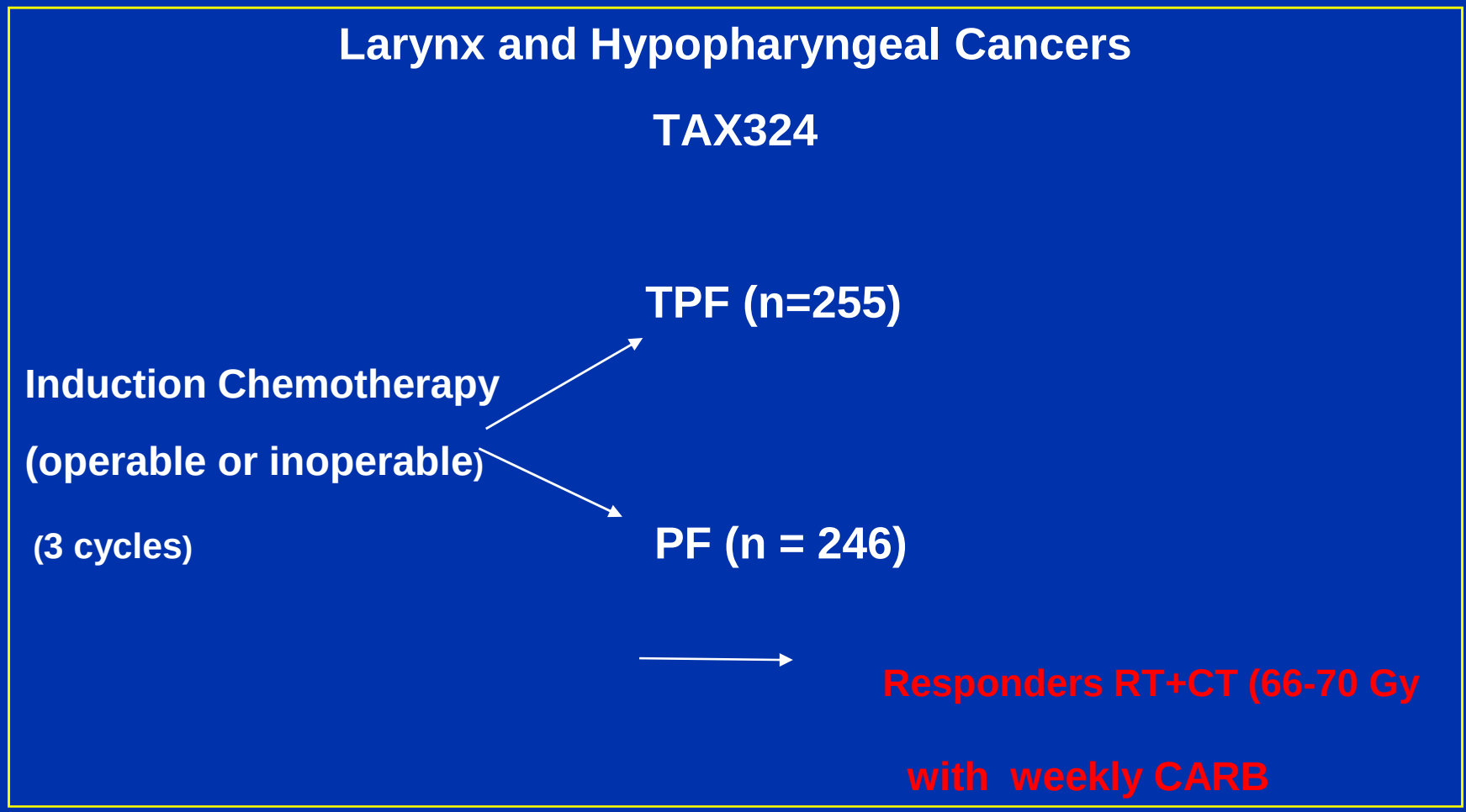
IJROBP Vol. 72 (2) pp 343-50, 2008

Locally advanced Head & Neck Cancers

Concurrent RT + CT Vs Radiation Alone

Neo Adjuvant Chemo Vs Concurrent Chemo-Radiation

Sequential Therapy of Locally advanced



Annals of Oncology 20:921-27,2009

EORTC 24971 / TAX 323

- **Induction TPF**

  Or

  66-70 Gy

- **PF 3-4 Cycles**

Responders → **Radiation**

NEJM 357, 1695 -1704, 2007

Chemo-RT Vs Radiation alone

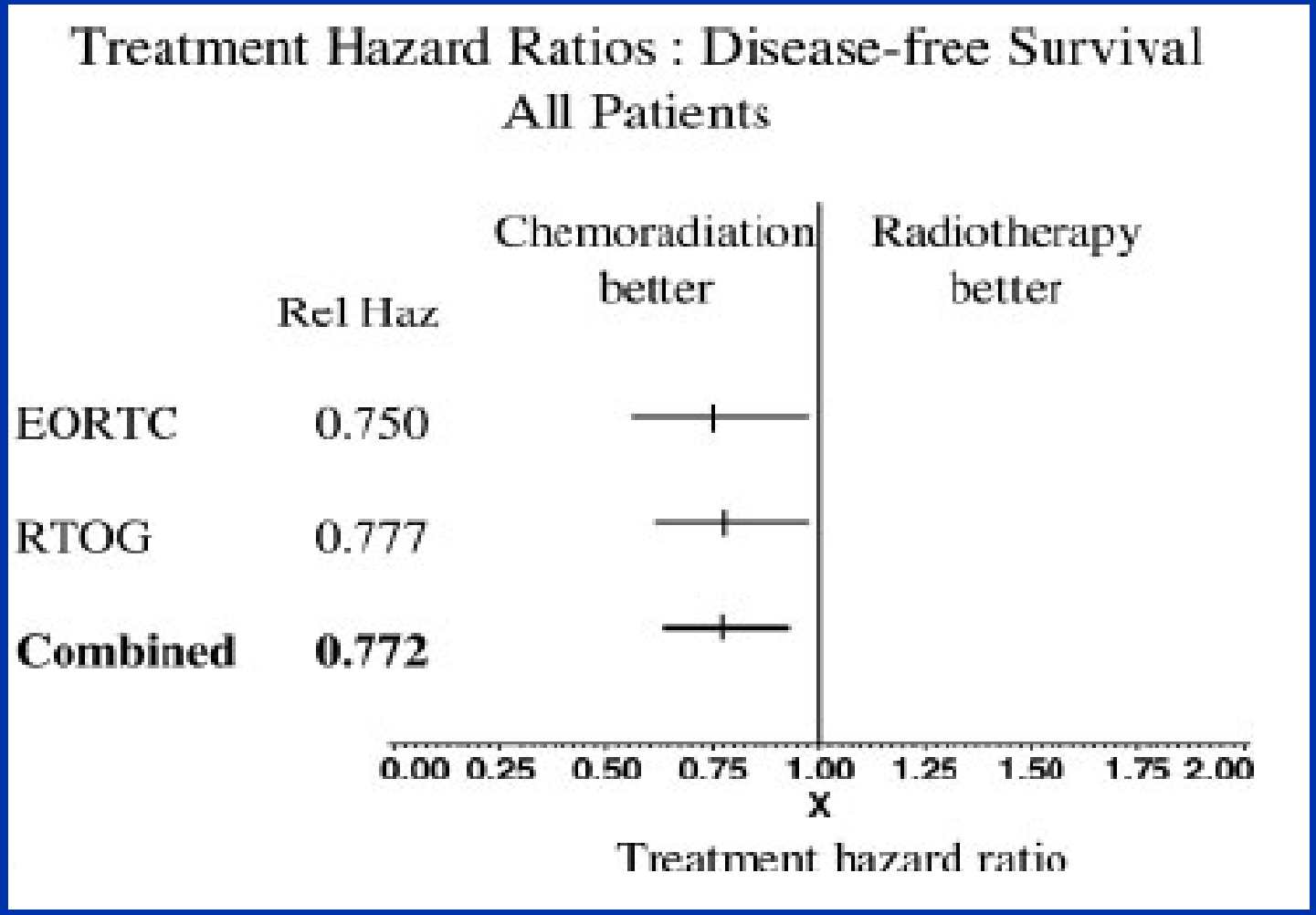
Table 1. Summary of trials.

Disease characteristic and outcome endpoint	EORTC #22931 (*N* = 334)	RTOG #9501 (*N* = 459; 414 analyzed)
Characteristic		
Primary site		
Oral cavity	26%	27%
Oropharynx	30%	42%
Larynx	22%	21%
Hypopharynx	20%	10%
Other	1%	<1%
T classification		
T1–2	33%	39%
T3–4	66%	61%
Unknown	1%	0%
N classification		
N0–1	43%	6%
N2–3	57%	94%
Outcome endpoint, chemoradiotherapy vs RT		
Locoregional failure rate	5-y estimate, 18% vs 31% (p = .007)	3-y estimate, 22% vs 33% (p = .01)
Disease-free survival rate	5-y estimate, 47% vs 36% (p = .04)	3-y estimate, 47% vs 36% (p = .04)
Overall survival rate	5-y estimate, 53% vs 40% (p = .02)	3-y estimate, 56% vs 47% (p = .09)

Abbreviations: EORTC, European Organization for Research and Treatment of Cancer; RTOG, Radiation Therapy Oncology Group; RT, radiotherapy.

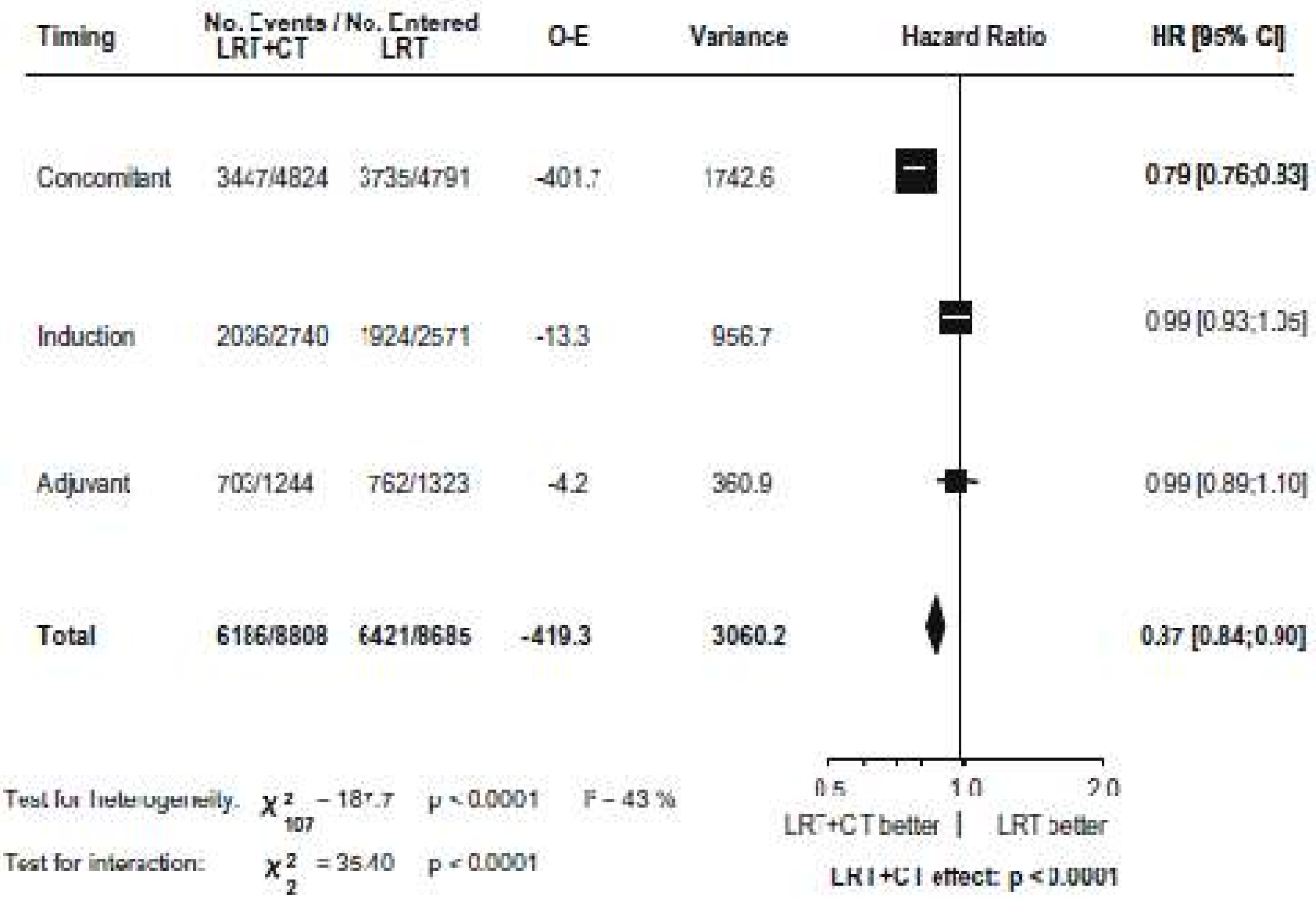
Bernier J et al. Wiley Inter Science: 2005; 843-850

Chemo-RT Vs Radiation Alone

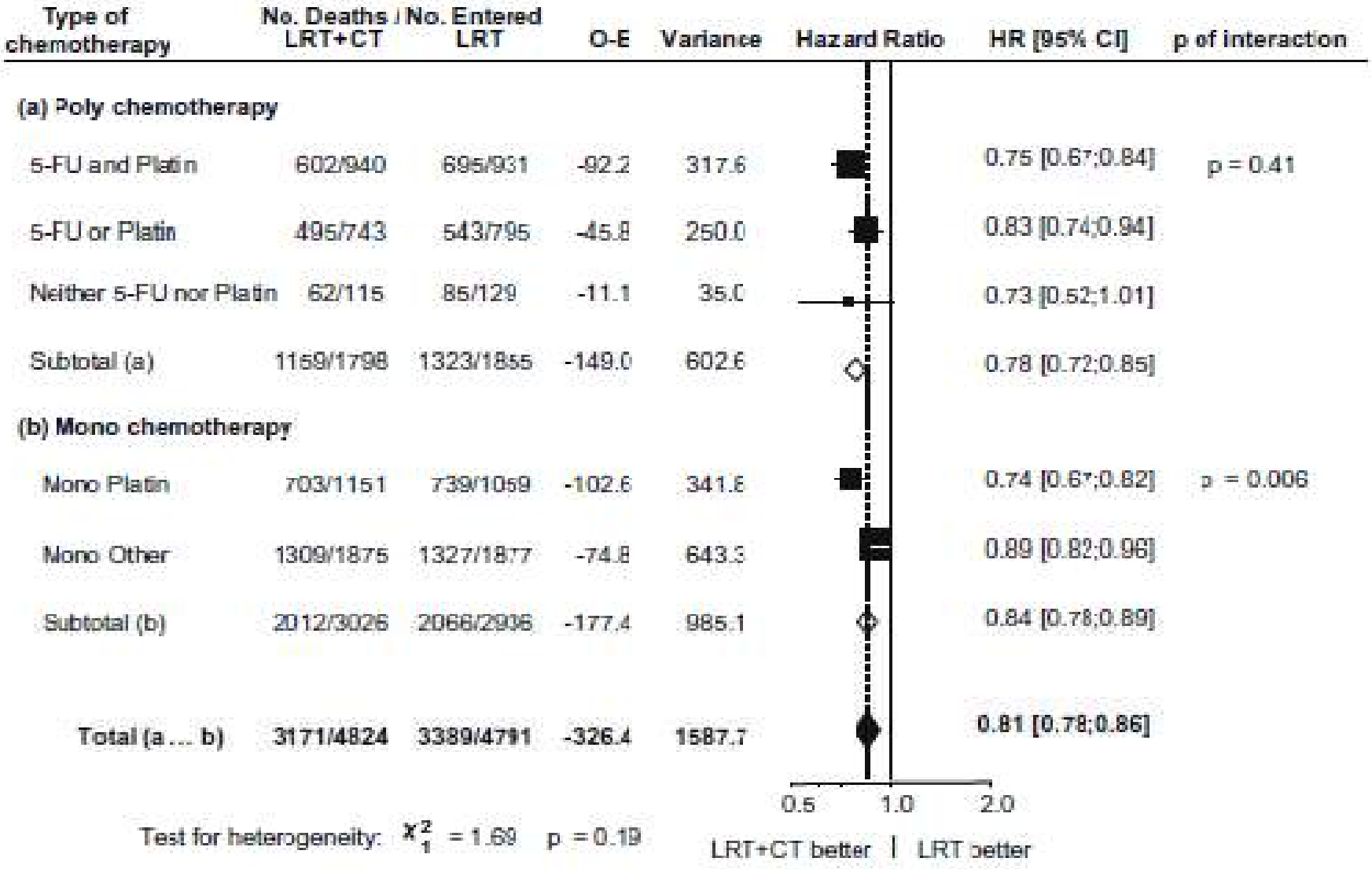


Bernier J et al. Wiley Inter Science: 2005; 843-850

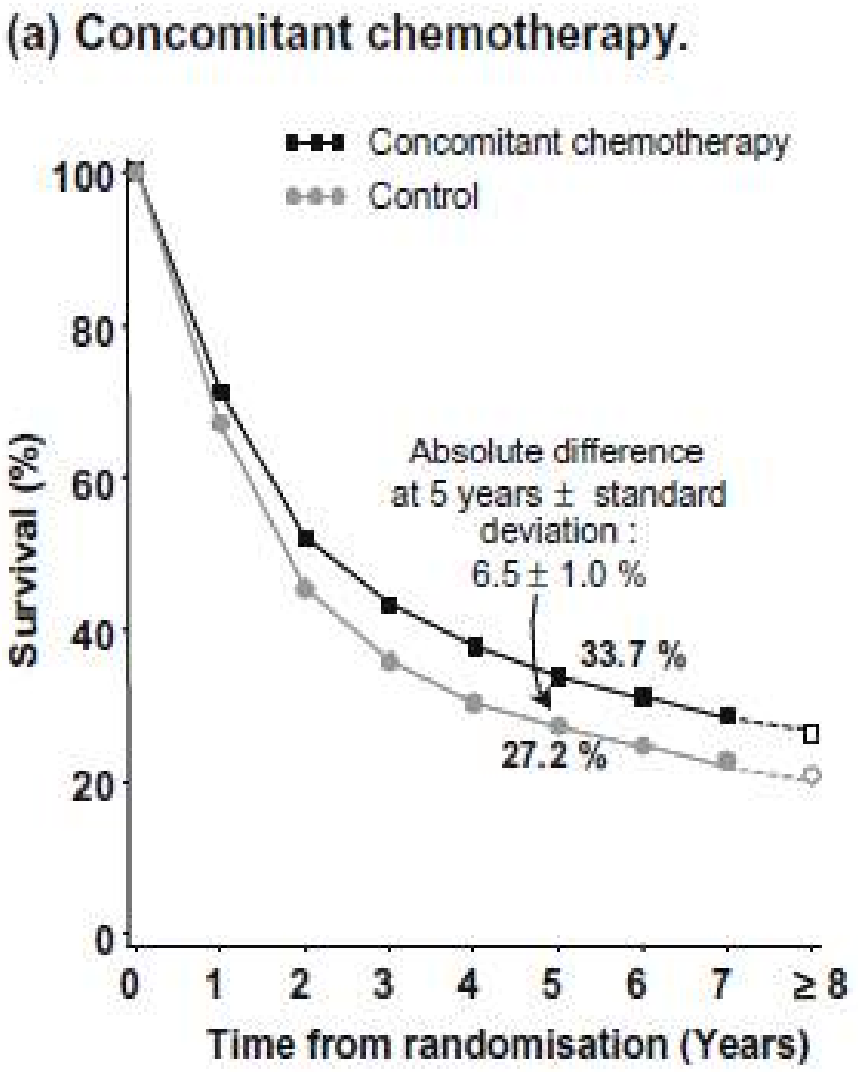
Hazard ratio with loco-regional treatment plus chemotherapy versus loco-regional treatment alone by timing of chemotherapy.
MACH-NC 2009 DATA

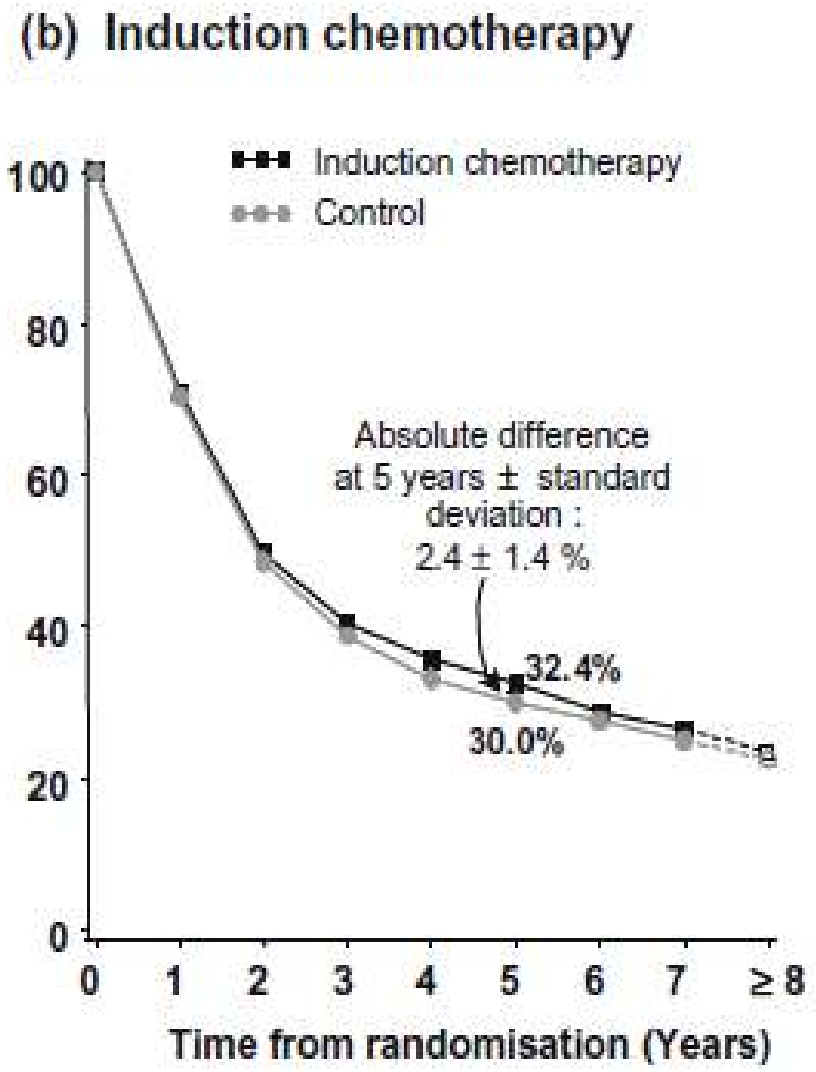


Hazard ratio of death with loco-regional treatment plus concomitant chemotherapy versus loco-regional treatment alone by type of chemotherapy. The test of HRs for poly and mono-chemotherapy. **MACH-NC UPDATE-2009(Radioth &Oncol92(2009)4-14**



MACH-NC ANALYSIS 2009





CONCURRENT Vs INDUCTION RT+CT in LAHNC

		TPF – RT+CT (TAX324)	EORTC 24971/TAX323	RT+Erb (Bonner et al)
PFS	2 Yrs (%)	48 %	25 %	50 %
	3 Yrs (%)	43 %	17 %	48 %
OS	2Yrs (%)	64 %	43 %	65 %
	3 Yrs (%)	57 %	37 %	55 %
LRF	(%)	32 %		
DM		6 %	12.9 %	
DM+LRF		1 %	2 %	
Second PRT		2 %		

Comparison of overall survival advantage of different combinations (MACH-NC meta-analyses, Bonner study)

	Hazard ratio (95% CI)	CT or Erbitux effect (p-value)	Absolute benefit	
			At 2 years[a]	At 5 years[a]
Adjuvant CT+RT[1]	**0.98 (0.85–1.19)**	**0.74**	**1%**	**1%**
Neoadjuvant CT +RT[1]	**0.95 (0.88–1.01)**	**0.10**	**2%**	**2%**
Concomitant CT + RT[1]	**0.81 (0.76–0.88)**	**<0.0001**	**7%**	**8%**
ERBITUX + RT[2]	0.73 (0.56–0.95)	0.02	7%	10%

[a]Assuming survival rates of 50% at 2 years and 32% at 5 years in control groups

Pignon JP, et al. Lancet 2000;355:949–955

Bonner J.A, et al. as presented ASTRO 2008

Concurrent RT + CT in Oral Cancers

- **Usually Post-operative.**
- **Indicated in "High Risk" patients.**
  - **R1 – Resection (margin positive).**
  - **Nodal Metastasis with Extra Capsular Extension (ECE).**
  - **pT3 or pT4 primary.**
  - **N2 or N3 nodal disease**
  - **Nodal disease in levels IV or V**
  - **Perineural invasion**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Postoperative Irradiation with or without Concomitant Chemotherapy for Locally Advanced Head and Neck Cancer

Jacques Bernier, M.D., Ph.D., Christian Domenge, M.D., Mahmut Ozsahin, M.D., Ph.D., Katarzyna Matuszewska, M.D., Jean-Louis Lefèbvre, M.D., Richard H. Greiner, M.D., Jordi Giralt, M.D., Philippe Maingon, M.D., Frédéric Rolland, M.D., Michel Bolla, M.D., Francesco Cognetti, M.D., Jean Bourhis, M.D., Anne Kirkpatrick, M.Sc., and Martine van Glabbeke, Ir., M.Sc., for the European Organization for Research and Treatment of Cancer Trial 22931

Bernier J et al. NEJM 2004; 1945-1952

Primary tumor site — no. (%)			
Oral cavity	46 (28)	41 (25)	87 (26)
Oropharynx	47 (28)	54 (32)	101 (30)
Hypopharynx	34 (20)	34 (20)	68 (20)
Larynx	38 (23)	37 (22)	75 (22)
Unknown	2 (1)	1 (1)	3 (1)

Bernier J et al. NEJM 2004; 1945-1952

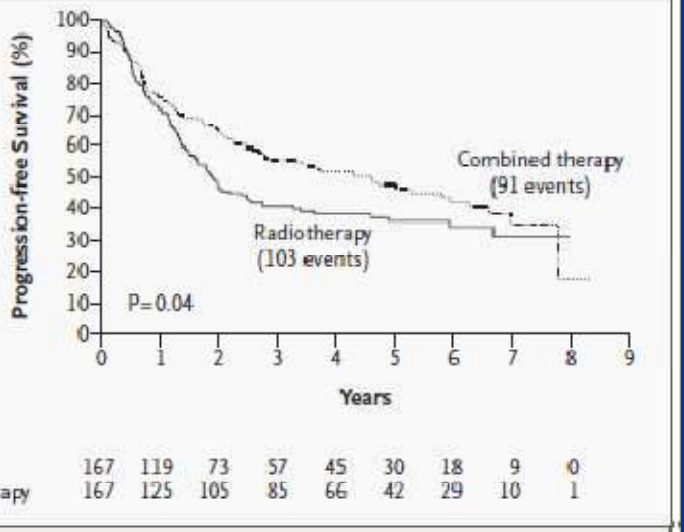


Figure 1. Kaplan–Meier Estimates of Progression-free Survival.
Patients assigned to combined therapy had higher rates of progression-free survival than those assigned to radiotherapy (hazard ratio for progression, 0.75; P=0.02).

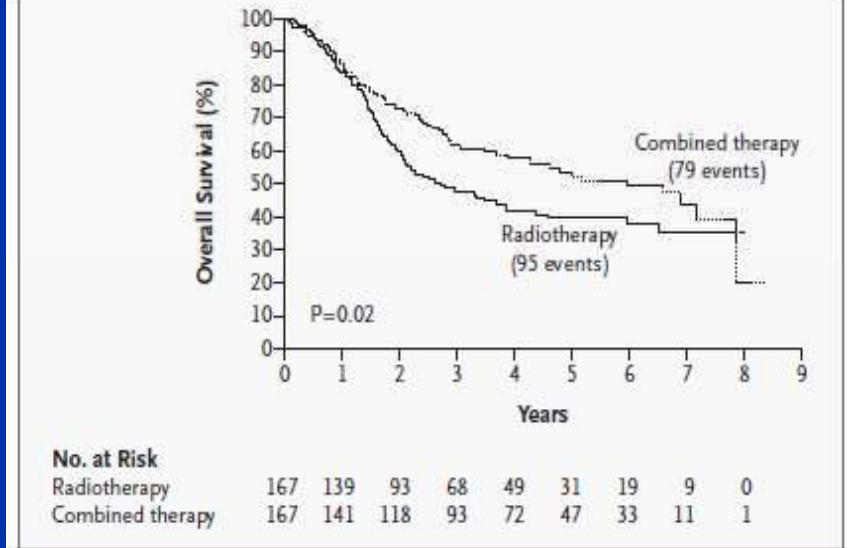


Figure 2. Kaplan–Meier Estimates of Overall Survival.
Patients assigned to combined therapy had higher survival rates than those assigned to radiotherapy (hazard ratio for death, 0.70; P=0.04).

Bernier J et al. NEJM 2004; 1945-1952

EORTC 24971 /Tax 323

Febrile Neutropenia	**5.2 % TPF**
Neutropenia	**76.9 %**
Anemia	**9.2 %**
Thrombocytopenia	**5.2 %**
Infection	**12 %**
Deaths	**2.3 % (5.5 % PF)**
Stomatitis	**23.7 %**
esophageal dysphagia	**13.9 %**

Grade 3-4 Toxicities

	TPF	PF	CRT
Nonhematologic toxicity	47%	31%	52%
Neutropenia	25%	25%	24%
Febrile neutropenia	25%	3%	3%
Toxic death	7%	5%	7%

TPF = docetaxel + cisplatin + fluorouracil; PF = cisplatin + fluorouracil; CRT = chemoradiotherapy

Hitt R et al. J supportive Oncol 2005; 23 (suppl 16): Abstract 5578

Swallowing Toxicity after Chemoradiation for Head & Neck Cancer

Chemoradiation Trials -Therapeutic and Functional Outcomes

Trial	Radiation	Chemotherapy	Swallowing Toxicity
RTOG 99 -14 [94]	72 Gy over 6 weeks; single arm;phase II	Cisplatin	FT rate ,82.9%, 1 year 40.9%;2year,21.8%
Starr [95] 25% p= .02	69.9Gy over 38 sdays	Fluoroucil +carboplatin	2 Year FT rates 51% v
RTOG 91-116 groups had	70Gy over 7 weeks	Cisplatin	14%,16% of both of "difficult swallowing"
Intergroup 0126 acute FT ratios	70Gy over 7 weeks	Cisplatin	52%v 40%;P=0.08
Abitol chronic;7%	74.4Gy over 16 weeks	Cisplatin Flurocil+mitomycin-C	8% FT dependency
Erbuch	70Gy ,single arm phase 1	Gemcitabine	Chronic FT rate 28%
GORTEC 94.0196 15% ,	70Gy over 7 weeks	Cisplatin +Fluorocil	FT rate overall,37% v p=.02;15%
Kies 97	75 Gy over 9 weeks :single arm phase 1	Pacilitaxel; Carboplatin; Fluoroucil ,	1 year FT rates 20%

FT- Feeding Tube

Int. J. Radiation Oncology Biol. Phys., Vol. 45, No. 1, pp. 21–32, 1999

0360-3016/99/$–see front matter

PII S0360-3016(99)00181-7

CLINICAL INVESTIGATION — Head and Neck

SMART (SIMULTANEOUS MODULATED ACCELERATED RADIATION THERAPY) BOOST: A NEW ACCELERATED FRACTIONATION SCHEDULE FOR THE TREATMENT OF HEAD AND NECK CANCER WITH INTENSITY MODULATED RADIOTHERAPY

E. Brian Butler, M.D.,* Ben S. Te
Barry M. Uhl, M.D.,* Ronald B. I
Donald T. Donovan, M.I

*Department of Radiation Oncology, Baylor College of Medici
R. Alford Department of Otorhinolaryngo

Purpose: To report the initial experience in the deliv
(Simultaneous Modulated Accelerated Radiation Th
(Intensity Modulated Radiotherapy). The following
response, clinical feasibility, dosimetry and cost.

Methods and Materials: Between January 1996 and
carcinomas were treated with SMART boost techn
targets. The primary target included palpable and v
risk for microscopic disease. Daily fractions of 2.4 Gy
secondary targets to a total dose of 68 Gy and 80 Gy
conventional anterior portal. This fractionation sche
Toxicity was evaluated by RTOG acute toxicity gra
sites, subjective salivary function, weight loss, and th
Initial tumor response was assessed by clinical and
ated by the criteria: time to treat patient, immobili
we evaluated the mean doses of both targets and e
evaluate cost, Medicare allowable charge for SMAR
and accelerated radiotherapy.

Results: Acute toxicity: None of the patients had a screw site infection and all patients healed well after completion of radiotherapy. Sixteen of 20 patients (80%) completed the treatment within 40 days without any split.

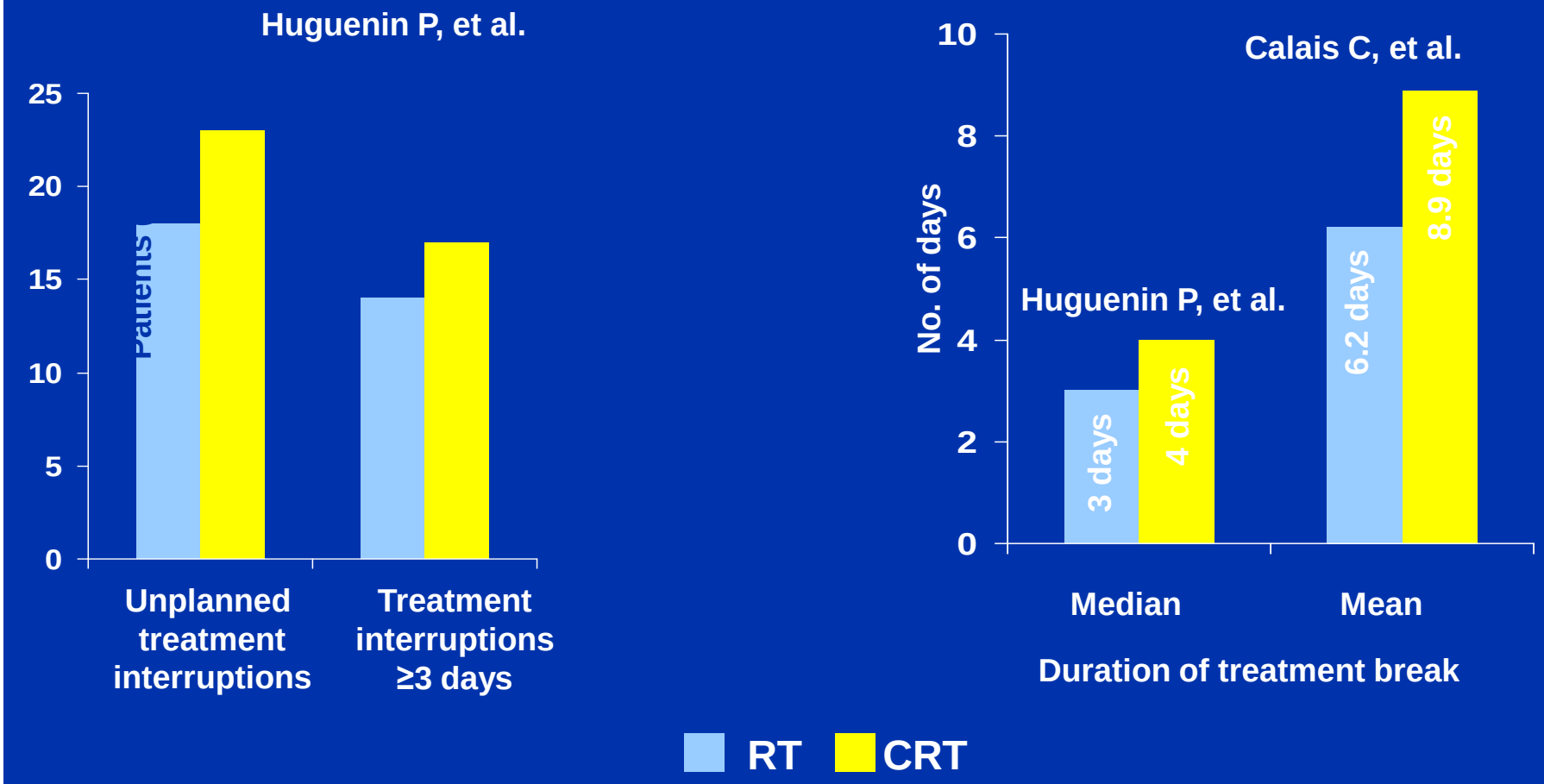
. The patient with PR had stable disease on imaging at 12 months follow-up. Two patients were found to have lung metastases at 2 months and 5 months follow-up. To date, there have been two local recurrences in the complete responders. Both patients had nasopharyngeal primary; one was retreated with radioactive Cesium-137 implant and the other died from the disease. Clinical feasibility: The average treatment time for a three-arc treatment was 17.5 minutes and 2.5 minutes for each additional arc. Eleven patients (55%) had four-arc treatment while six patients (30%) had five-arc treatment and three patients (15%) had three-arc treatment. Immobilization was reproducible within less than 2 mm. The treatment planning, QA and documentation prior to treatment averaged 2 days. Dosimetry: The mean dose to the primary and secondary targets were 64.4 Gy and 54.4 Gy, respectively; 8.9% of the primary target volume and 11.6% of the secondary target volume were below prescribed dose goal. The mean dose delivered to the mandible was 30 Gy, spinal cord 17 Gy, Ipsilateral parotid 25 Gy, and contralateral parotid 21 Gy. Cost: Total Medicare allowable charge for SMART boost was $7080 compared to $8600 (conventional) and $8400 (accelerated fractionation). **Conclusions:** SMART boost technique is an accelerated radiotherapy scheme that can be delivered with acceptable toxicity. It allows parotid sparing as evidenced both clinically and by dosimetry. Initial tumor response has been encouraging. It is clinically feasible and cost saving. A larger population of patients and a long-term follow-up are warranted to evaluate ultimate tumor control and late toxicity. © 1999 Elsevier Science Inc.

SMART boost, Intensity modulated radiotherapy, Head and neck carcinoma.

Sixteen patients (80%) had RTOG Grade 3 mucositis while 10 patients (50%) had Grade 3 pharyngitis. Three of 20 patients (15%) had weight loss greater than 10% of their pretreatment weight. Ten patients (50%) required intravenous fluids, tube feeding or both. Nine patients (45 %) reported moderate xerostomia with significant relief reported within 6 months. Initial tumor response: 19 patients (95%) had complete response (CR) while one had partial response (PR).

PEG-Insertion

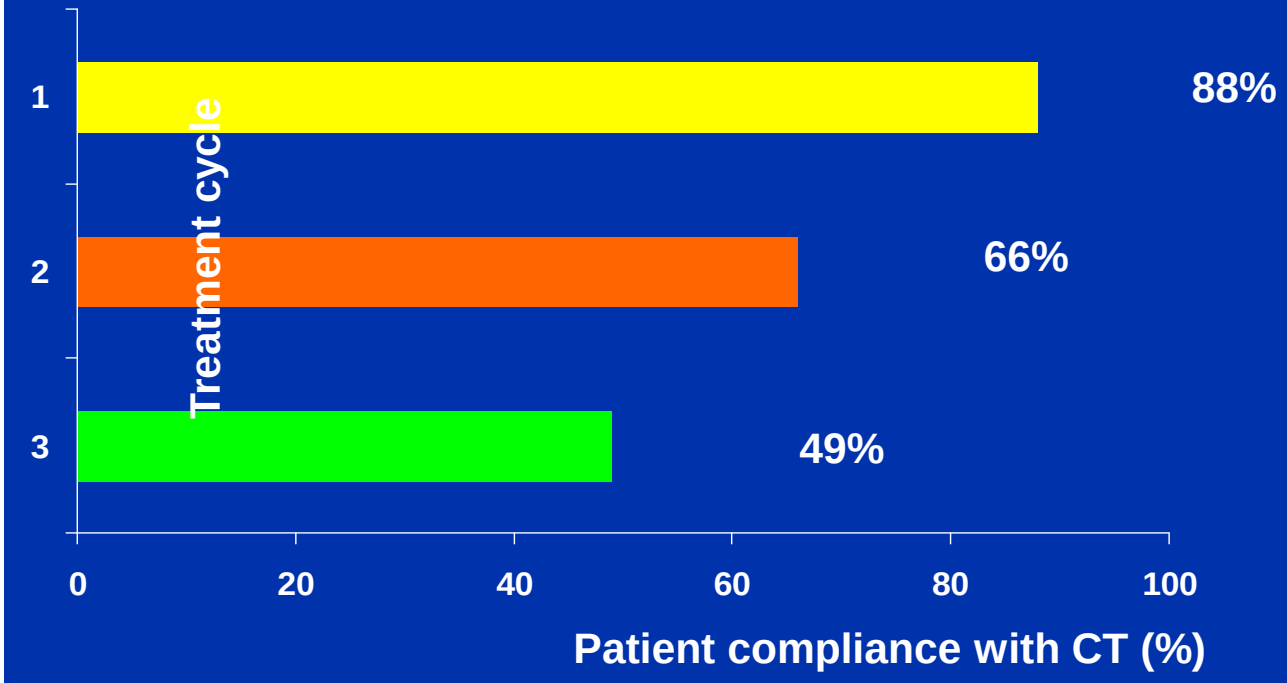
CRT is associated with more frequent and longer treatment interruptions than RT



Calais G, et al. J Natl Cancer Inst 1999;91:2081–2086; Huguenin P, et al. J Clin Oncol 2004;22:4665–4673

CRT: compromised postoperative adherence to CT

- Number of patients receiving cisplatin on time and without delay decreases over time



Bernier J, et al. N Engl J Med 2004;350:1945–1952

TOXICITY OF CONVENTIONAL RADIATION

CHRONIC TOXICITY

1. Xerostomia (dry mouth) : >66%
2. Difficulty eating / swallowing : 35%-68%
3. Sticky salvia : 33%
4. Decreased sense of taste : 25-50%
5. Dental problems : 33%
6. Pain : 15-30%
7. Appearance : 20-25%
8. Trismus
9. Silent Aspiration & Asp. Pneumonitis

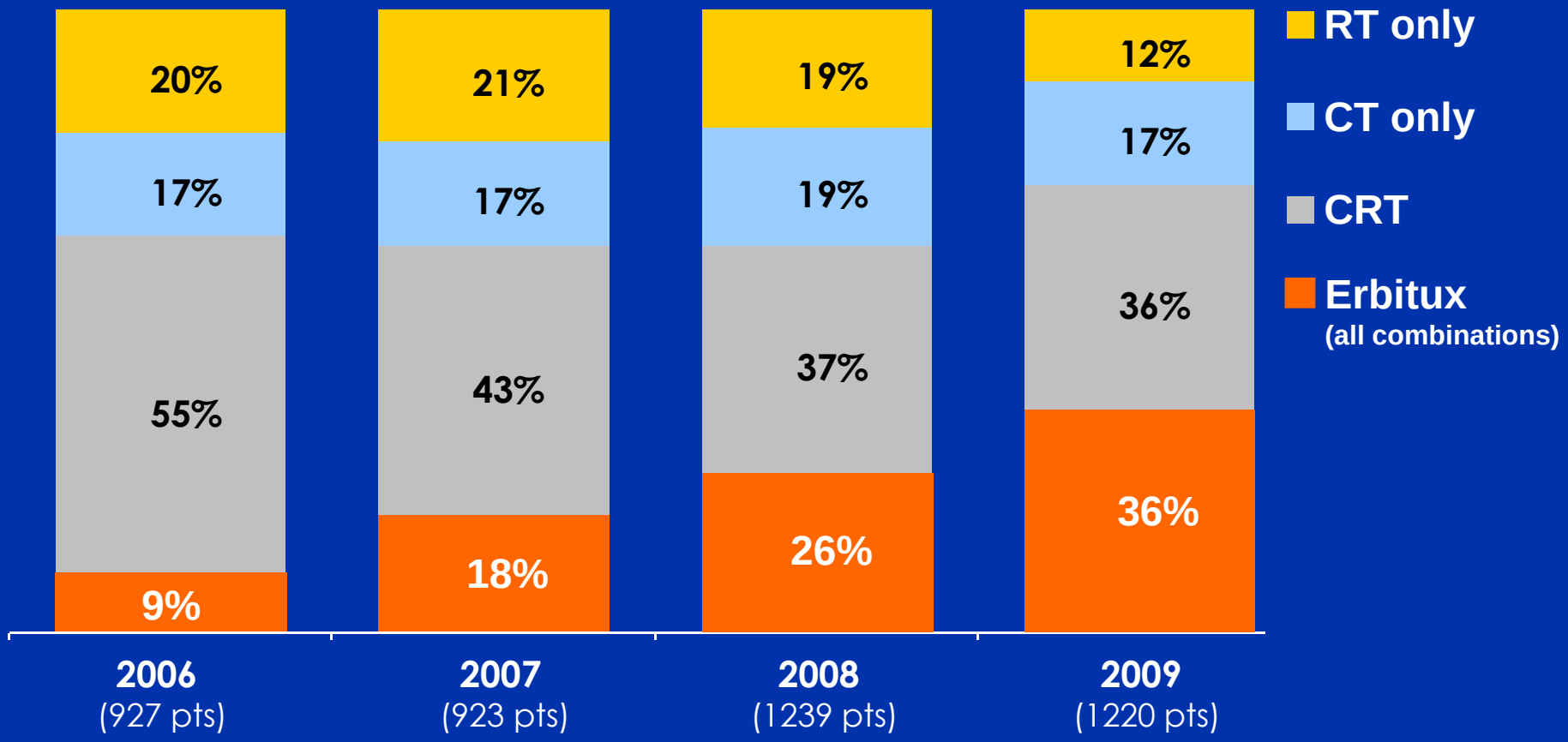
List MA et al Semin. Radiat. Oncol Vol:14, No-2: 2004

RT + Erbitux in locally advanced SCCHN

Patterns of care in locally advanced SCCHN

Treatment patterns in Europe*

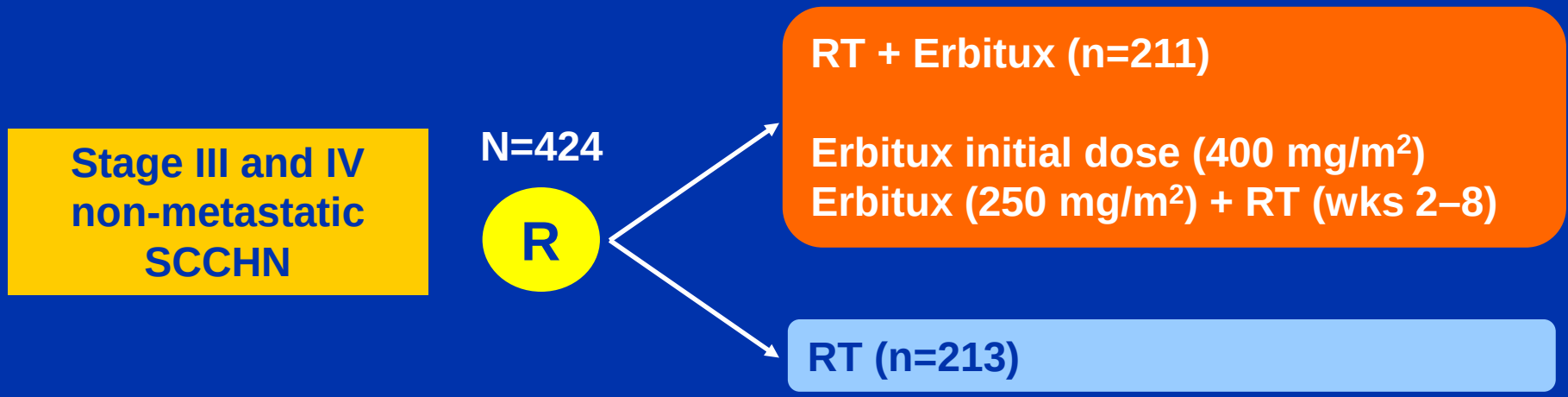
(incl. RT only, excluding surgery)



*Europe: France, Germany, Italy, Spain

Budach et al. ESMO 2010, Abstract No.1033P

Erbitux in locally advanced SCCHN: Bonner Phase III study

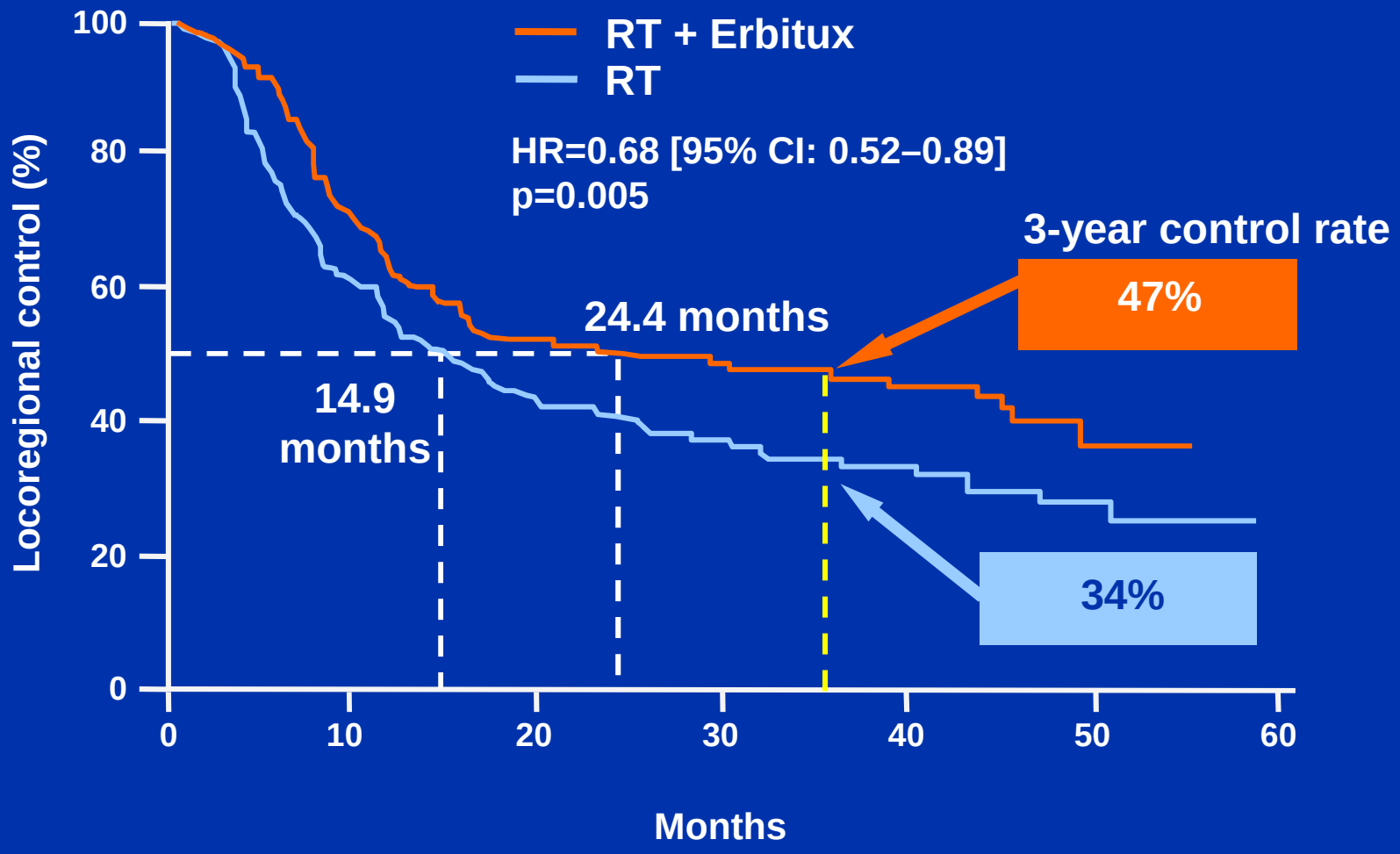


Primary endpoint: duration of locoregional control

Secondary endpoints: OS, PFS, RR, QoL, and safety

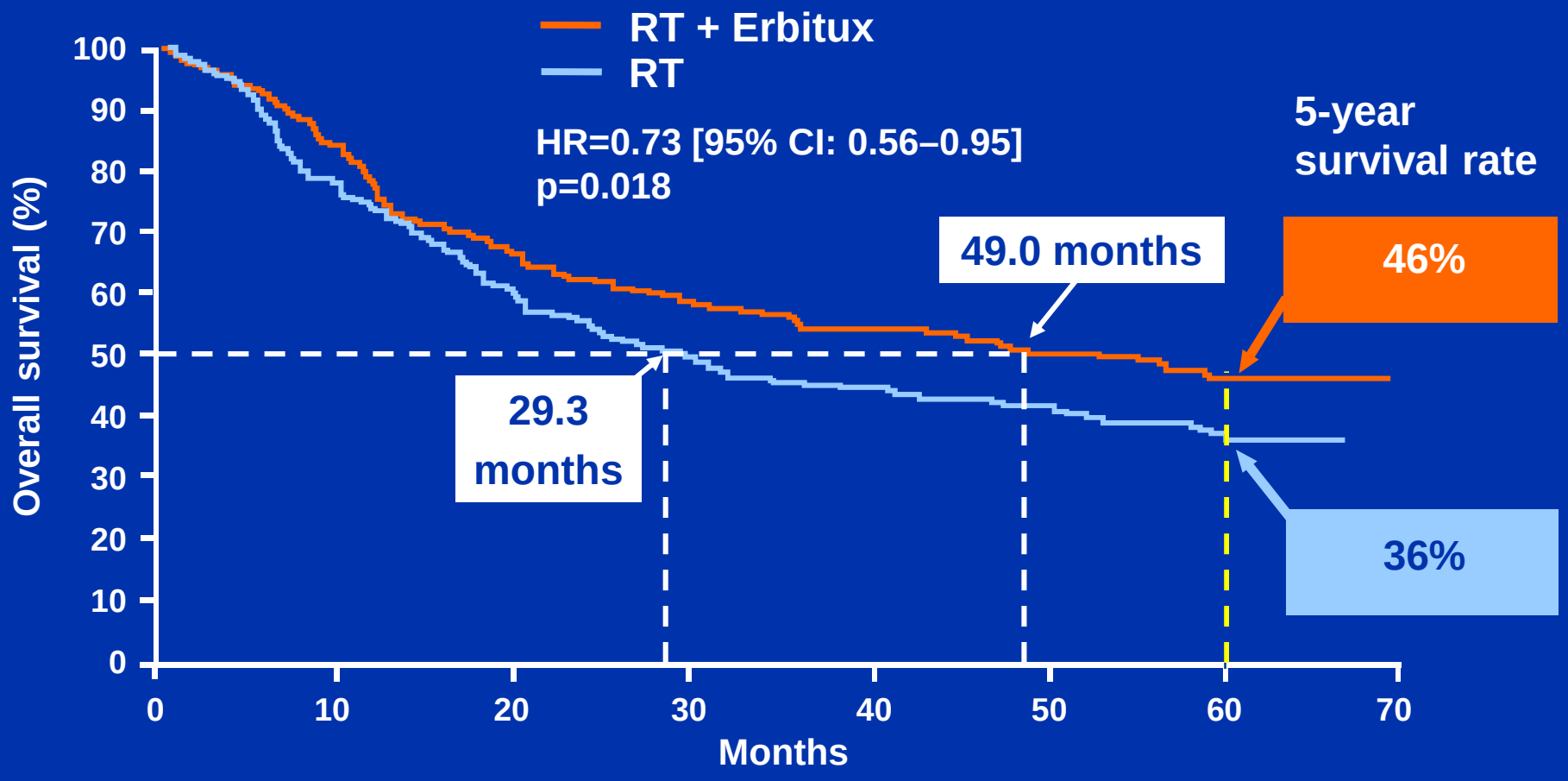
Bonner et al. NEJM 2006

Erbitux in locally advanced SCCHN: Significant benefit in locoregional control



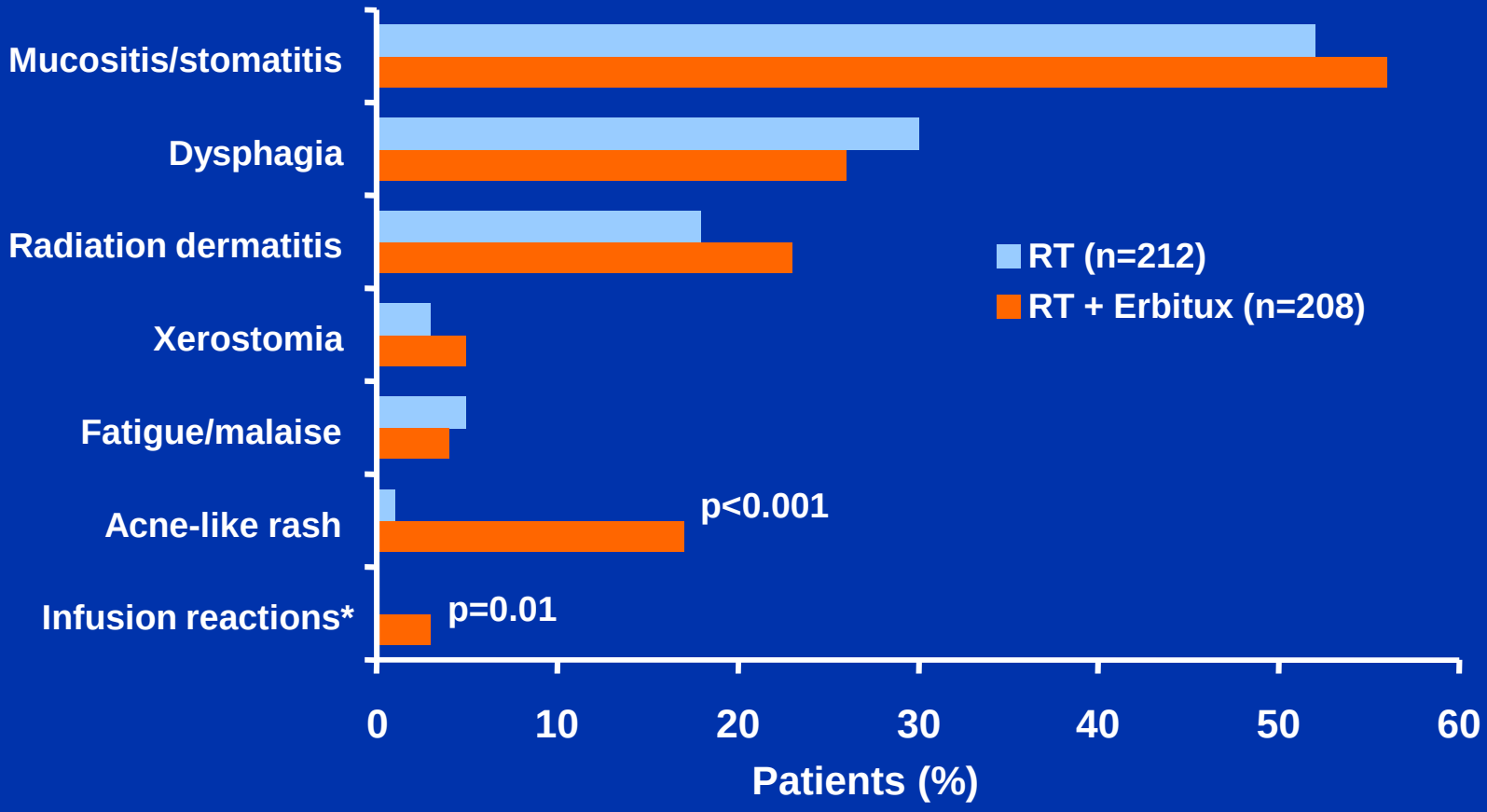
Bonner et al. NEJM 2006

Erbitux in locally advanced SCCHN: 5-year survival update



Bonner et al. Lancet Oncol 2010

RT + Erbitux: Relevant grade ≥3 adverse events

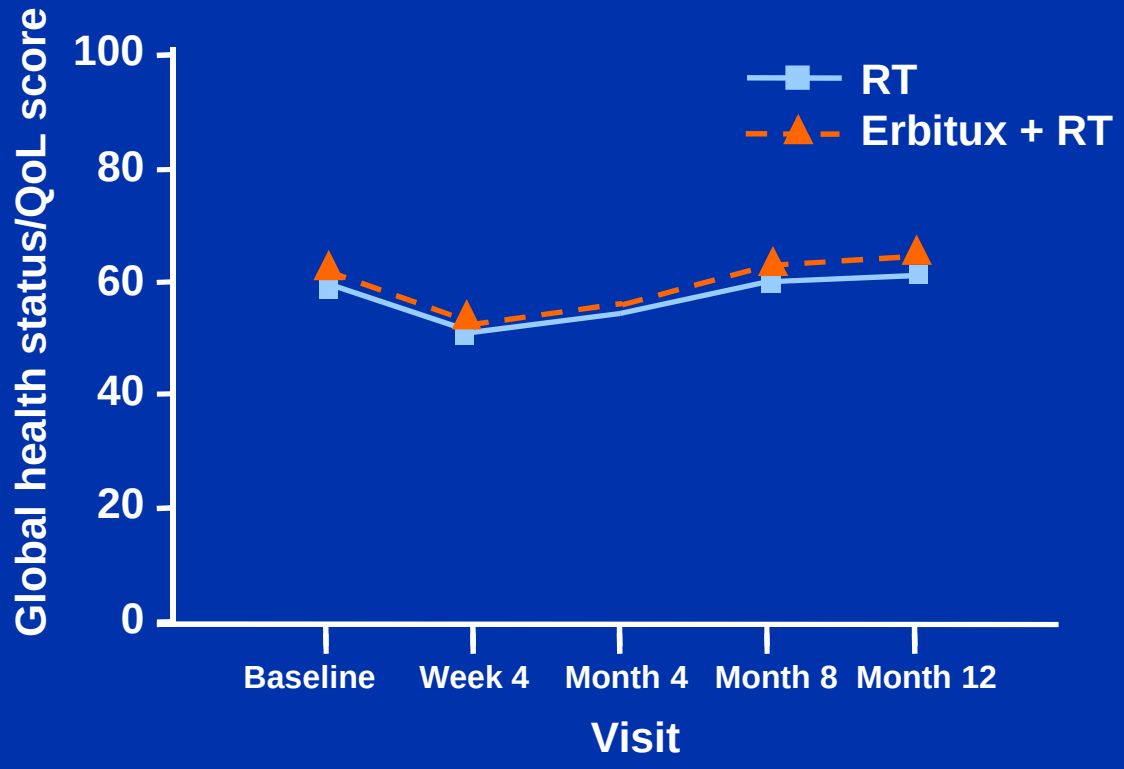


Median duration of any mucositis or dysphagia in the overall population: similar in both treatment groups (12–13 weeks)

*Listed for its relationship to Erbitux

Bonner et al. NEJM 2006

Adding Erbitux to RT increases survival without compromising QoL



QoL: post-baseline scores for the EORTC QLQ-C30

Curran et al. JCO 2007

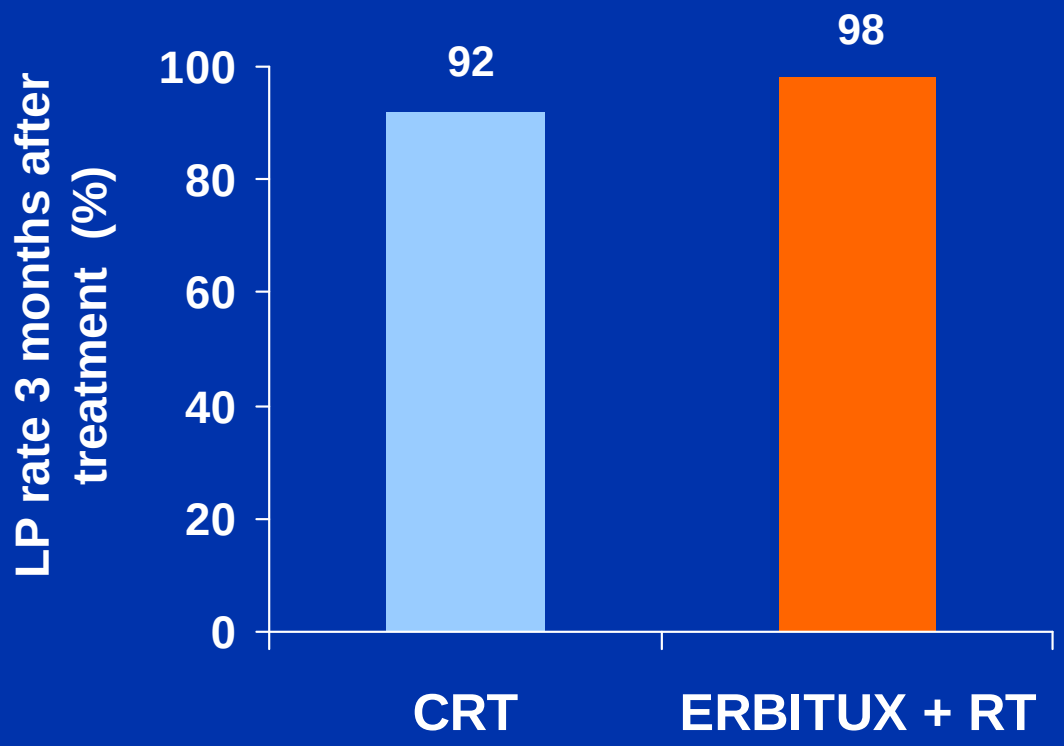
Efficacy: Survival benefit

Rx regimens	HR (95% CI)	Absolute Benefit 5-Year
RT + concurrent CT[1] vs RT alone	0.81 (0.76–0.88)	8%
Cisplatin + 5-FU	0.77 (0.69–0.85)	10%
Cisplatin alone	0.73 (0.56–0.95)	11%
RT + Erbitux vs RT alone[2,3]	0.73 (0.56–0.95)	9%
TPF (vs PF) ➔ RT[4]	0.73 (0.56–0.94)	
TPF (vs PF) ➔ RT + Carboplatin[5]	0.70 (0.54–0.90)	

[1]Pignon et al. Lancet 2000; [2]Bonner et al. NEJM 2006; [3]Bonner et al. Lancet Oncol 2010;
[4]Vermorken et al. NEJM 2007; [5]Posner et al. NEJM 2007

Adding ERBITUX to RT provides similar efficacy to concomitant CRT

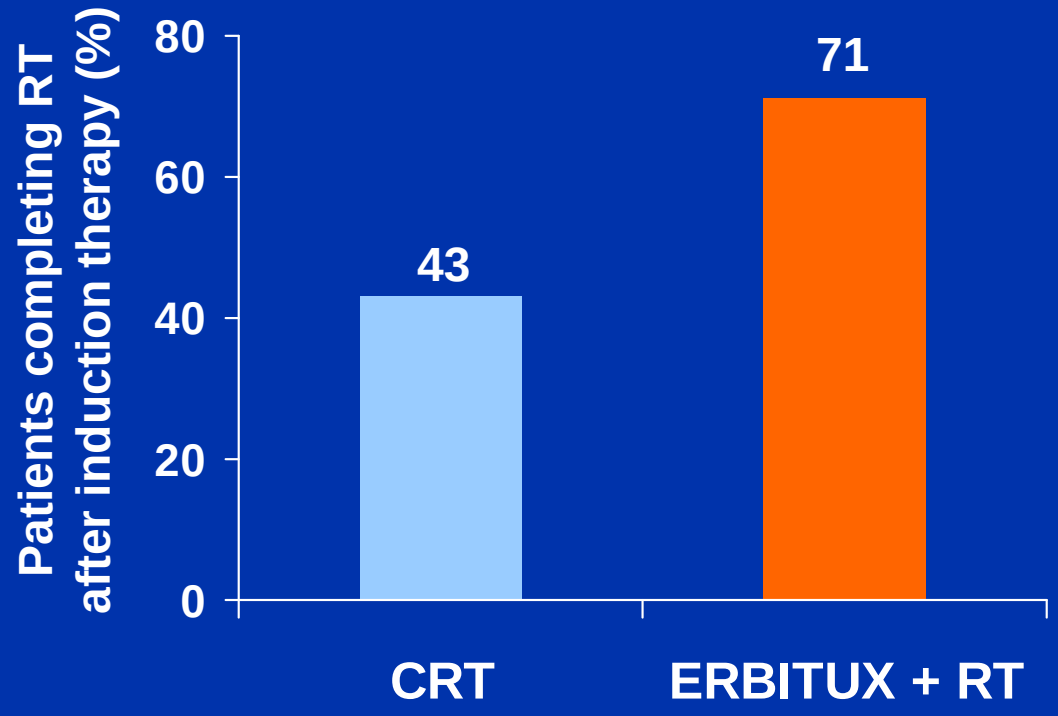
The immediate larynx preservation (LP) rate after TPF followed by ERBITUX + RT is similar to TPF followed by cisplatin + RT



Lefebvre J et al. J Clin Oncol 2009;27(Suppl. 15):Abstract 6010

Combining ERBITUX with RT ensures more patients will be treated as planned

More patients were able to complete their ERBITUX + RT course compared with patients receiving CRT



Lefebvre J et al. J Clin Oncol 2009;27(Suppl. 15):Abstract 6010

Why IMRT In Head & Neck Cancers ?

- Several critical organs in close proximity to the tumor
- Organ motion practically absent
- Patient set up uncertainties manageable
- Conventional radiation is associated with several side effects which can be permanent

IMRT IN HEAD & NECK CANCERS

ADVANTAGES OVER CONVENTIONAL RADIATION

IMPROVED TUMOUR DOSE

- Dose constraints on tumor reduced due to **sharp fall** of dose
- **Higher dose** of radiation can be delivered to the tumor due to better protection of critical organs like spinal cord, eye, optic nerve etc.

IMRT IN HEAD & NECK CANCERS

REDUCTION OF NORMAL TISSUES TOXICITY

TISSUES WITH TANGIBLE GAINS

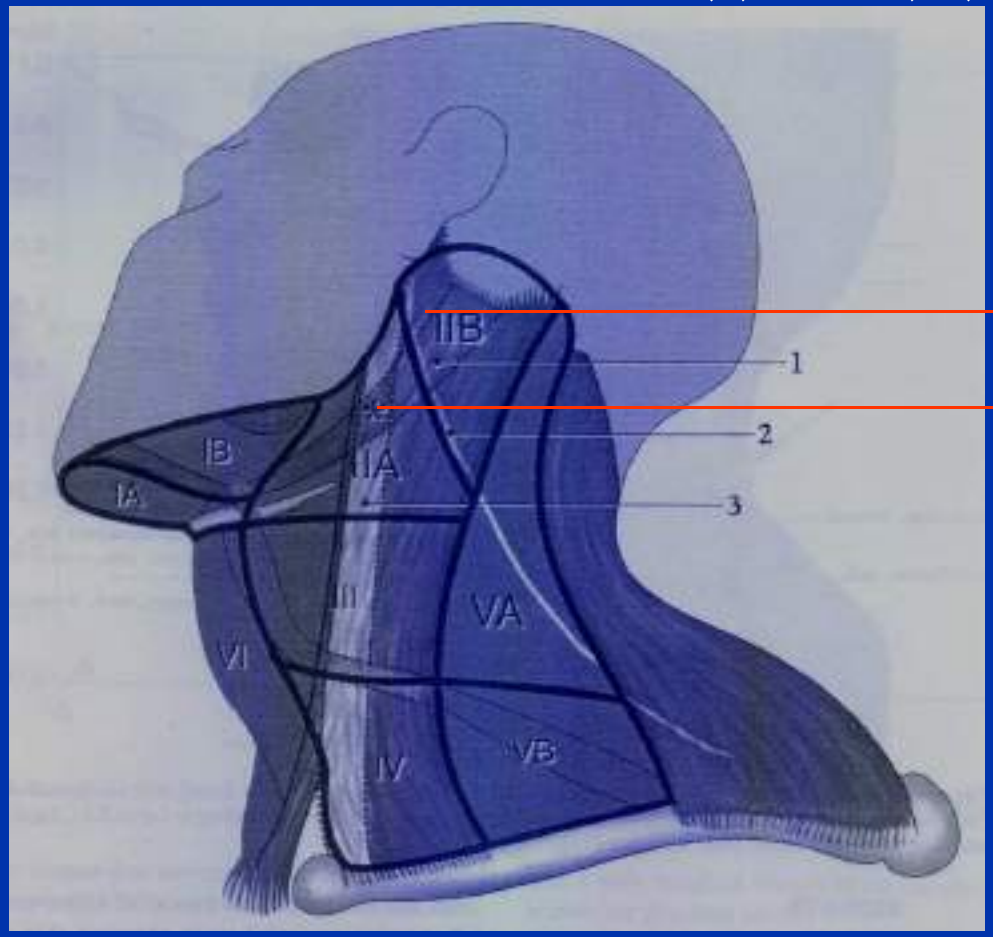
1. Sparing of parotids glands avoiding xerostomia and dental caries
2. Mandible
3. Pharyngeal mucosa & musculature
4. Inner & middle ear
5. Temporal mandibular joints
6. Temporal brain lobes
7. Optic pathways

Concurrent RT + CT in Oral Cancers

- **Critical Issues in Radiation Planning:**
  - **Identify Preoperative Tumor Extension with clinical and Radiological correlation.**
  - **Identify high risk areas – Bone Invasion, location of positive nodes and ECE for SIB if feasible.**
  - **Trace Cranial Nerves in Adenoid Cystic Carcinoma or Extensive PNI upto base of skull.**

Contralateral Neck – Level II classical – where Post belly of diagastric muscle is crossed by IJV

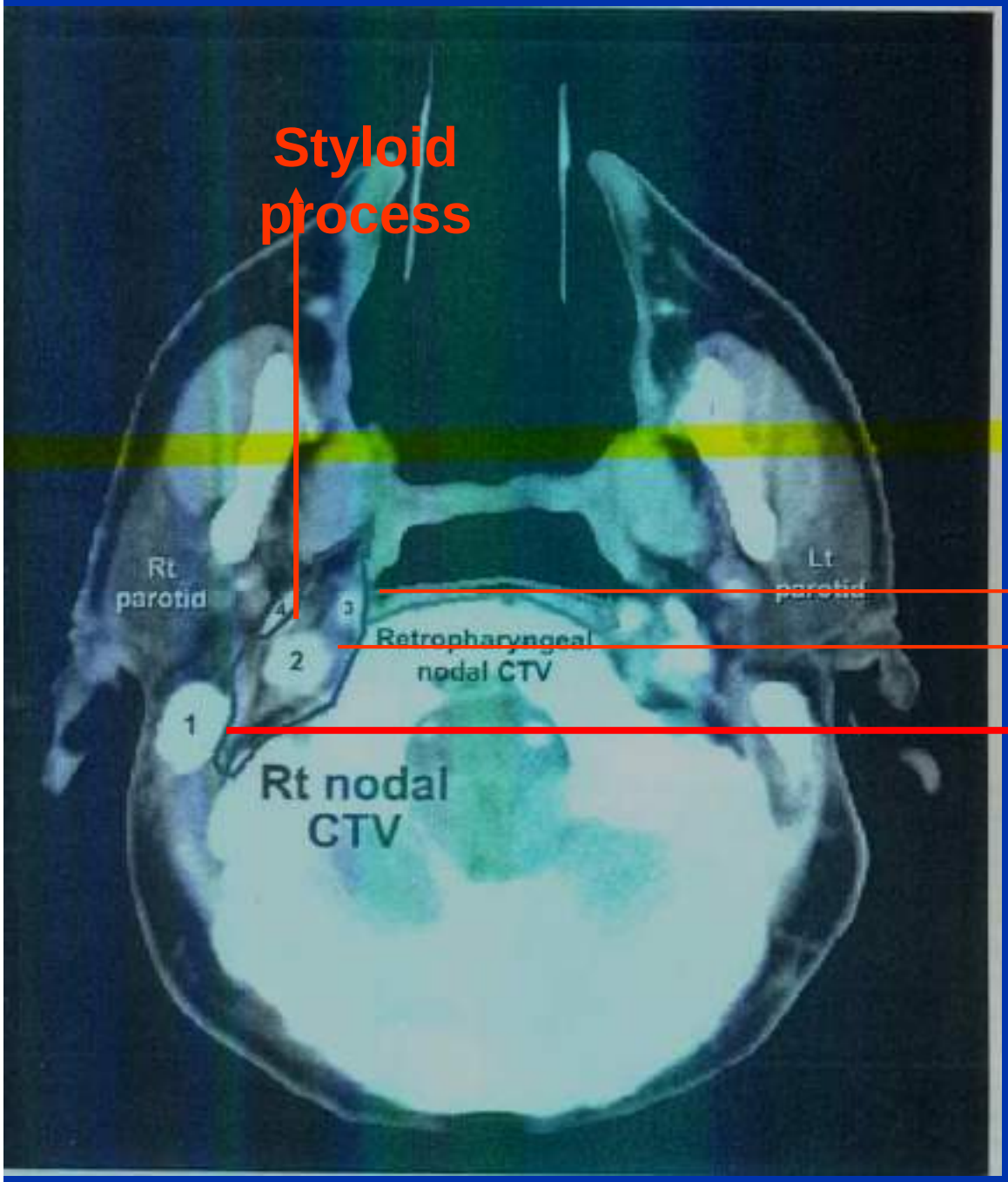
(* Eisbruch et al IJROBP 2004; 59(1): 28-42), (* Dawson et al)



Cranial extent of high risk neck

Diagastric Ms crossing IJV (Cranial extent of low risk neck)

HIGH RISK NECK



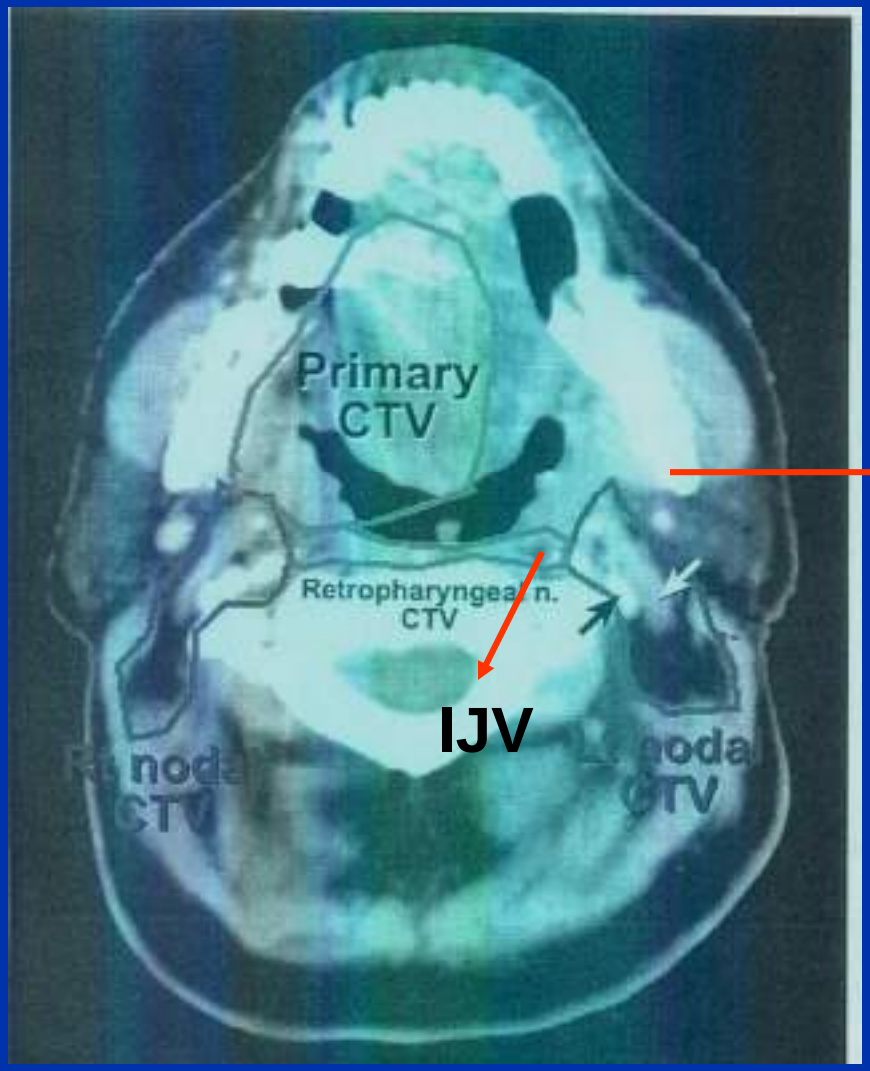
Superior most axial CT image at which level II nodal target delineated in side of neck Ipsilateral to primary tumor in post - styloid region.

Carotid artery

Internal jugular veins

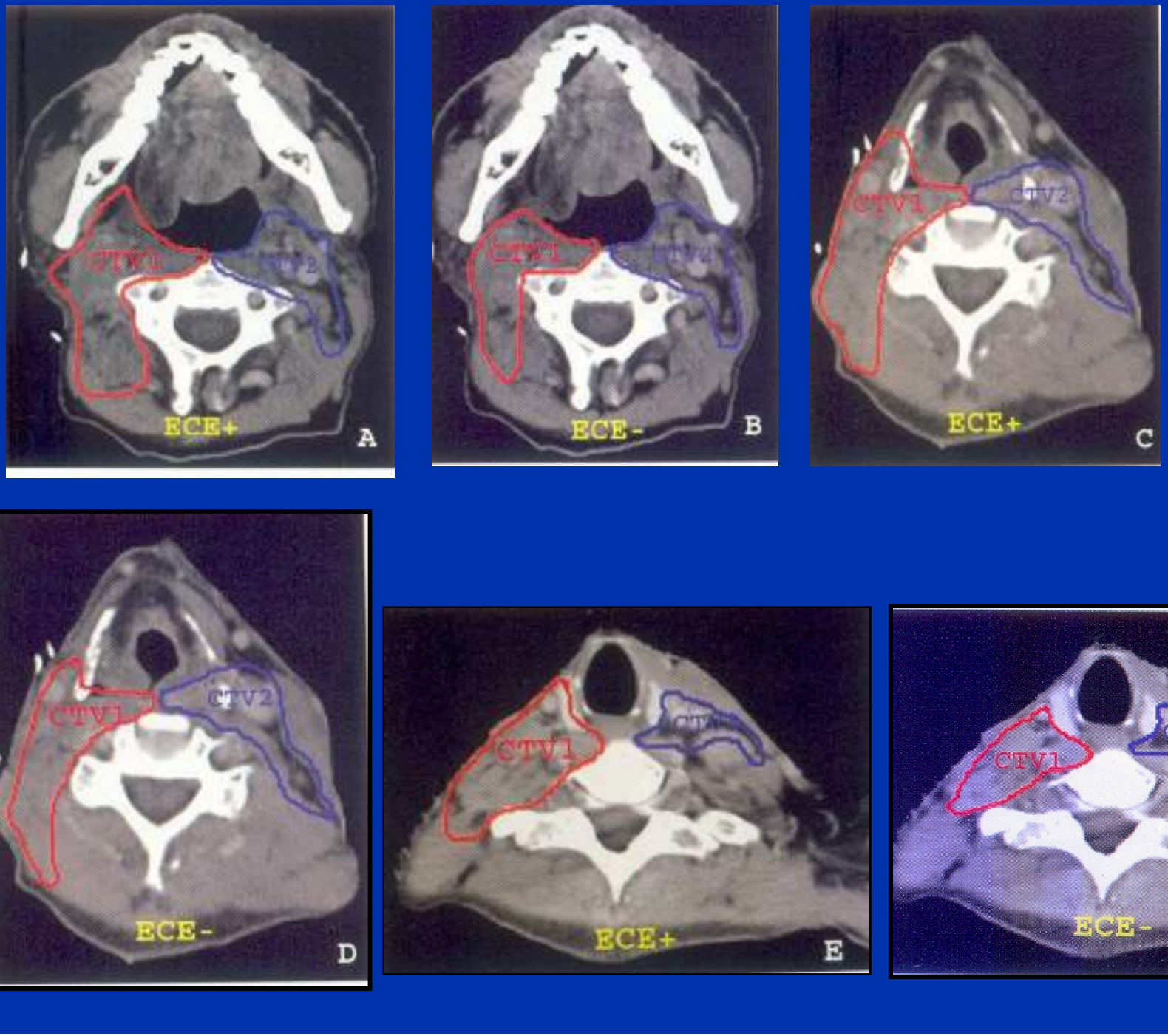
Tip of Mastoid

LOW RISK NECK

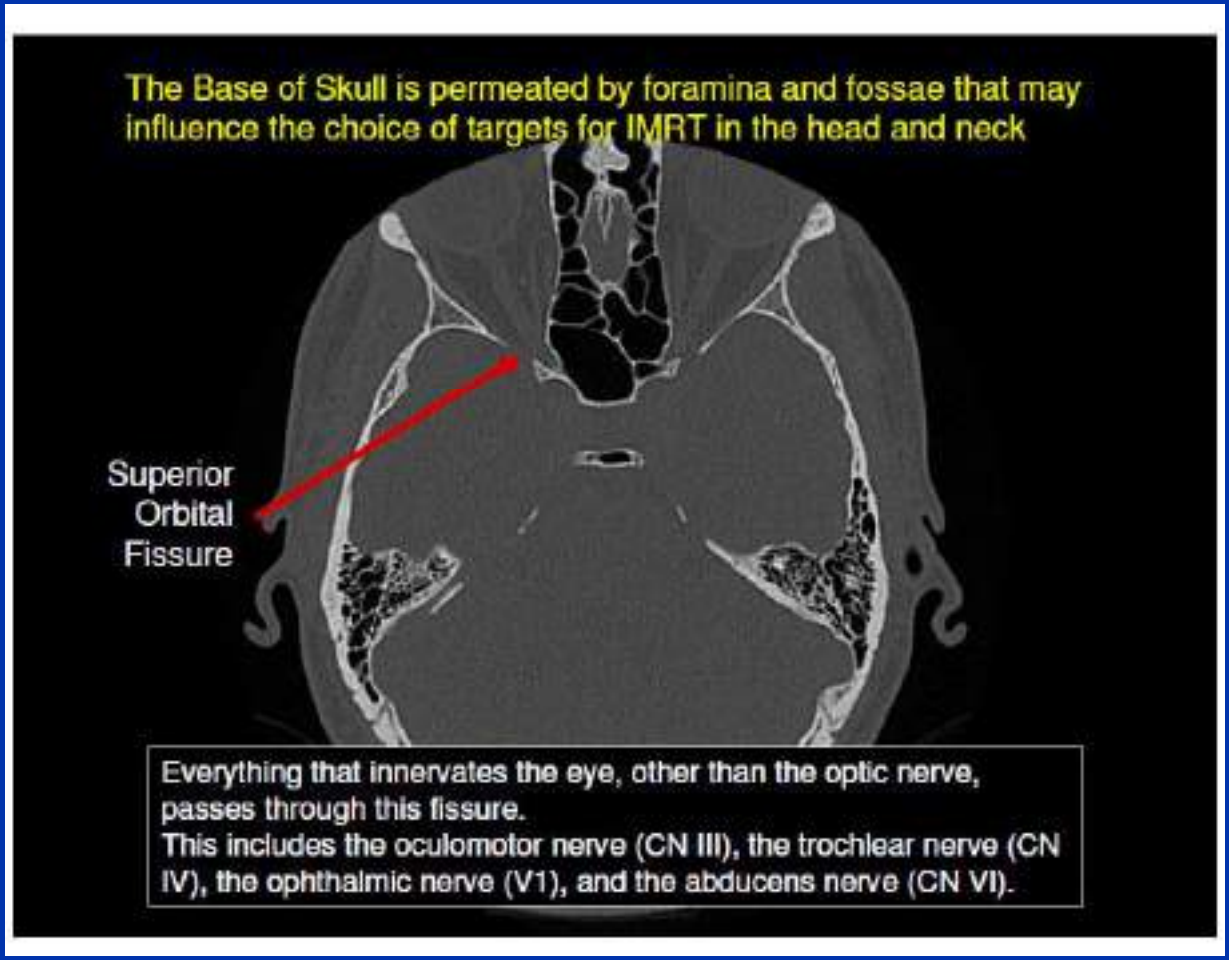


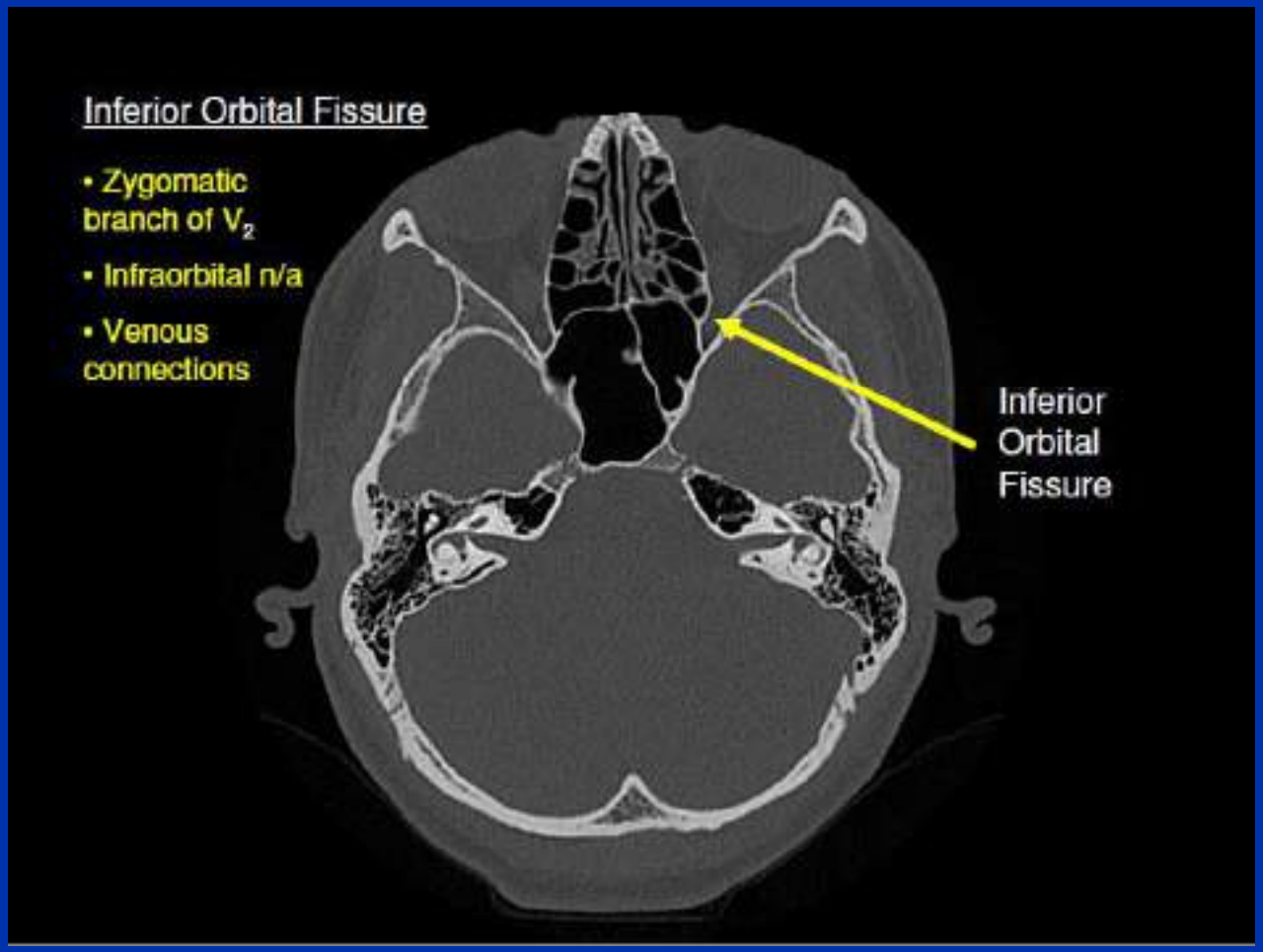
Superior most axial CT image at which level II nodal target delineated in side of neck contralateral to primary tumor.

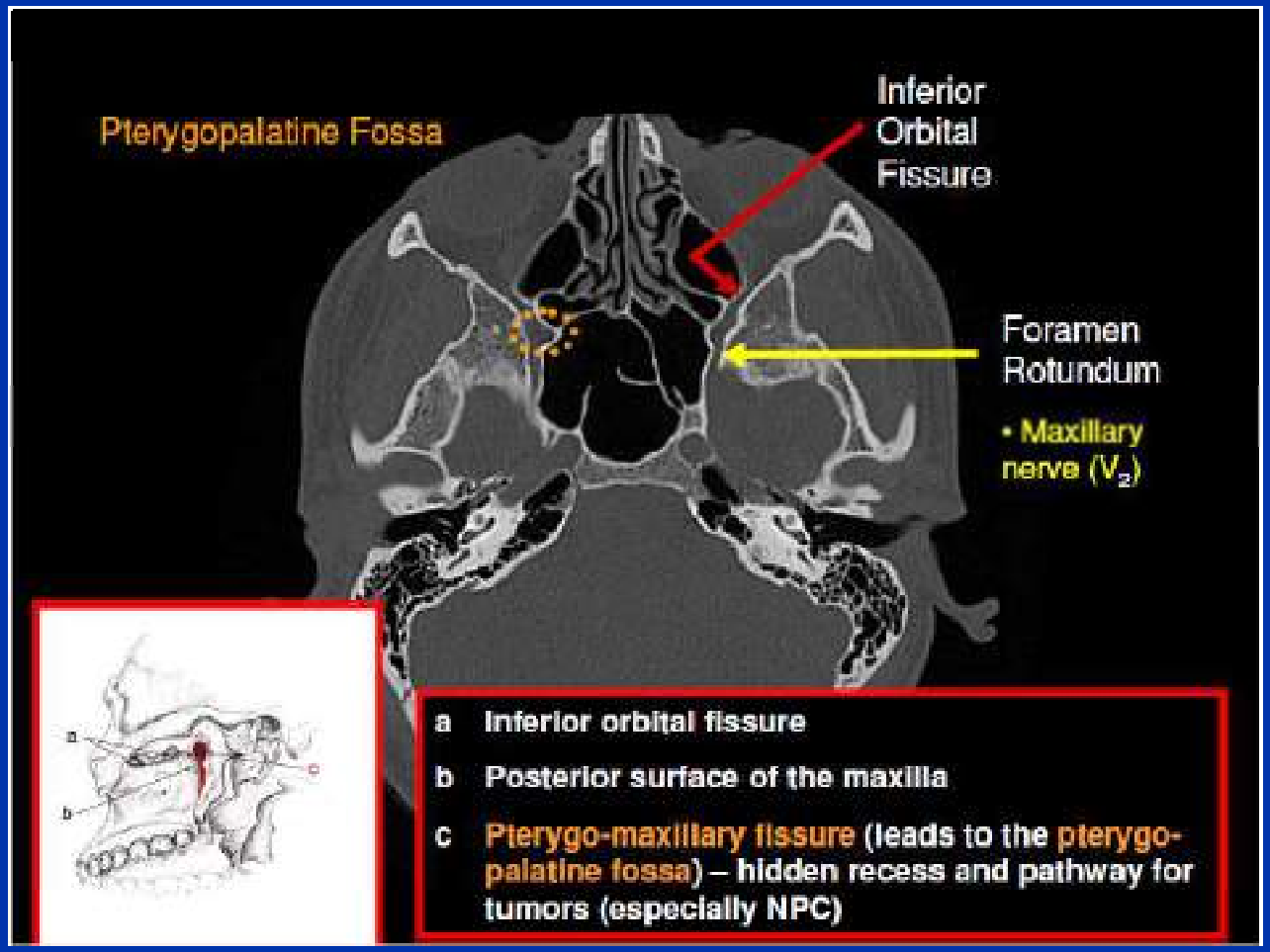
Diagastric Ms crossing IJV (Cranial extent of low risk neck)


CTV1
CTV2
ECE+
A
CTV1
CTV2
ECE-
B
CTV1
CTV2
ECE+
C
CTV1
CTV2
ECE-
D
CTV1
ECE+
E
CTV1
CTV2
ECE-
F

Knowledge of Radiological Anatomy needs to be enhanced



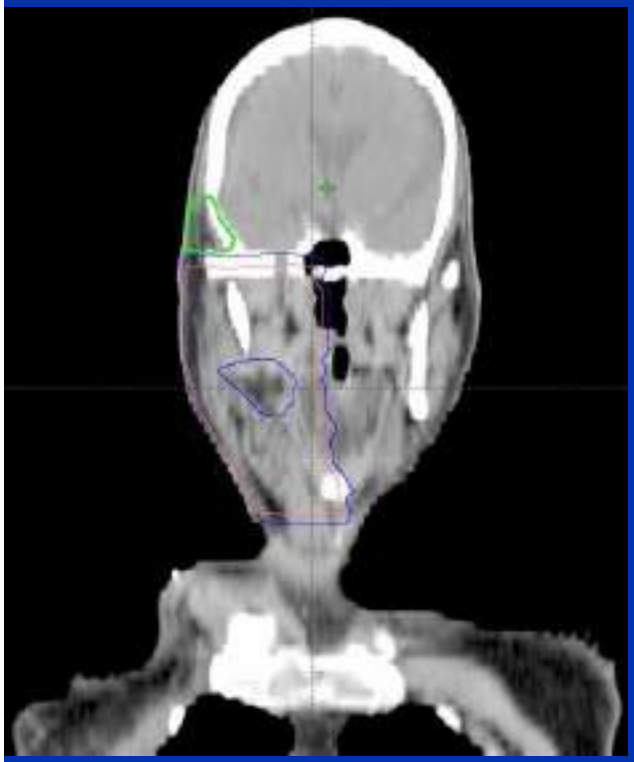

Inferior Orbital Fissure
• Zygomatic branch of V_2
• Infraorbital n/a
• Venous connections
Inferior Orbital Fissure

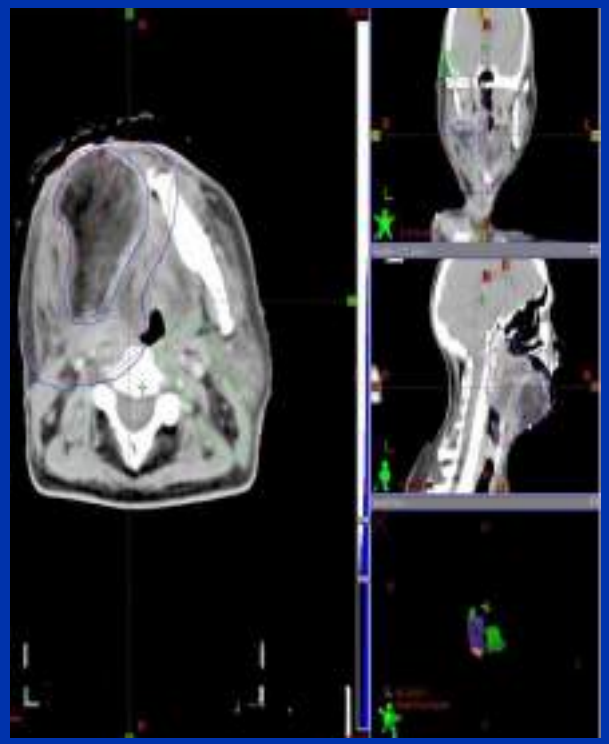

Pterygopalatine Fossa
Inferior Orbital Fissure
Foramen Rotundum
• Maxillary nerve (V_2)
a
b
c
a Inferior orbital fissure
b Posterior surface of the maxilla
c Pterygo-maxillary fissure (leads to the pterygo-palatine fossa) – hidden recess and pathway for tumors (especially NPC)

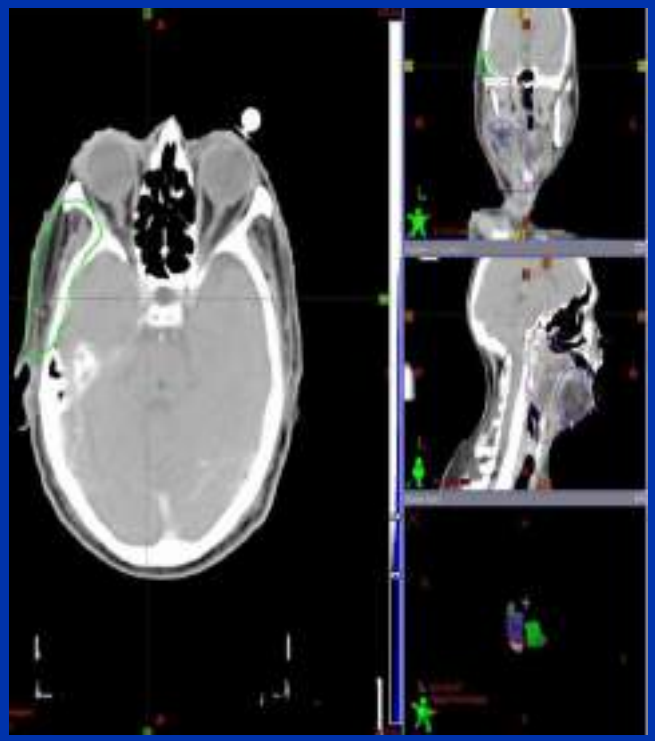
- **Buccal Mucosa – Inclusion of ITF (Infratemporal fossa) in upper alveolus RMT lesions.**

Ca Right Buccal Mucosa (recurrent), T4N0M0-Infratemporal fossa inclusion

Pt. name – S.J., Age – 54/F, Reg. No. – SKDD. 392184

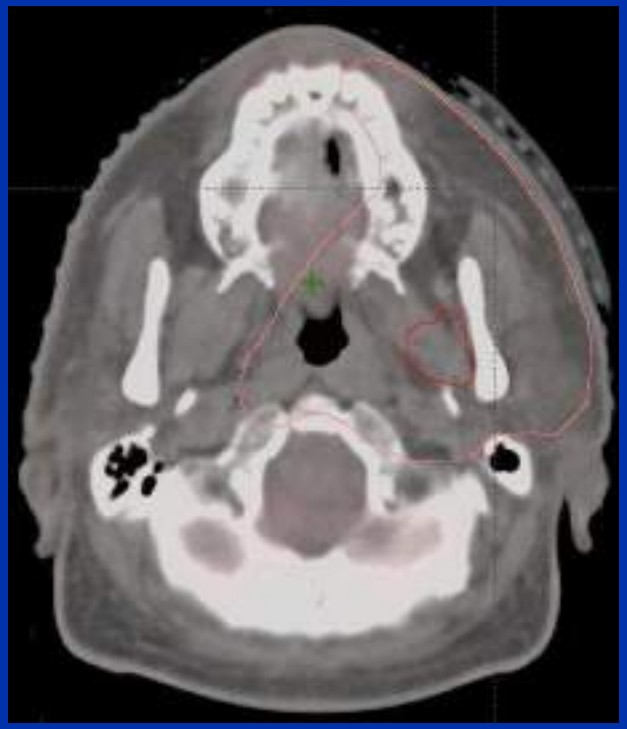


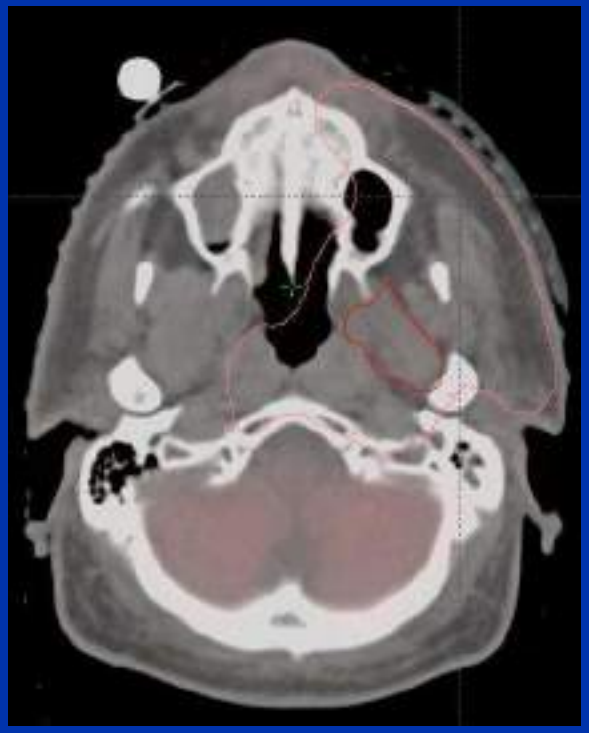


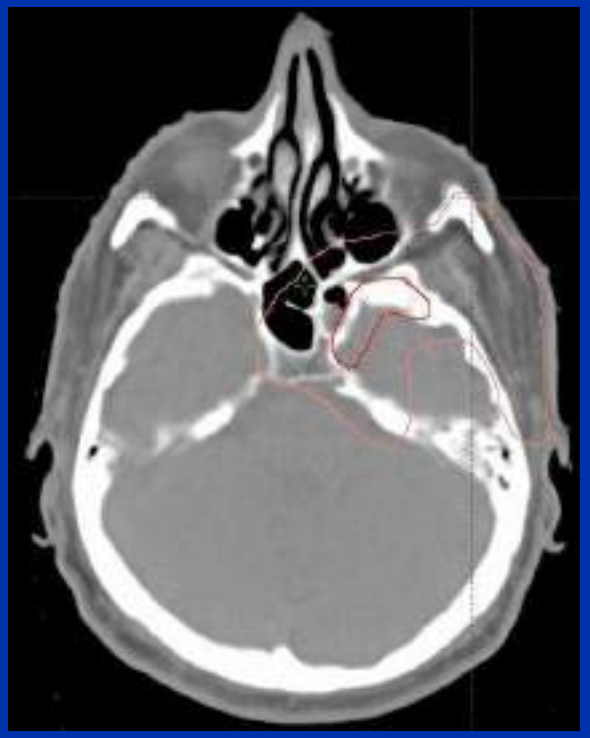


Ca upper alveolus with Extensive PNI & Cranial Ns involv.

Pt. name – A.P., Age – 54/M, Reg. No. – SKDD. 335034

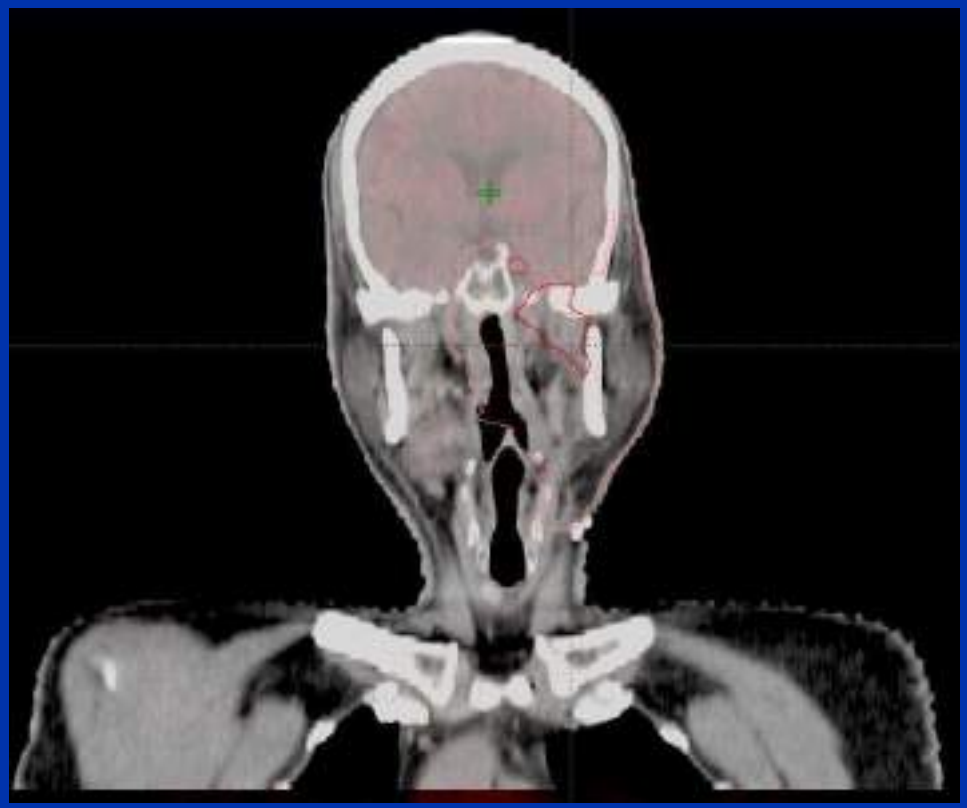


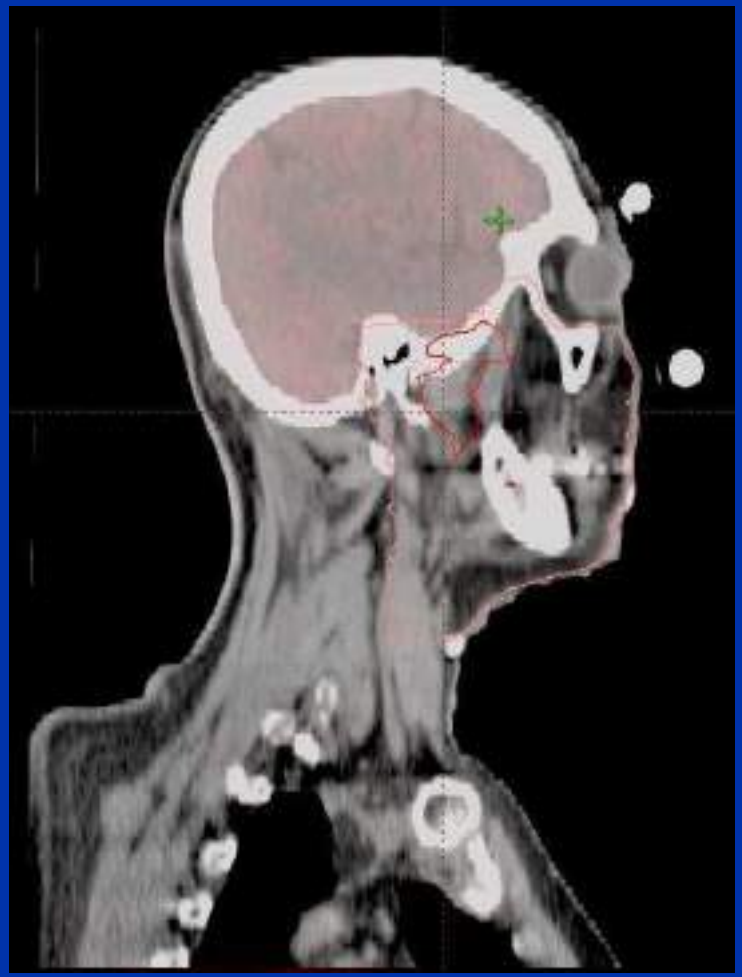




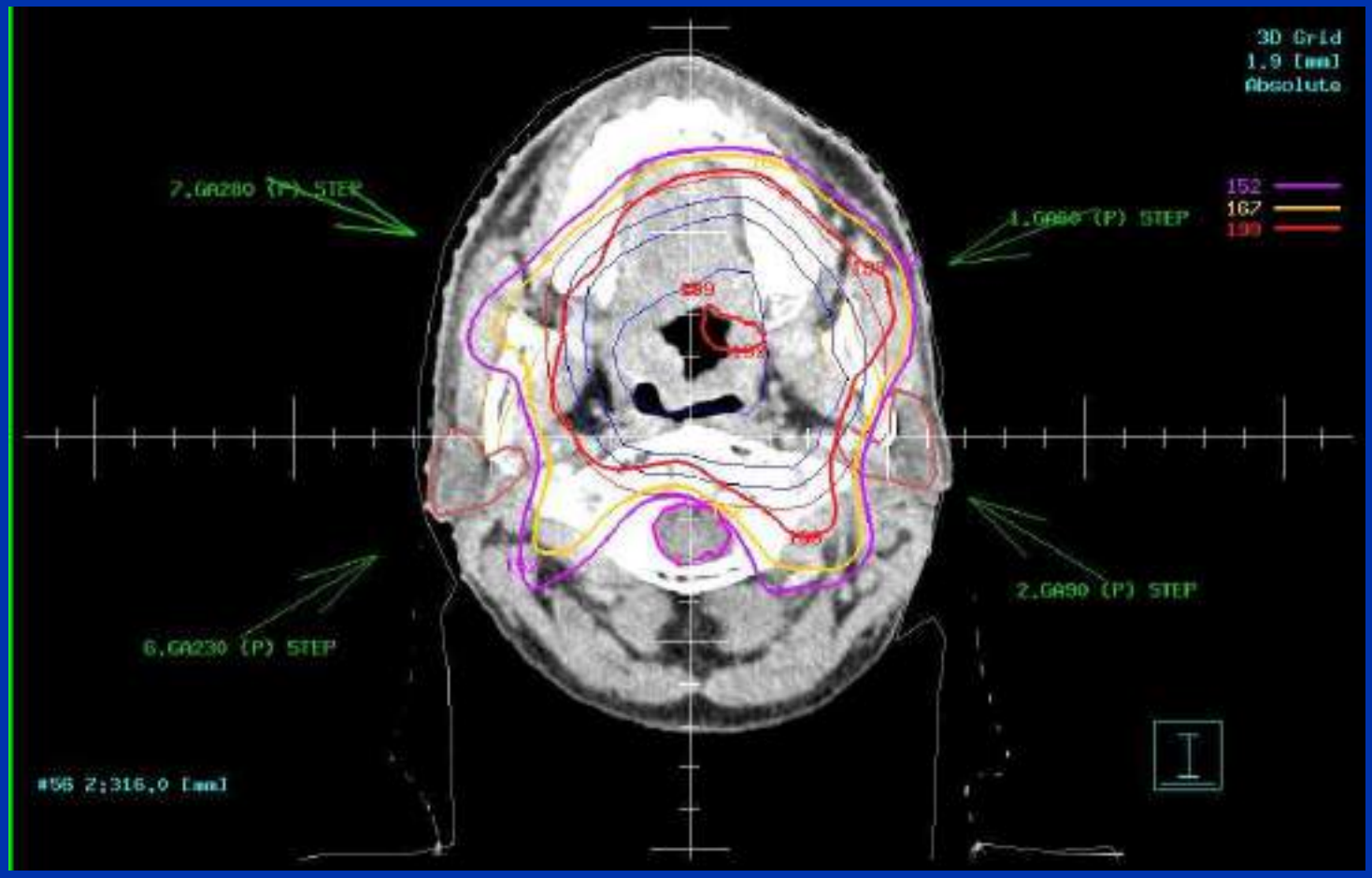
Ca upper alveolus with Extensive PNI & Cranial Nerves involv –Target Delineation

Pt. name – A.P., Age – 54/M, Reg. No. – SKDD. 335034



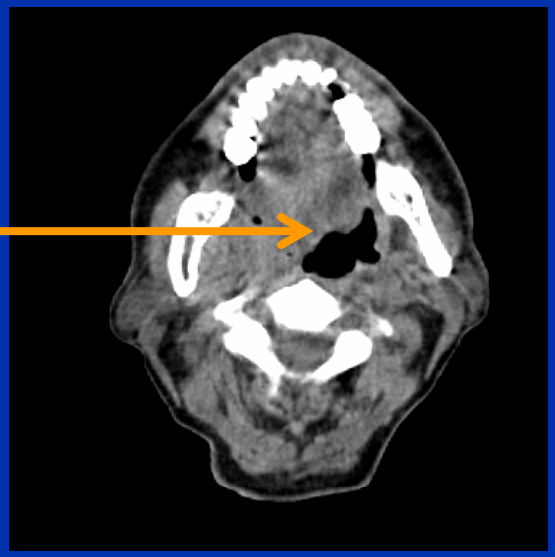


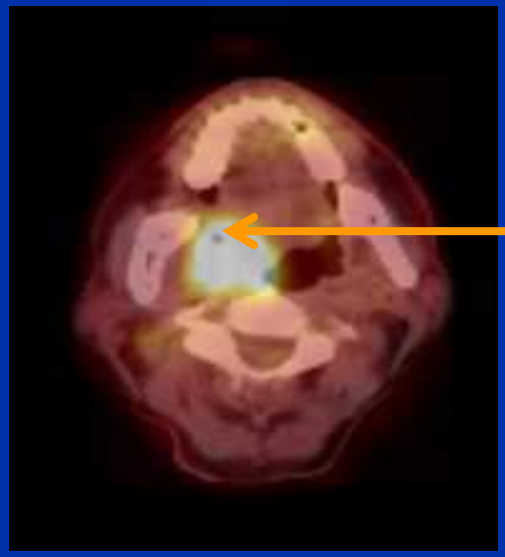
CA TONSIL TREATED WITH IMRT – PAROTID SPARING



Ca Oropharynx – FDG avid tumor at Primary site and Metastatic Lymphnode. Target volume with CT-PET fusion

ill defined Primary Tumor definition

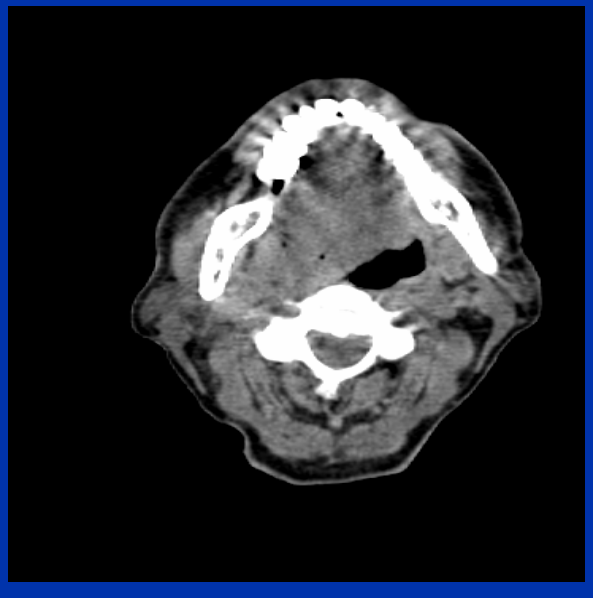


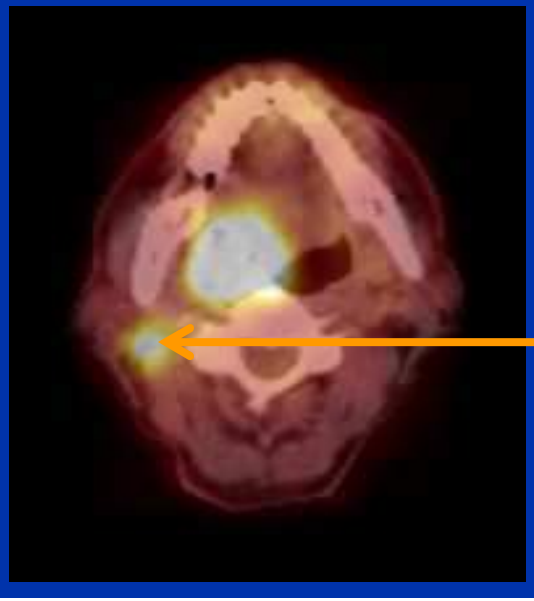


Well defined Primary Tumor definition

CECT

CT-PET Fusion



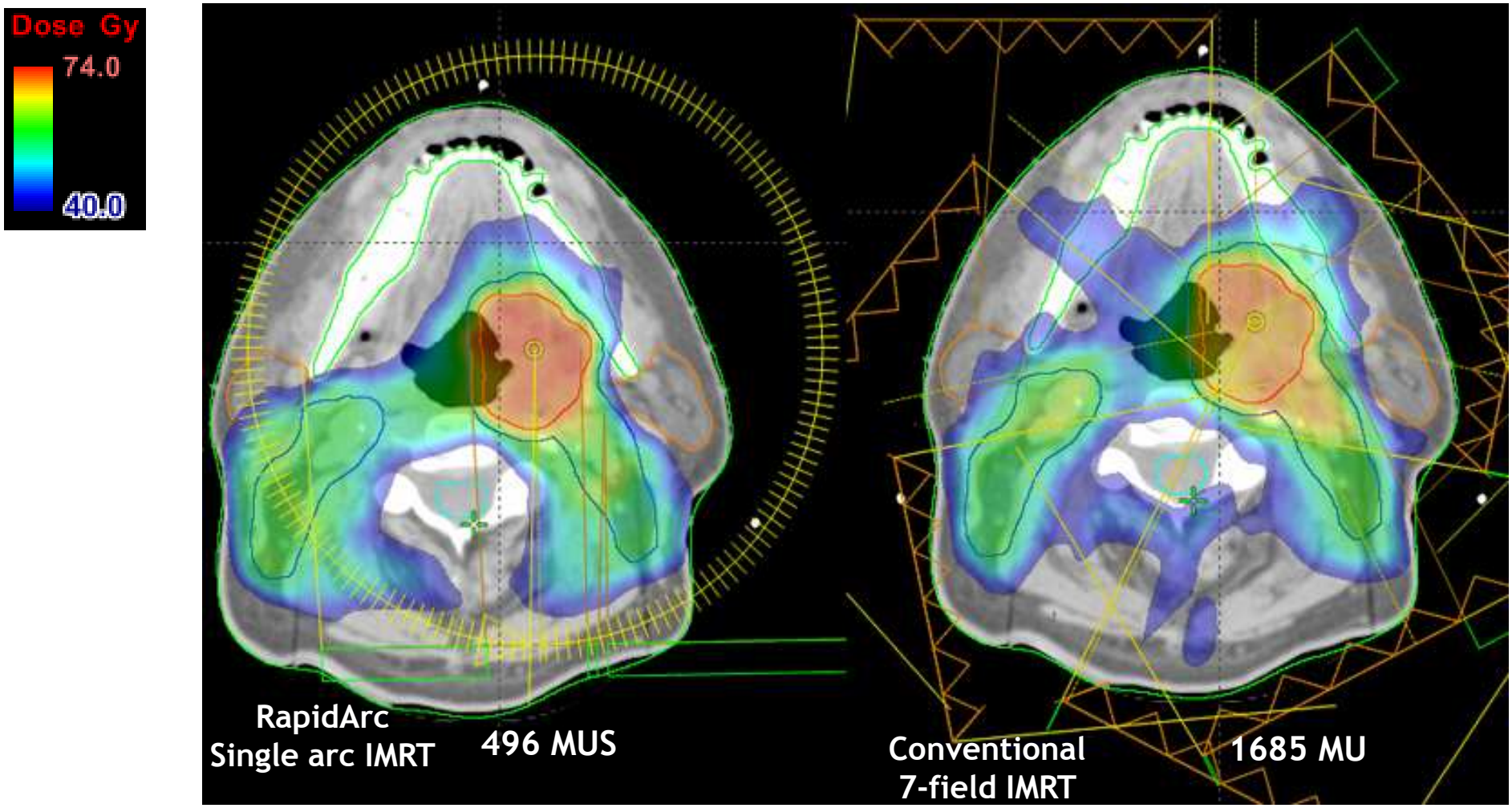


Well defined Lymphnode showing metastasis

Rapid Arc™ Objectives

- Single arc IMRT
- IMRT quality
  - Uniform target coverage
  - Improved normal tissue sparing
- Treat in 2 minutes or less
  - Highly efficient
  - Low peripheral dose
- Simple planning and delivery

Rapid Arc - IMRT Quality



IMRT IN HEAD AND NECK CANCERS

RESULTS: **Conventional Radiation** **best results with Conventional Radiation reported in RTOG 9003 STUDY – On Locally Advanced Head & Neck Cancers 2 Years Loco Regional Control - 54.5%**

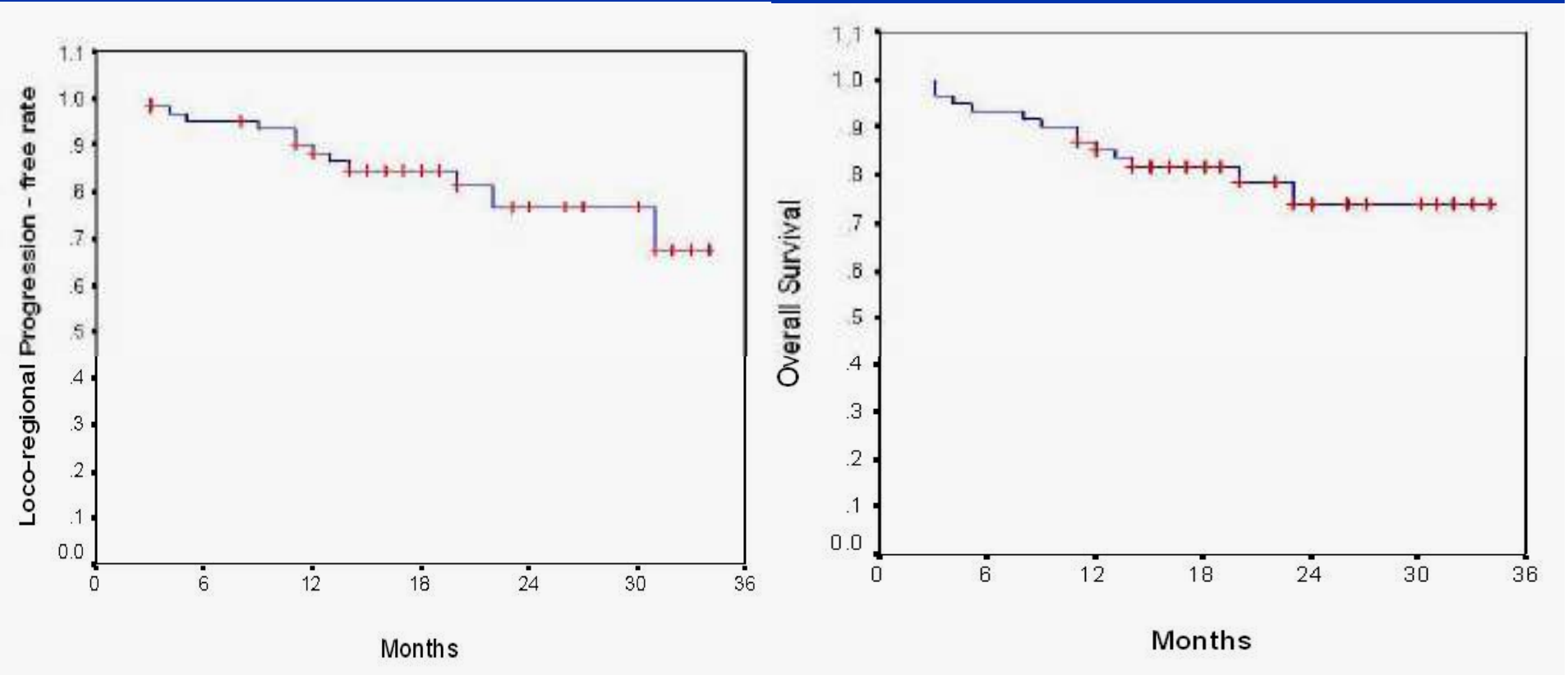
IMRT

	Patient No.	Sites	Median Follow-up (Months)	Local-Regional Control
Lee et al	67	Nasopharynx	31	97% (4yr)
Chao et al	126	Head & Neck	26	85% (2yr)
Yau et al	60	Head & Neck	17.5	87% (1yr)
Dawson et al	58	Head & Neck	27	79% (2yr)
Anand et al	62	Head & Neck	19	77% (2yr)

Table 1: Patient Characteristics (n =62)

1	Age - Median – 56yrs, Range – 27 – 85yrs	
2	Sex - Male – 48, Female – 14 [Ratio 3.4:1]	
3	Site	Number (%)
	Ca - Nasopharynx	15 (24.1)
	Ca – Larynx	13 (20.9)
	Ca – Oropharynx	10 (16.1)
	Ca – Tongue (ant 2/3rd)	09 (14.5)
	Ca – Hypopharynx	08 (12.9)
	Ca – Alveolus	04 (6.4)
	Ca – Paranasal sinus	03 (5)
4	Histology	
	Squamous Cell Ca	55 (88.7)
	Adenoid cystic Ca	04 (6.4)
	Mucoepidemoid Ca	02 (3.2)
	Adenocarcinoma	01 (1.6)
5	Stage	
	Stage I	04 (6.4)
	Stage II	10 (16.1)
	Stage III	17 (27.4)
	Stage IV A	24 (38.7)
	Stage IV B	07 (11.2)
6	Mode of Treatment	
	Definitive IMRT Only	16 (25.8)
	IMRT + Concurrent Chemotherapy	29 (46.7)
	Post-operative IMRT	17 (27.4)

IMRT +/- Chemotherapy Experience (n=62)



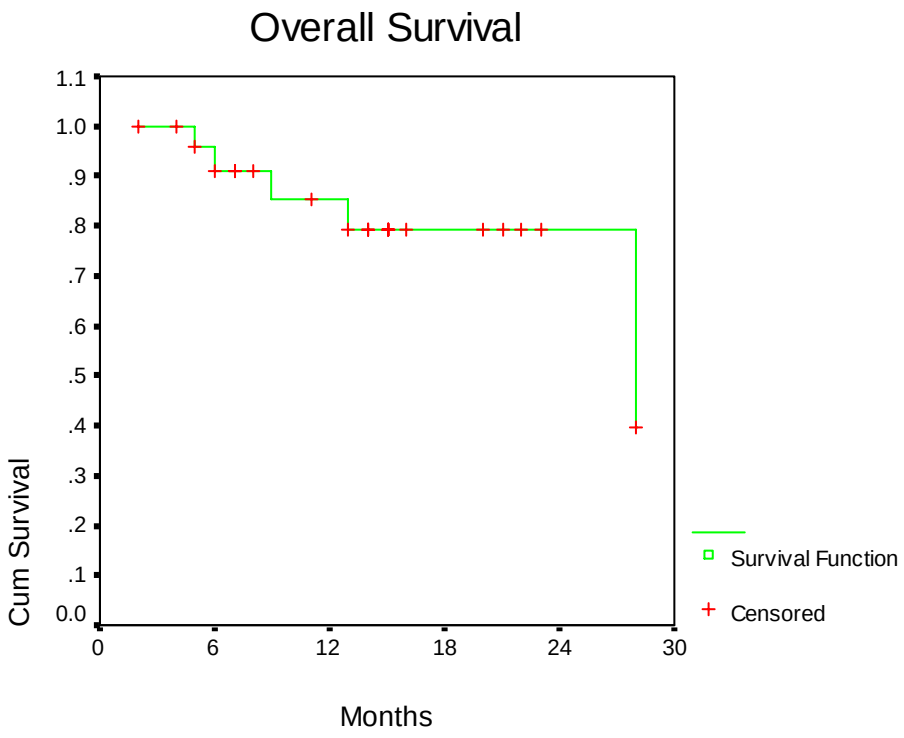
Kaplan Meier estimate of Loco-regional control (A) and Overall survival (B)

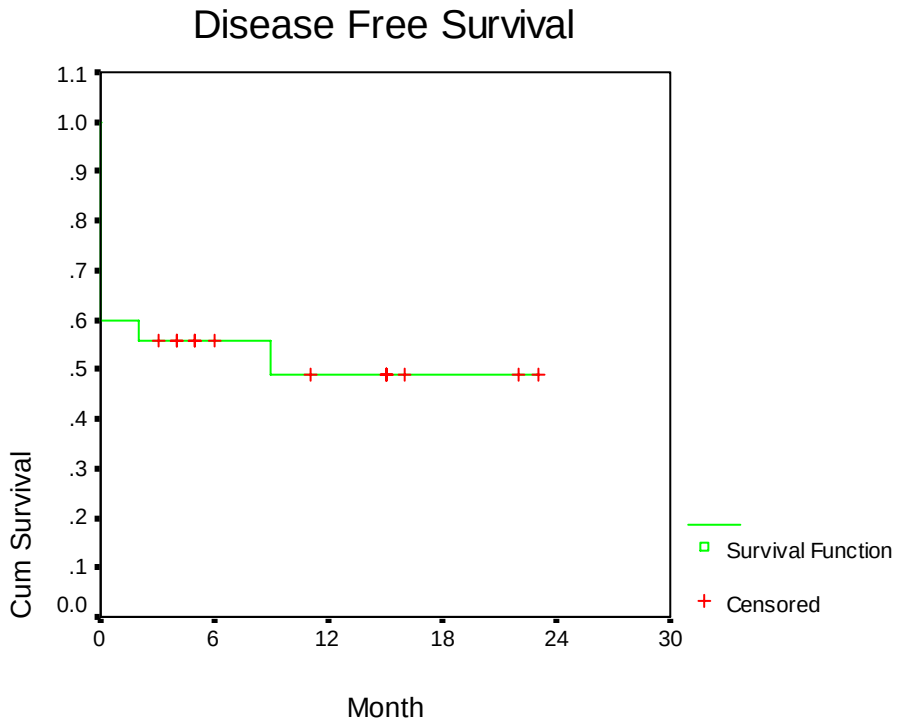
Anand et.al, **British Journal of Radiology (2008) 81,** 865-871

Table 4. Acute toxicity of intensity-modulated radiotherapy ($n=62$)

	Number (%)
Mucositis	
Grade I	2 (3.22)
Grade II	27 (43.54)
Grade III	33 (53.22)
Skin reactions	
Grade I	0 (0.00)
Grade II	8 (12.90)
Grade III	2 (3.22)
Radiation interruption	13 (20.9)
Enteral tube feeding	22 (35.48)
Intravenous fluids (day care/hospitalization)	27 (43.54)
Ototoxicity	
Otitis media	3 (4.83)
Hearing loss (unilateral)	1 (1.61)
Anaemia	
Grade I	3 (4.83)
Grade II	2 (3.22)
Grade III	0 (0)
Neutropenia	
Grade I	5 (8.06)
Grade II	4 (6.45)
Grade III	4 (6.45)
Thrombocytopenia	
Grade I	2 (3.22)
Grade II	1 (1.61)
Grade III	1 (1.61)

Anand et.al, **British Journal of Radiology (2008) 81,** 865-871





Overall Survival of RT + Erb ± Cisplat.

Disease Free Survival of RT + Erb. ± Cisplat.

IMRT IN HEAD AND NECK CANCERS

Impact on mucositis

- There is no reduction in the severity of mucositis with IMRT. Mucositis is usually exaggerated in the area of SIB to the primary site.

- Upto 40% of patients need PEG insertion in patients treated with IMRT + Concurrent CT

Int. J. Radiation Oncology Biol. Phys., Vol. 72, No. 2, pp. 375–382, 2008

0360-3016/08/$–see front matter

doi:10.1016/j.ijrobp.2007.12.033

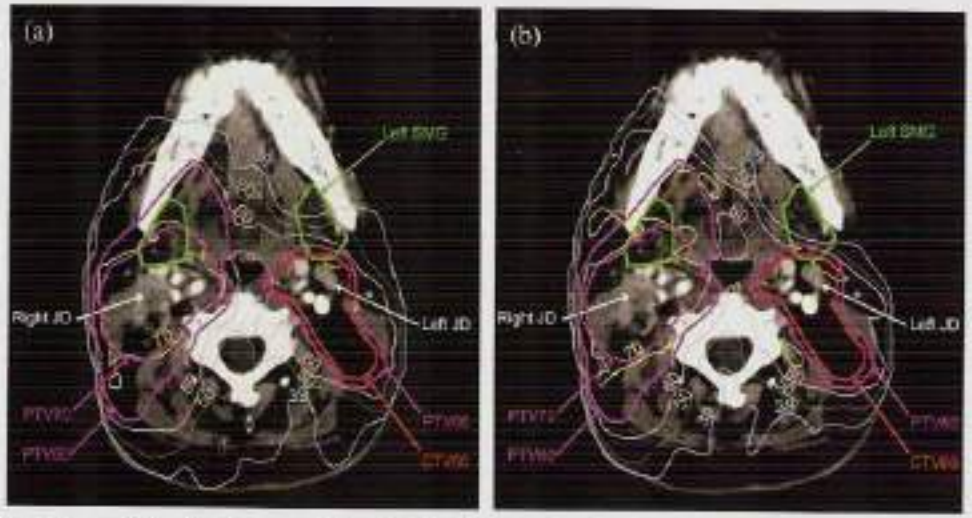
CLINICAL INVESTIGATION — Head and Neck

DOSE-EFFECT RELATIONSHIPS FOR THE SUBMANDIBULAR SALIVARY GLANDS AND IMPLICATIONS FOR THEIR SPARING BY INTENSITY MODULATED RADIOTHERAPY

Carol-Anne Murdoch-Kinch, D.D.S., Ph.D.,* Hyugnjin M. Kim, Sc.D.,† Karen A. Vineberg, B.Sc.,‡ Jonathan A. Ship, D.M.D.,* and Avraham Eisbruch, M.D.‡

Sparing of Submandibular gland with IMRT

- Mean threshold dose of SMG was 36 Gy
- Usually C/L SMG was spared



Comparison of dose distributions in the original plan (a), and replanning (b) containing a cost function to reduce mean contralateral (Lt) submandibular salivary glands (SMG) dose to <39 Gy. Note that the contralateral jugulodigastric (subdigastric, JD) lymph node lies immediately posterior to the contralateral SMG; no planning target volume underdosage was therefore allowed while sparing the gland. The ipsilateral (Rt) JD node is involved with gross metastasis.

Radiation + Erbitux in locally advanced Head & Neck Cancers –

Indian Experience (Aug 2005 – 2009)

TABLE -1 PATIENTS CHARACTERISTICS
(AUG 2005 – MAY 2009)
(n=25)

Ca Alveolus	1	Inoperable		
Ca Buccal Mucosa	3	Surgery Refused		
Ca Ant 2/3 Tounge	10	Med. Inoperable	1	
		Unresectable	1	
		WLE + MRND	2	High Risk Post Op Margins +ve nodes > 2 / ECE +ve
		Tongue Commando	3	
		WLE (Residual++)	1	
Ca Base of Tongue	1			
Ca Oropharynx	1			
Ca Pyriform Fossa	4			
Ca Supralottic Larynx	2			
Ca Post Cricoid	1			
Ca Nasopharynx	1			
Ca Parotid (Unresectable)	1			

TABLE – 2
STAGE DISTRIBUTION ,(n=25)

	N0	N1	N2	N3
T1	--	--	--	--
T2	1	2	1	
T3	3	4	3	
T4	3	5	2	1

STAGE IIB – 4
STAGE III – 10
STAGE IVA – 10
STAGE iV B- 1

RADIATION AND CONCURRENT CETUXIMAB (ERBITUX) IN HNC

CHEMO-IMMUNOTHERAPY SCHEDULE		
Inj ERBITUX	**400mg / m2**	**Day (-7)**
	250mg / m2	**Weekly**
Inj CISPLATINUM + ERB	**35mg / m2**	**Weekly**

RADIATION AND CONCURRENT CETUXIMAB (ERBITUX) IN HNC

DOSE:- RADIATION THERAPY			
DOSE DELIVERED			
RADICAL INTENT	**CTV**	**55.26 -- 60.6Gy**	**4 (old age, Prev Gamma knife)**
	CTV	**65.0 -- 70.2 Gy**	**13**
POST OPERATIVE	**CTV**	**54 -- 60.6 Gy**	**6**
		47* -- 52.0 Gy*	**2**

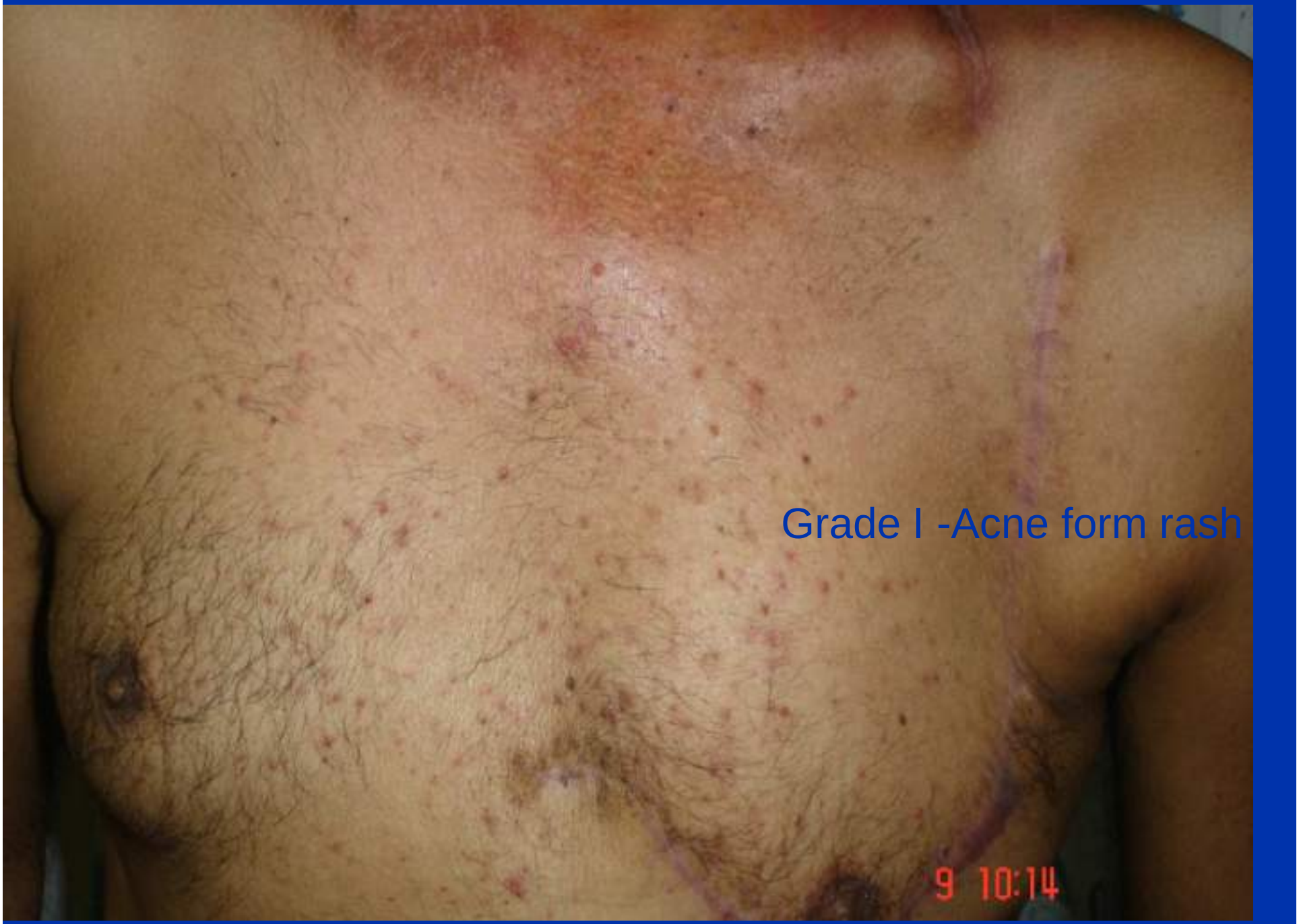
* preop/ re-radiation for 2nd malignancy

RADIATION AND CONCURRENT CETUXIMAB (ERBITUX) IN HNC

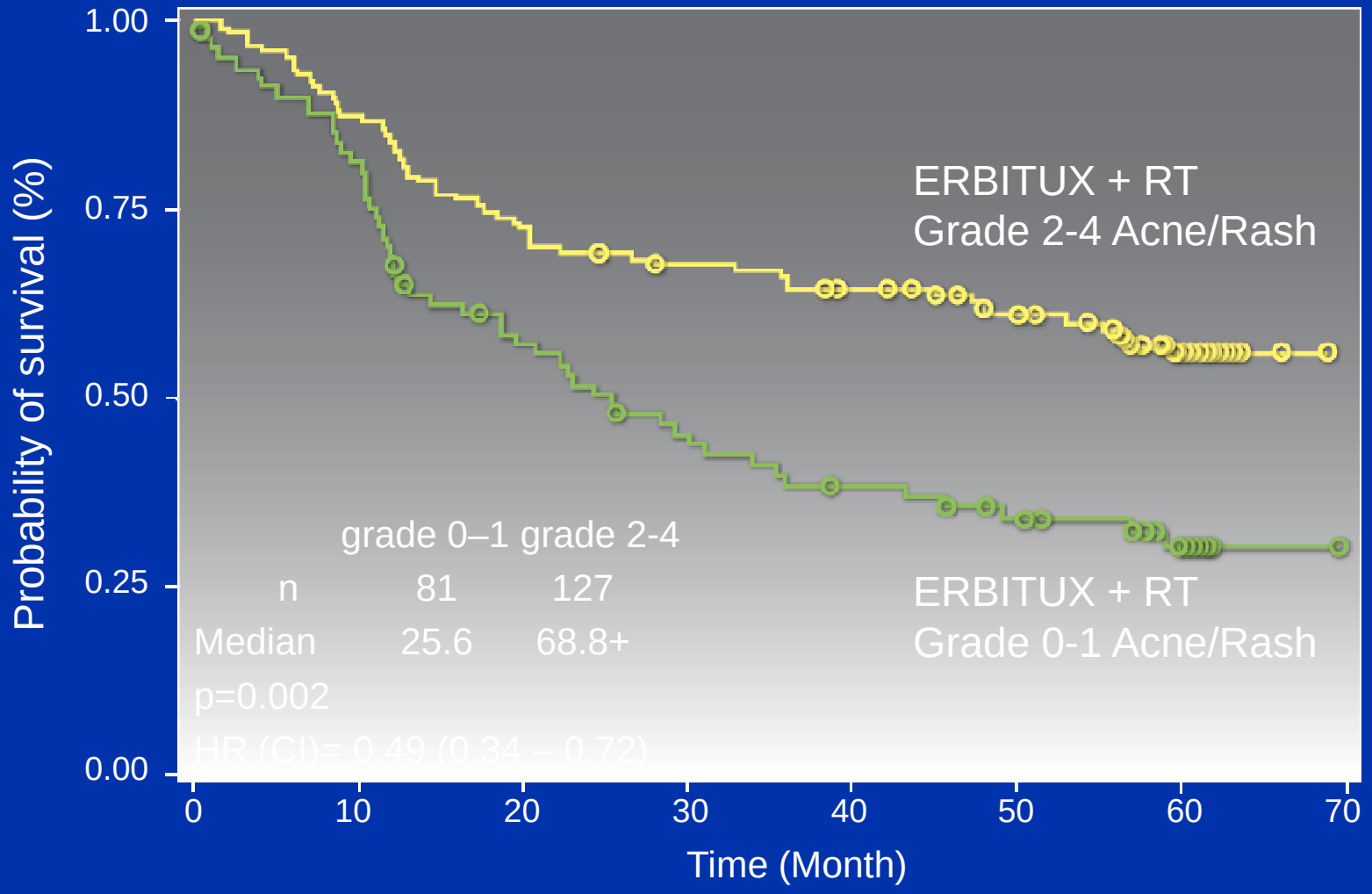
RESPONSE ASSESSMENT		
	RT + ERB n=13#	RT + Cisp + ERB n=12
RESPONSE AT 3 MONTHS		
CR	***9 (69.23%)**	****7 (58.33%)**
PR	**3**	**4**
PD	**--**	**1**
SD	**--**	**---**
STATUS AT LAST FOLLOW FU		
FOLLOW UP RANGE-: 2-28 MONTHS, MEDIAN – 13 MONTHS		
	Alive NED - 8	**Alive NED -7**
	Alive with disease - 2	**Alive with disease - 2**
	Died with disease - 3	**Died with disease - 3**
	***Post Op 3/8**	****Post Op 4/7**

1 pt LFU


Radiotherapy + Cispl + Erb
Gr. II Skin rash
Gr. I - II Mucositis

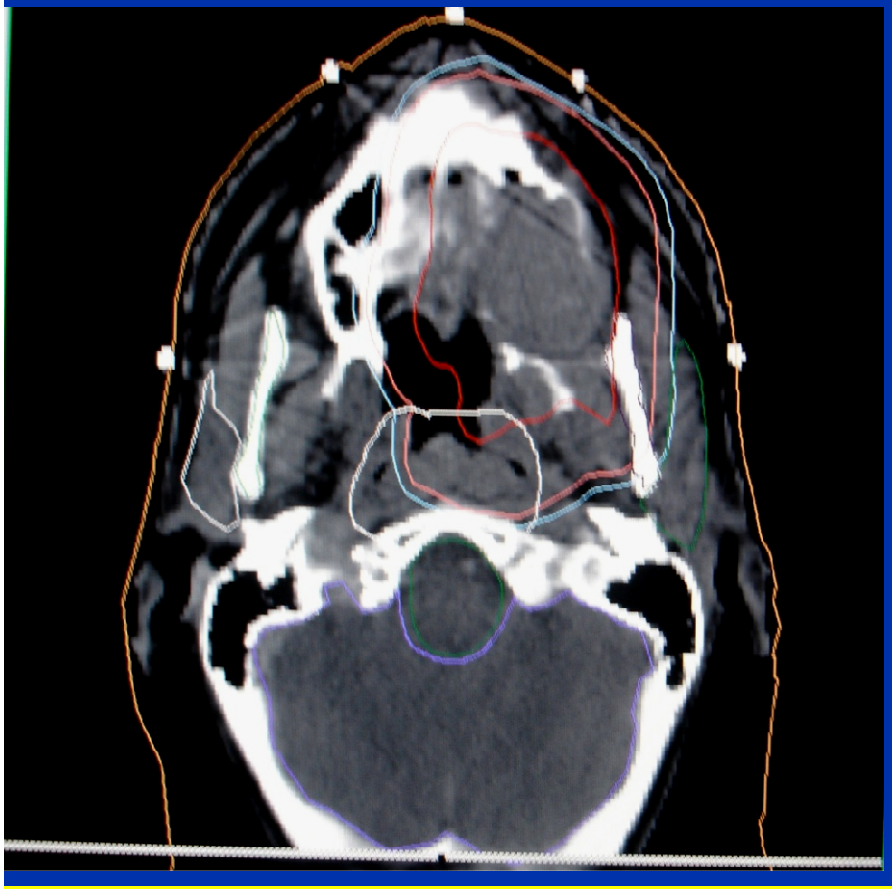

Grade I -Acne form rash
9 10:14

ERBITUX + RT: Overall Survival by Severity of Acne/Rash

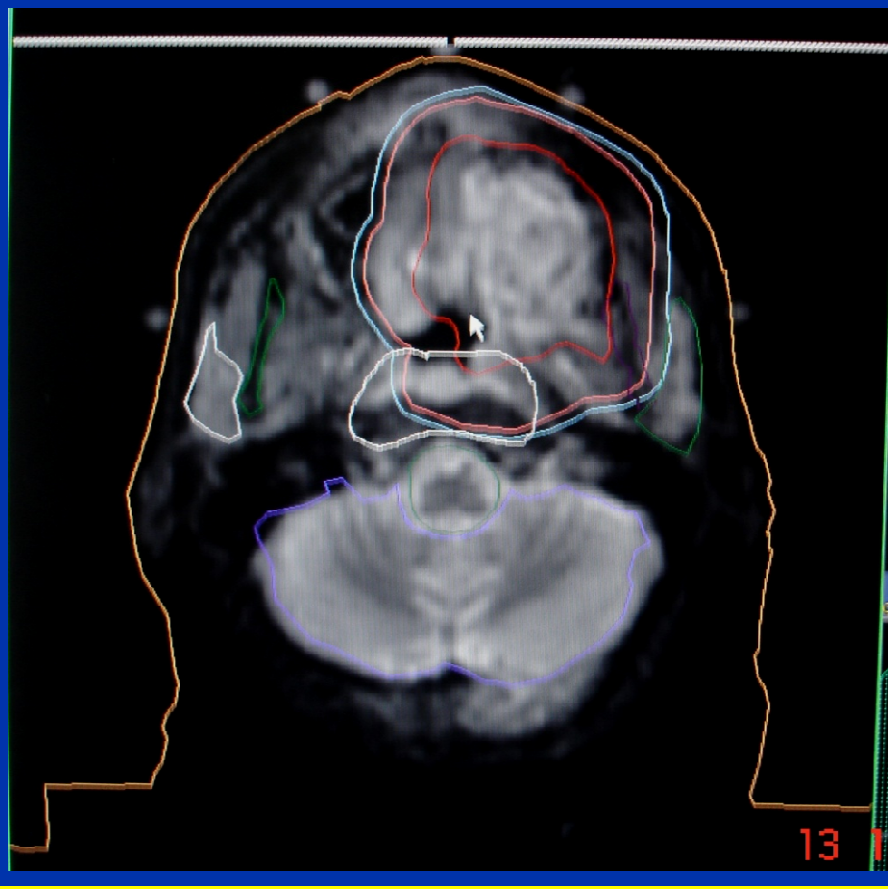


Bonner J.A, et al. as presented ASTRO 2008

CA LT. UPPER ALVEOLUS WITH INTRACRANIAL EXTENSION Treated with IMRT + ERBITUX

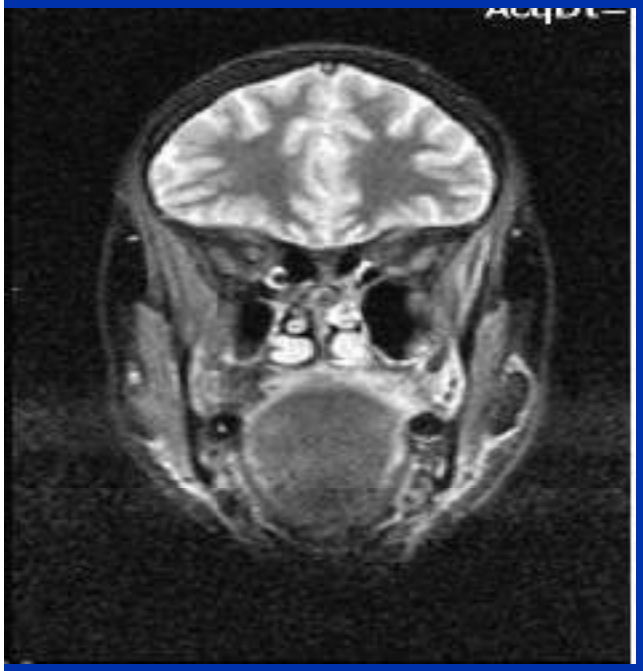


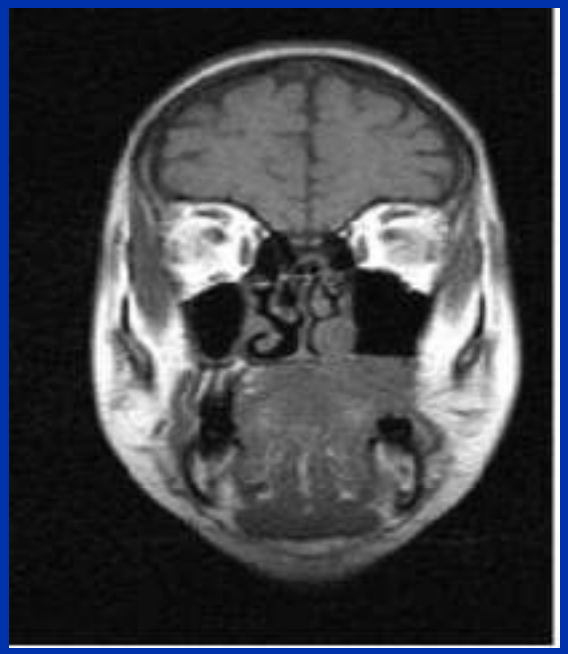
CT Showing GTV

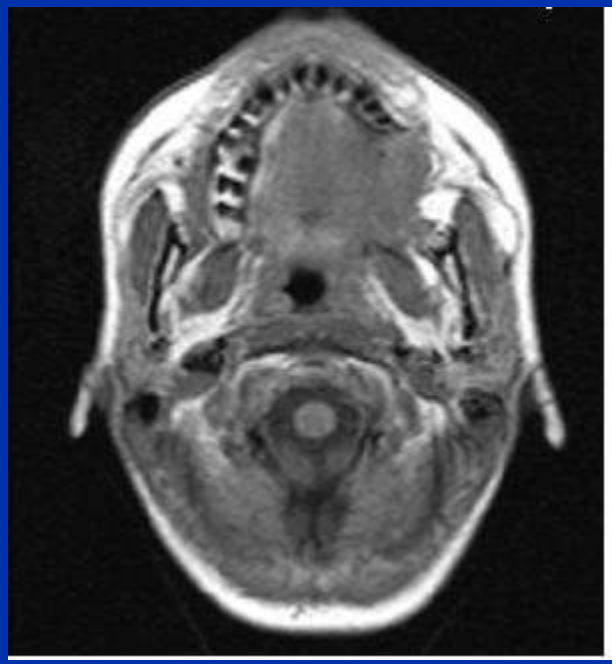


MRI Showing GTV at same slice

CA LT. UPPER ALVEOLUS WITH INTRACRANIAL EXTENSION

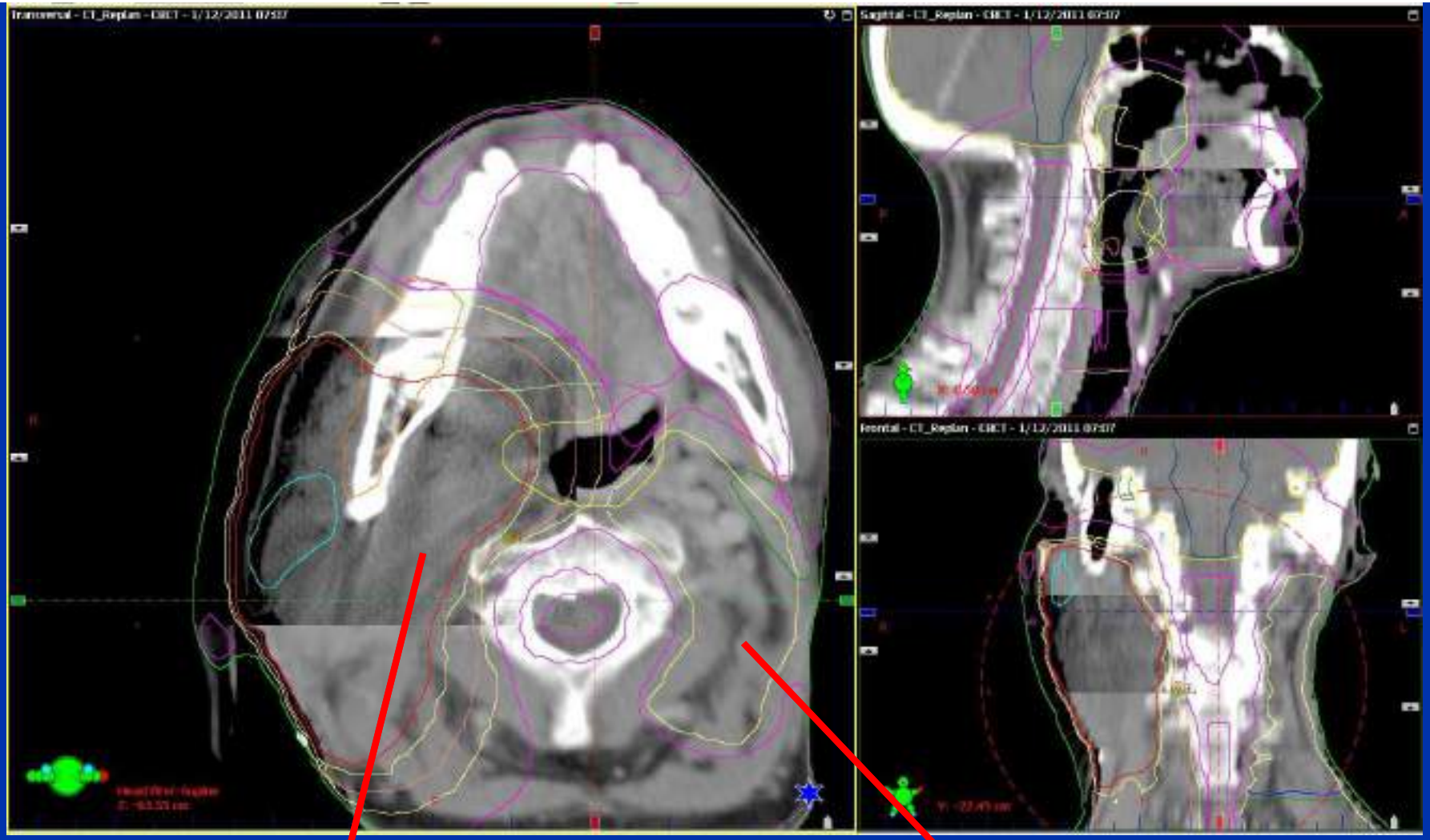






MRI Done 4 months later shows complete response
with residual non enhancing thickening at the site of previous tumor

MRI & CT-PET- complete Response, NED till 36 months



Cone Beam CT Image

Planning CT Image

Tumor Shrinkage after 3 weeks of IMRT

Note medical deviation of residual tumor parotid gland and DARS

Medical Deviation of Target Volume by 1.3cm

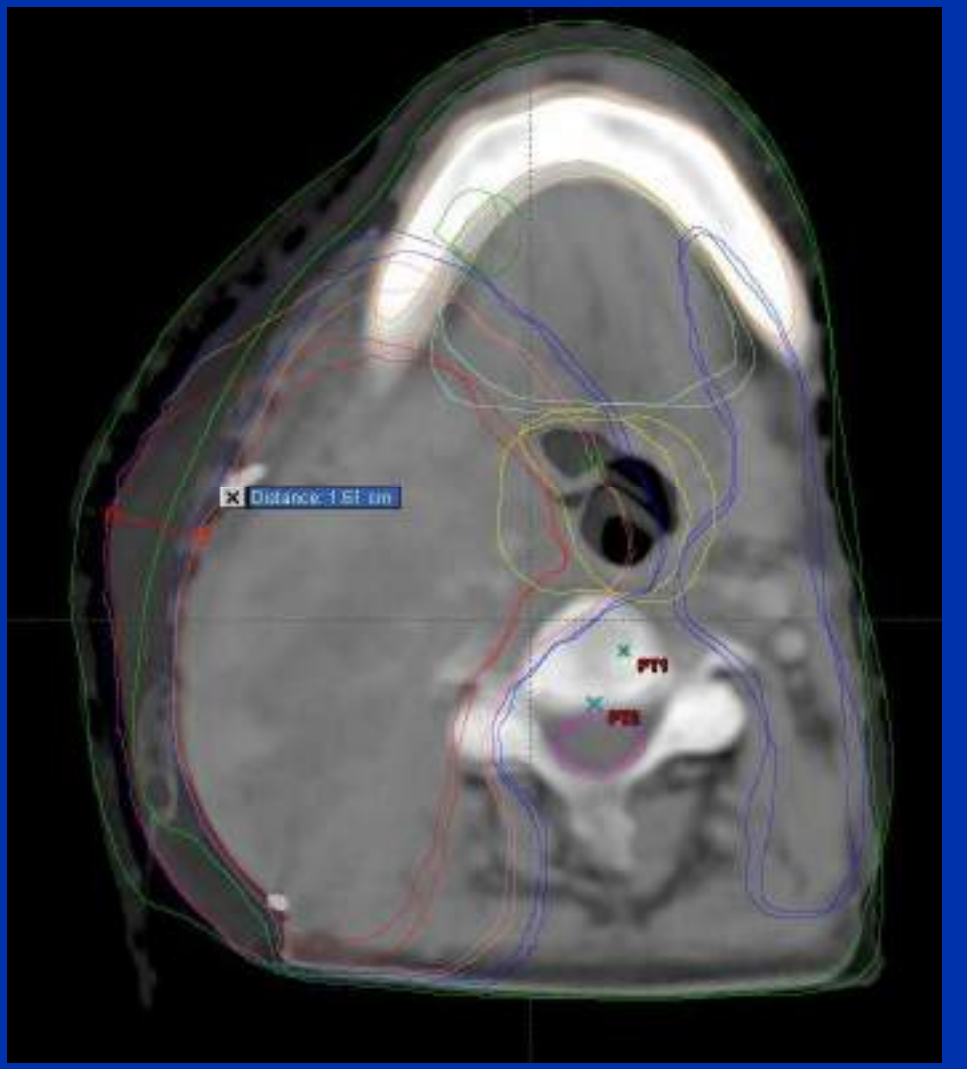


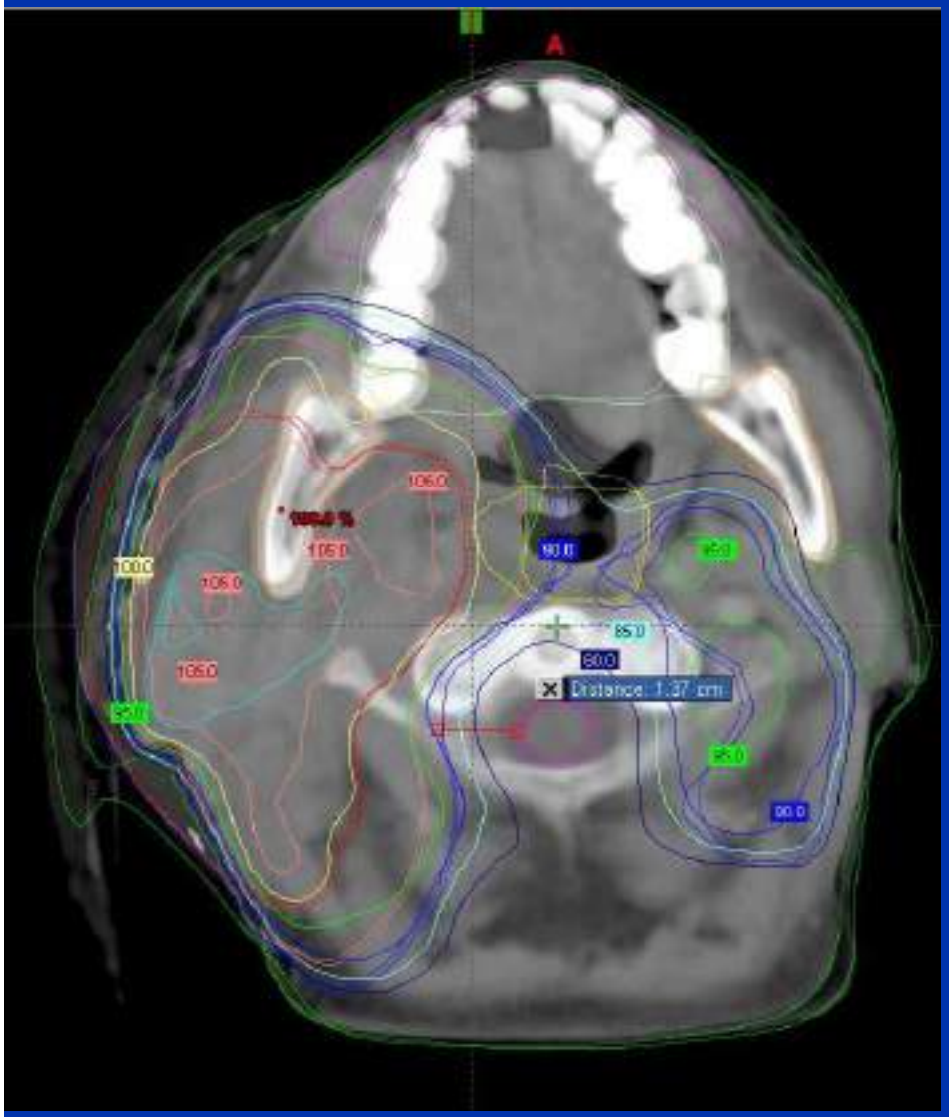
Image-Guided Radiation Therapy with ExacTrac

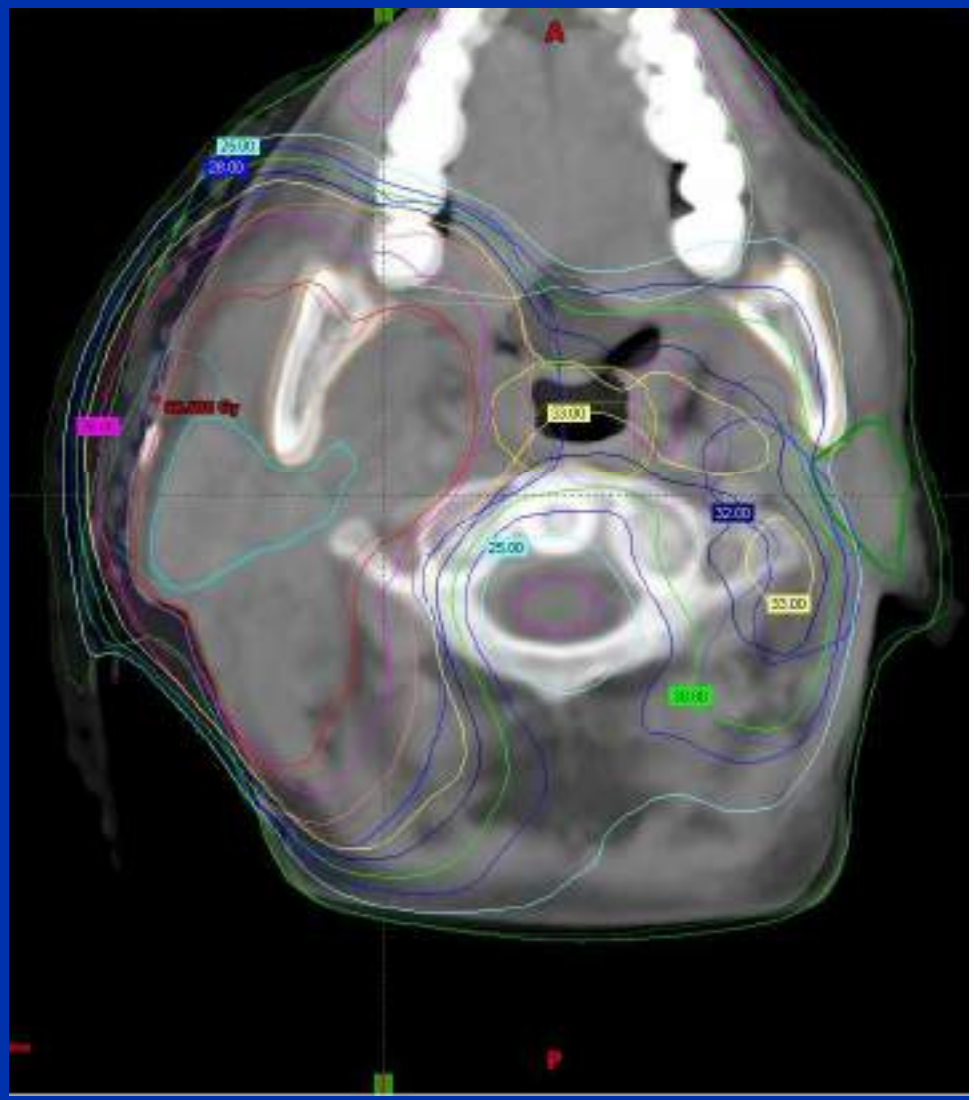
Fast, easy, precise daily positioning

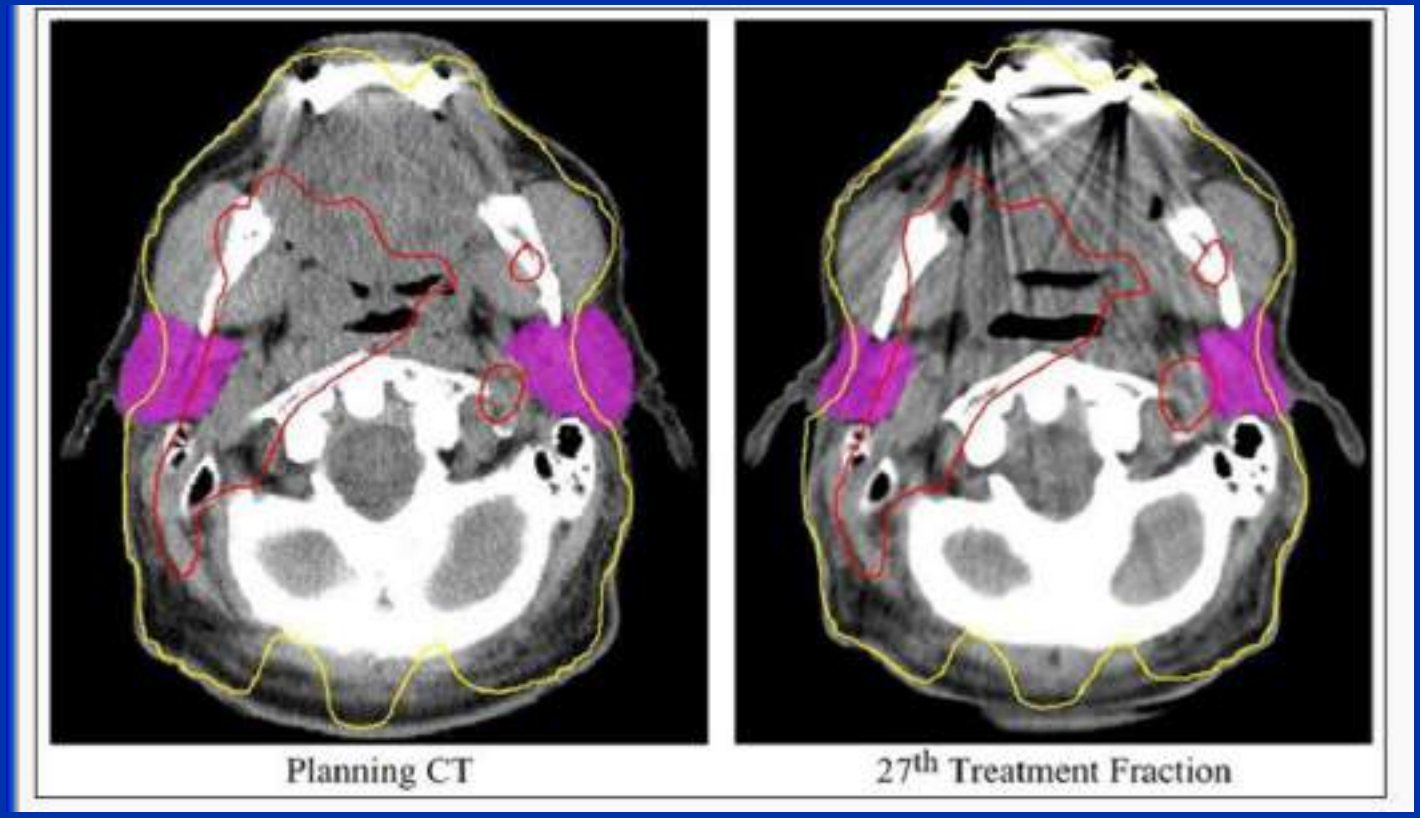
- Instantly Ready Stereoscopic Imaging
- Bony anatomy or implanted markers
- Setup verification before and during treatment (Snap Verification)
- 6D patient setup (translations & rotations)
- Adaptive Gating
- System set-up accuracy 1mm [1]
- Patient set-up accuracy 2mm [2,3]
- May be used daily for all extracranial and frameless radiosurgery patients

1) A phantom study on the pos. accuracy of the Novalis Body system. Yan H, *et al.*; Med. Phys. 30 (12), Dec.03: 3052–3060;
2) Image-Guided and IMRS for patients with Spinal Metastasis. Ryu S, *et al.*; CANCER April 03 / Vol.97;
3) A Technique for IMRS for Spinal Tumors. Yin F-F, *et al.*; Med. Phys. 29 (12), Dec.02: 2815–2822;

Medial shift of Isodose curves due to Tumour shrinkage







Weight loss,parotid gland shrinkage, and parotid centre- of-volume medial displacement during a course of radiation therapy leads to an increase in the parotid gland mean dose. Red denotes 63Gy and yellow 26Gy.

Int J Radiat Oncol Biol Phys. 2007 November 15; 69(4): 1290–1296.

IMPACT OF IMRT

ON

XEROSTOMIA

Clinical Oncology (2006) **18:** 497–504
doi:10.1016/j.clon.2006.04.014

Original Article

Can Dose Reduction to One Parotid Gland Prevent Xerostomia? — A Feasibility Study for Locally Advanced Head and Neck Cancer Patients Treated with Intensity-modulated Radiotherapy

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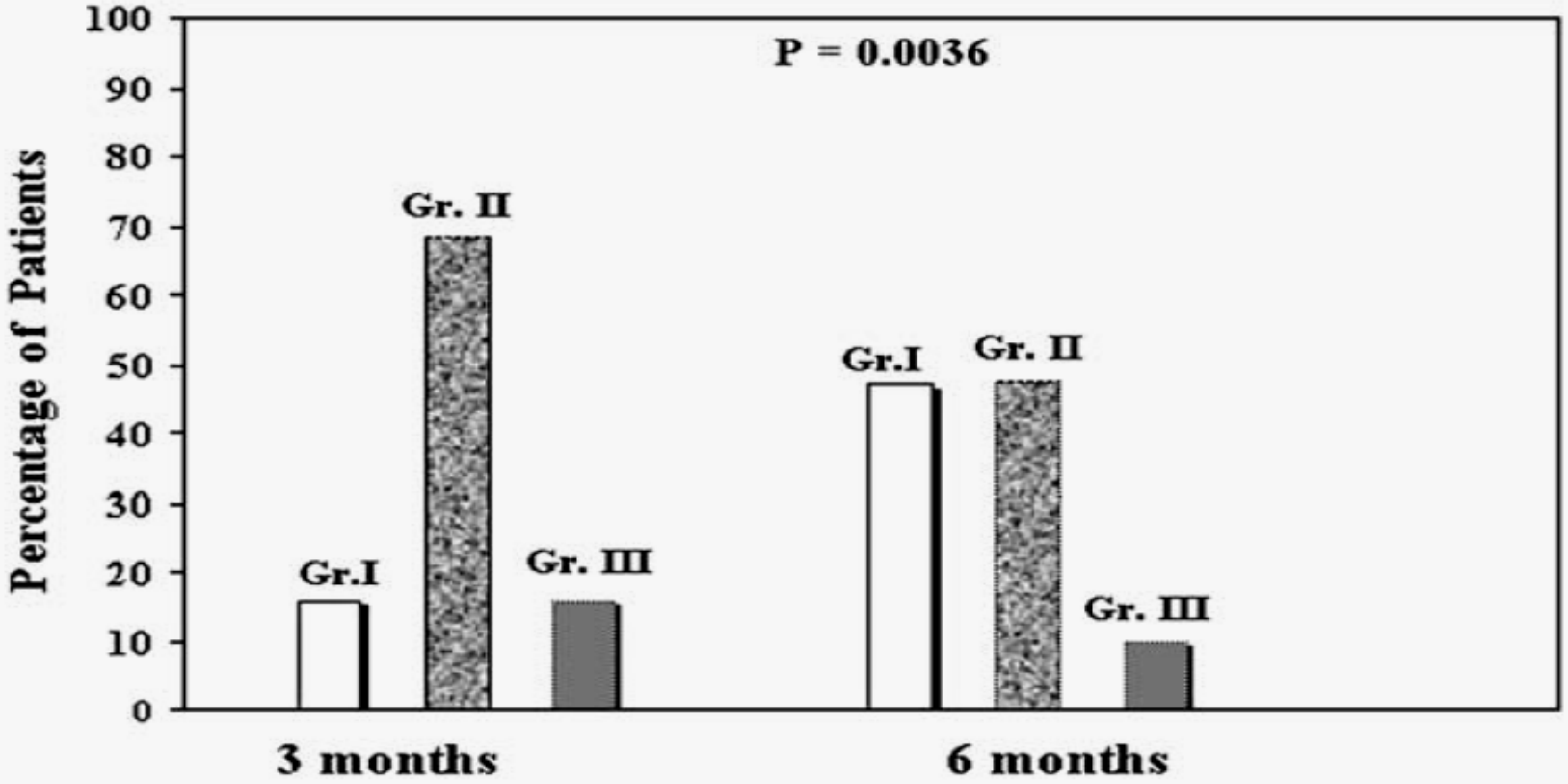
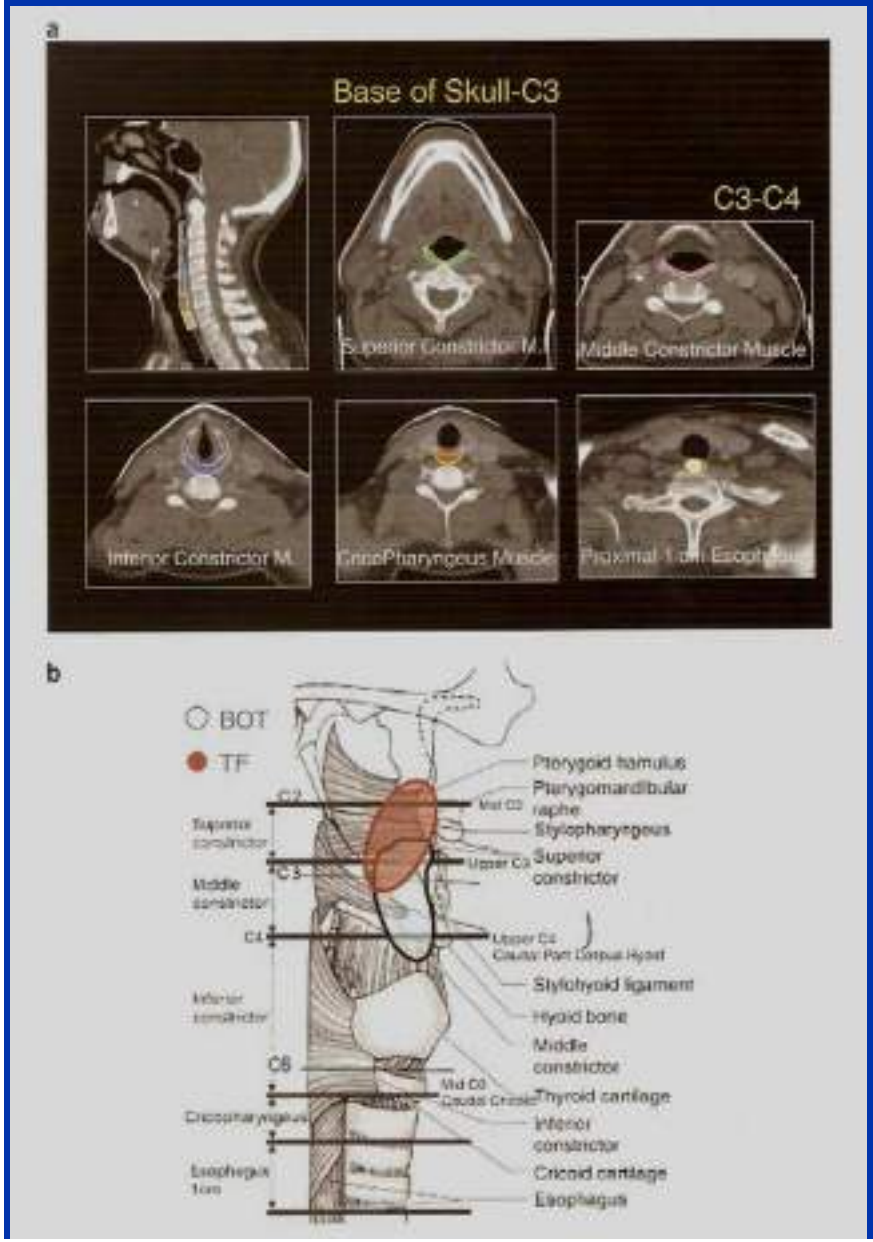


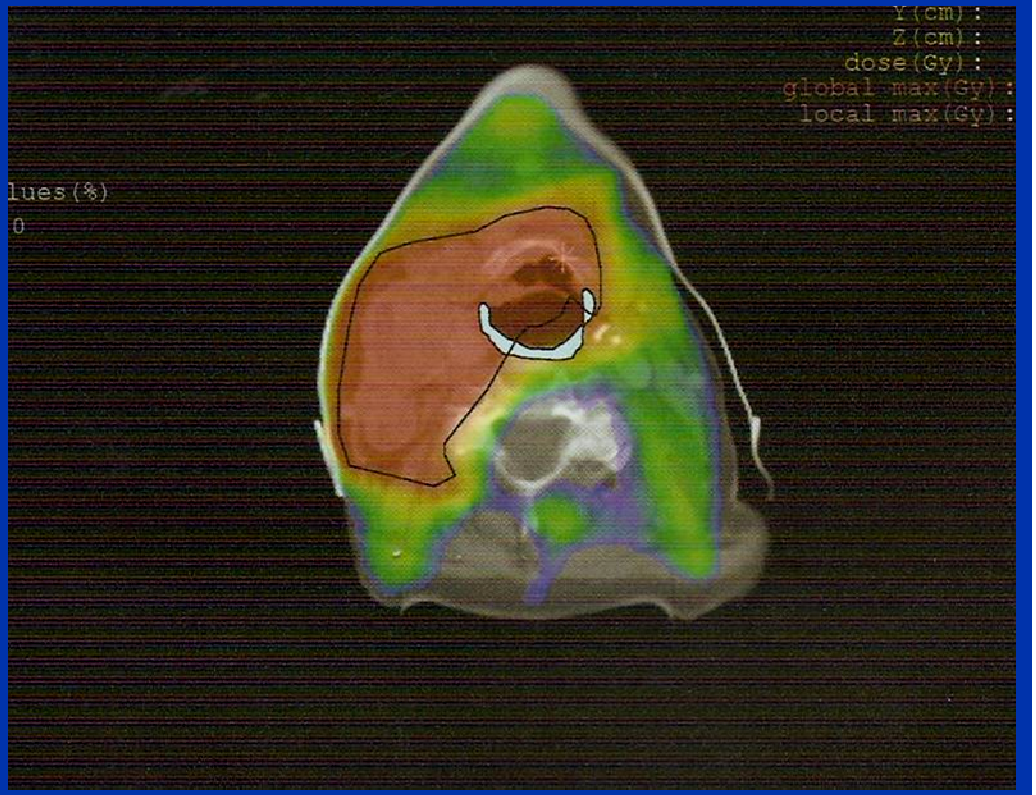
Grade of subjective salivary toxicity at 3 and 6 months after intensity-modulated radiotherapy.

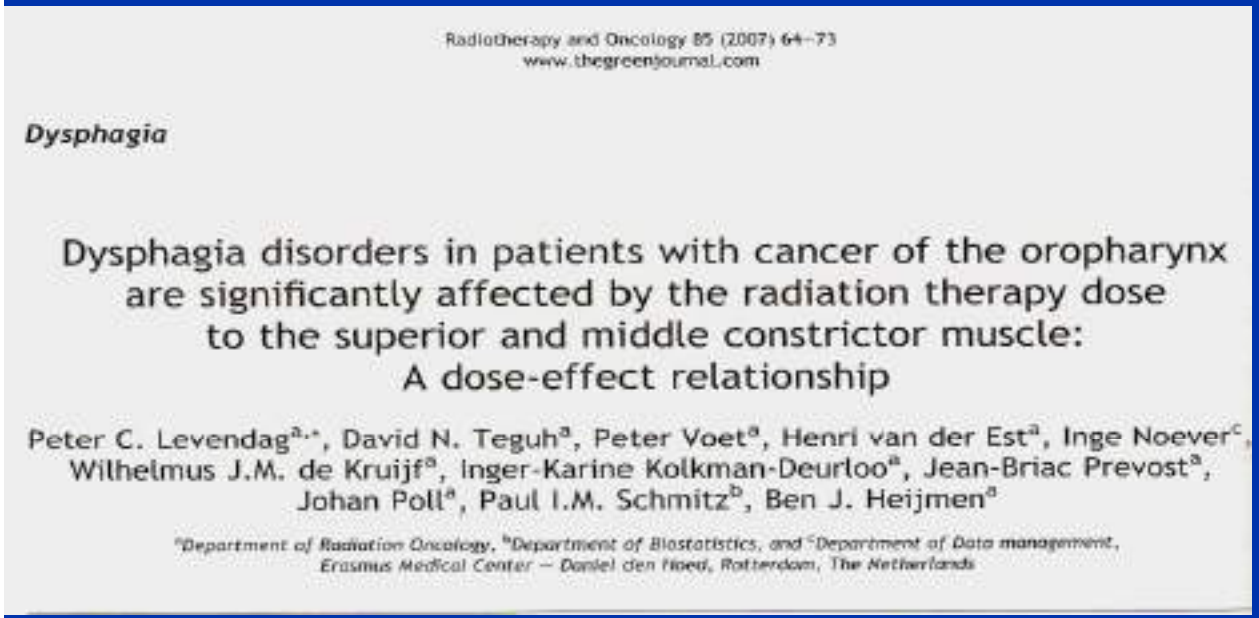
Anand et al: Clinical Oncology (2006) 18: 497 - 504

IMPACT OF IMRT ON CHRONIC DYSPHAGIA

DYSPHAGIA RELATED ANATOMICAL STRUCTURES







Radiotherapy and Oncology 85 (2007) 64–73
www.thegreenjournal.com

Dysphagia

Dysphagia disorders in patients with cancer of the oropharynx are significantly affected by the radiation therapy dose to the superior and middle constrictor muscle: A dose-effect relationship

Peter C. Levendag[a,*], David N. Teguh[a], Peter Voet[a], Henri van der Est[a], Inge Noever[c], Wilhelmus J.M. de Kruijf[a], Inger-Karine Kolkman-Deurloo[a], Jean-Briac Prevost[a], Johan Poll[a], Paul I.M. Schmitz[b], Ben J. Heijmen[a]

[a]Department of Radiation Oncology, [b]Department of Biostatistics, and [c]Department of Data management, Erasmus Medical Center – Daniel den Hoed, Rotterdam, The Netherlands

- 23% experienced late Dysphagia Gr. III or IV
- Probability of swallowing disorders increased significantly with dose to constrictor muscles- ± 19% per 10Gy after 55Gy

Int. J. Radiation Oncology Biol. Phys., Vol. 60, No. 5, pp. 1425–1439, 2004

0360-3016/04/$ see front matter

doi:10.1016/j.ijrobp.2004.05.050

CLINICAL INVESTIGATION **Head and Neck**

DYSPHAGIA AND ASPIRATION AFTER CHEMORADIOTHERAPY FOR HEAD-AND-NECK CANCER: WHICH ANATOMIC STRUCTURES ARE AFFECTED AND CAN THEY BE SPARED BY IMRT?

AVRAHAM EISBRUCH, M.D.,* MARCO SCHWARTZ, M.SC.,† COEN RASCH, M.D.,†
KAREN VINEBERG, B.SC.,* EUGENE DAMEN, PH.D.,† CORINA J. VAN AS, PH.D.,‡§
ROBIN MARSH, B.SC.,* FRANK A. PAMEIJER, M.D.,¶ AND ALFONS J. M. BALM, M.D.‡

*Department of Radiation Oncology, University of Michigan, Ann Arbor, MI; Departments of †Radiation Oncology, ‡Otolaryngology-Head and Neck Surgery, and ¶Radiology, and §Section of Speech Therapy, The Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands

The British Journal of Radiology, 81 (2008), 865–871

Favourable impact of intensity-modulated radiation therapy on chronic dysphagia in patients with head and neck cancer

[1]A K ANAND, MD, [1]A R CHAUDHOORY, MD, [1]A SHUKLA, MD, [2]P S NEGI, MSc, [2]S N SINHA, MSc, [2]A A G BABU, MSc, [2]R K MUNJAL, MSc, DipRP, [3]A K DEWAN, MCh, [3]K KUMAR, MS, FICS, [4]D C DOVAL, MAMS and [4]A K VAID, DM

Departments of [1]Radiation Oncology, [2]Division of Medical Physics, [3]Surgical Oncology and [4]Medical Oncology, Rajiv Gandhi Cancer Institute and Research Centre, Delhi, India

Table 3. Dose (Gy) delivered to different volumes of dysphagia-related structures

Volume	Conventional radiotherapy	Intensity-modulated radiotherapy
100%	Mean: 45.95 Range: 7.45–51.20)	Mean: 21.16 Range: 2.57–32.49
90%	Mean: 52.74 Range: 50.89–55.68)	Mean: 34.74 Range: 4.87–47.04
80%	Mean: 52.76 Range: 52.15–65.90)	Mean: 47.39 Range: 38.57–51.37
67%	Mean: 57.60 Range: 52.99–67.09)	Mean: 54.55 Range: 53.22–56.89
50%	Mean: 58.40 Range: 53.62–68.43	Mean: 60.29 Range: 56.94–66.46
33%	Mean: 59.34 Range: 54.25–68.96	Mean: 63.11 Range: 58.8–70.79
5%	Mean: 62.40 Range: 55.72–73.22	Mean: 67.84 Range: 62.63–77.02

Anand et.al, **British Journal of Radiology (2008) 81,** 865-871

Table 5: Chronic Toxicity of IMRT

	Chronic Dysphagia		Xerostomia		
	Subjective		Subjective		Objective (Parotid Scintigraphy†)
Grade	At 3 months (n=59)*	At 6mo (n=57)*	At 3mo (n=59)*	At 6mo (n=57)*	At 3 months (n = 26)
Grade 0	41 (69.4)	44 (77.1)	31 (52.5)	35 (61.4)	15 (57.6)
Grade 1	7 (11.8)	6 (10.5)	24 (40.6)	18 (31.5)	9 (34.6)
Grade 2	11 (18.7)	7 (12.3)	4 (6.8)	4 (7.01)	2 (7.7)

* 3 patients died within 3 months and 2 more died in next 3 months.
† Toxicity scoring done qualitatively based on scintigraphy findings.
Figures in parenthesis indicate percentage.

Anand et.al, **British Journal of Radiology (2008) 81,** 865-871

NAME: J. B

DATE: 21st JULY 2004, Post op Ca Tongue treated with IMRT

NAME: COL. B.S CRNO: 48936, CA NASOPHARYNX, TREATED IN DEC' 2003 WITH IMRT + CT

NAME: MRS. R. K, CRNO: 57793,
IMRT BASE OF TONGUE,
Treated in Aug'2003

Skin Fibrosis

- Grade 3 xerostomia ---11.8% ---- IMRT

  53.4% ---- Conventional RT

- Grade 3 dysphagia -----0% ---- IMRT

  26.7%---- Conventional RT (p=0.01)

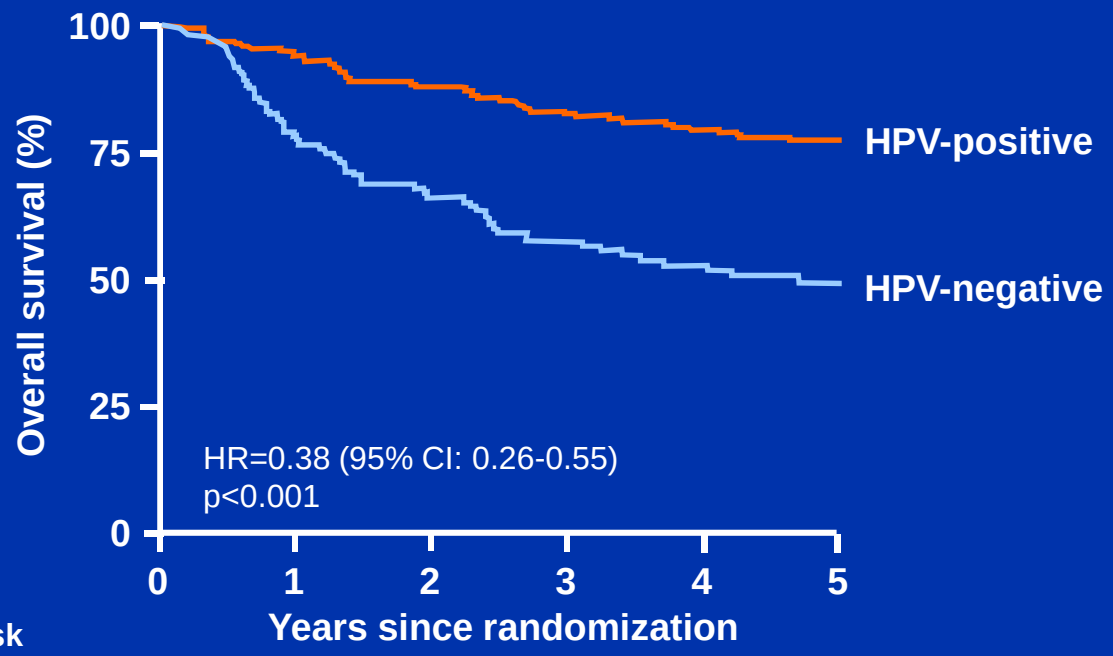
- Skin Fibrosis ----- 0% ---- IMRT

  26.7% ---- Conventional RT (p=0.03)

Where do we go from here?

Survival outcomes by HPV status RTOG 0129 study

- Phase III RTOG 0129 study in patients with stage III-IV oropharyngeal cancer receiving standard FX or accelerated RT and cisplatin
- Survival data from 323 patients with HPV-evaluable tumors were analyzed



No at risk						
HPV-positive	206	193	179	165	151	73
HPV-negative	117	89	76	65	51	22

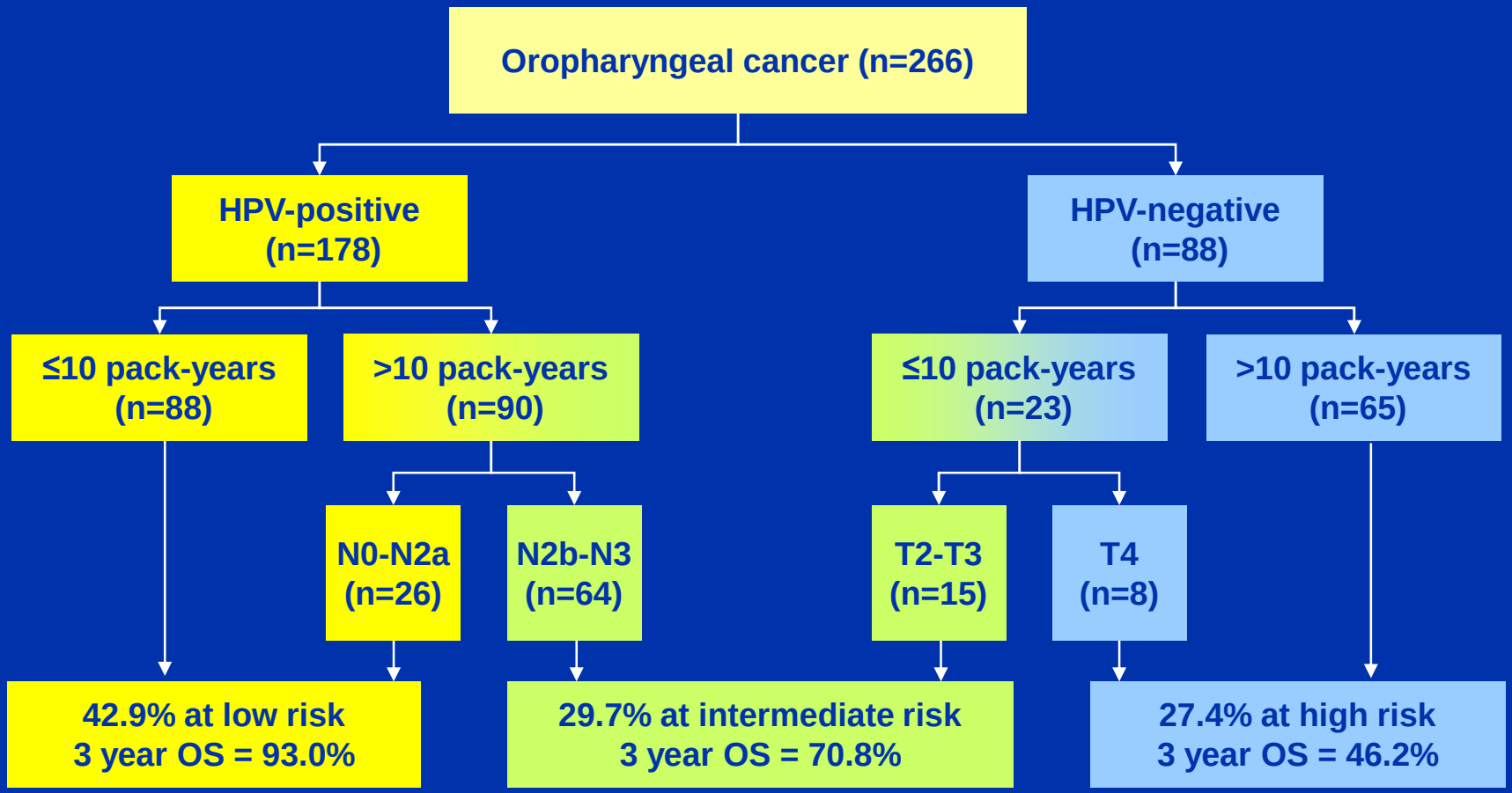
Ang et al. NEJM 2010

Three-year outcomes by HPV status RTOG 0129 study

Variable	HPV-positive (%)	HPV-negative (%)	p-value
Overall survival	82.4	57.1	<0.001
Progression-free survival	73.7	43.4	<0.001
Local-regional failure	13.6	35.1	<0.001
Distant metastases	8.7	14.6	0.23
Second primary tumor	5.9	14.6	0.02

Ang et al. NEJM 2010

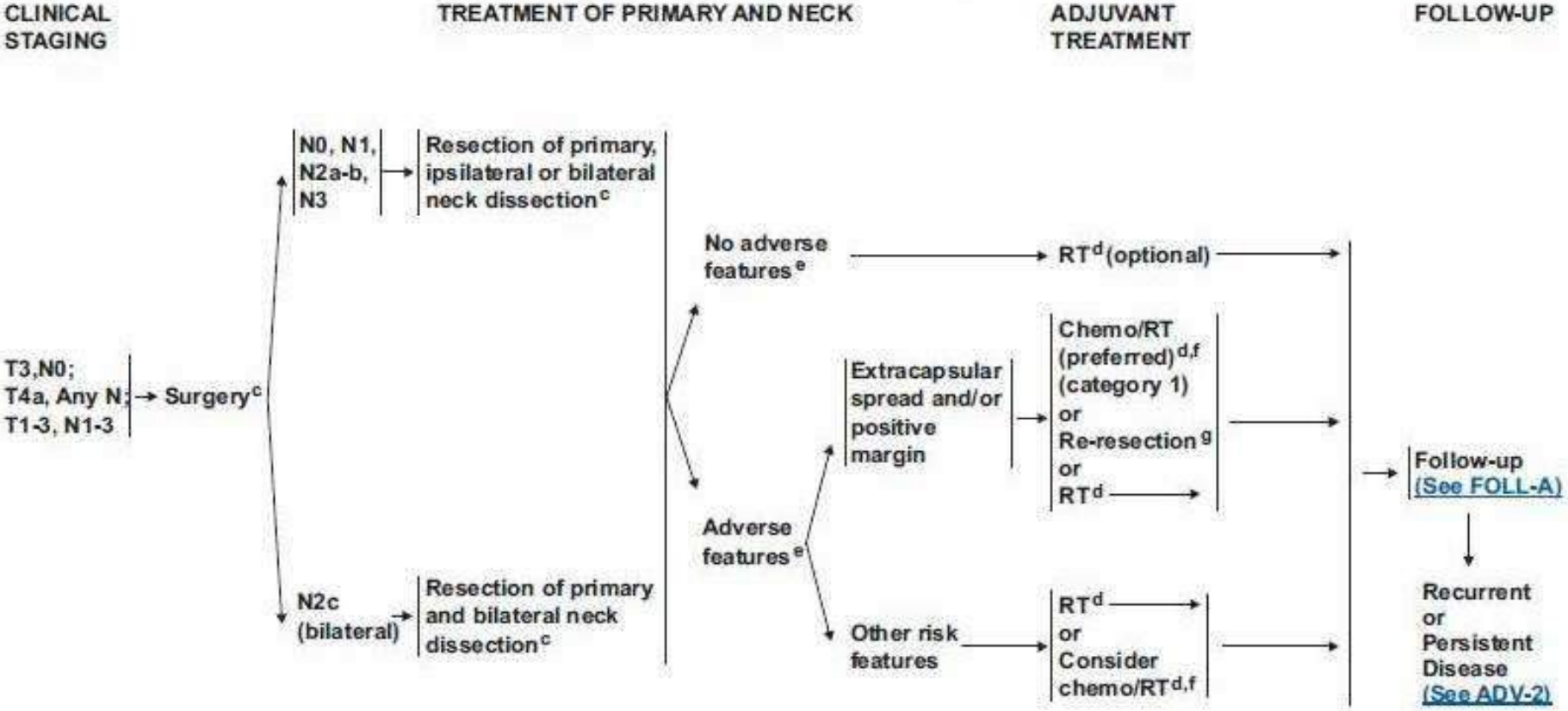
Oropharynx: Classification of patients into risk-of-death categories



Recursive-partitioning analysis identified prognostic factors with the most predictive significance

Ang et al. NEJM 2010

Buccal mucosa, floor of mouth, anterior tongue, alveolar ridge, retromolar trigone, hard palate



[c] See Principles of Surgery (SURG-A).

[d] See Principles of Radiation Therapy (OR-A).

[e] Adverse risk features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism (See Discussion).

[f] See Principles of Systemic Therapy (CHEM-A).

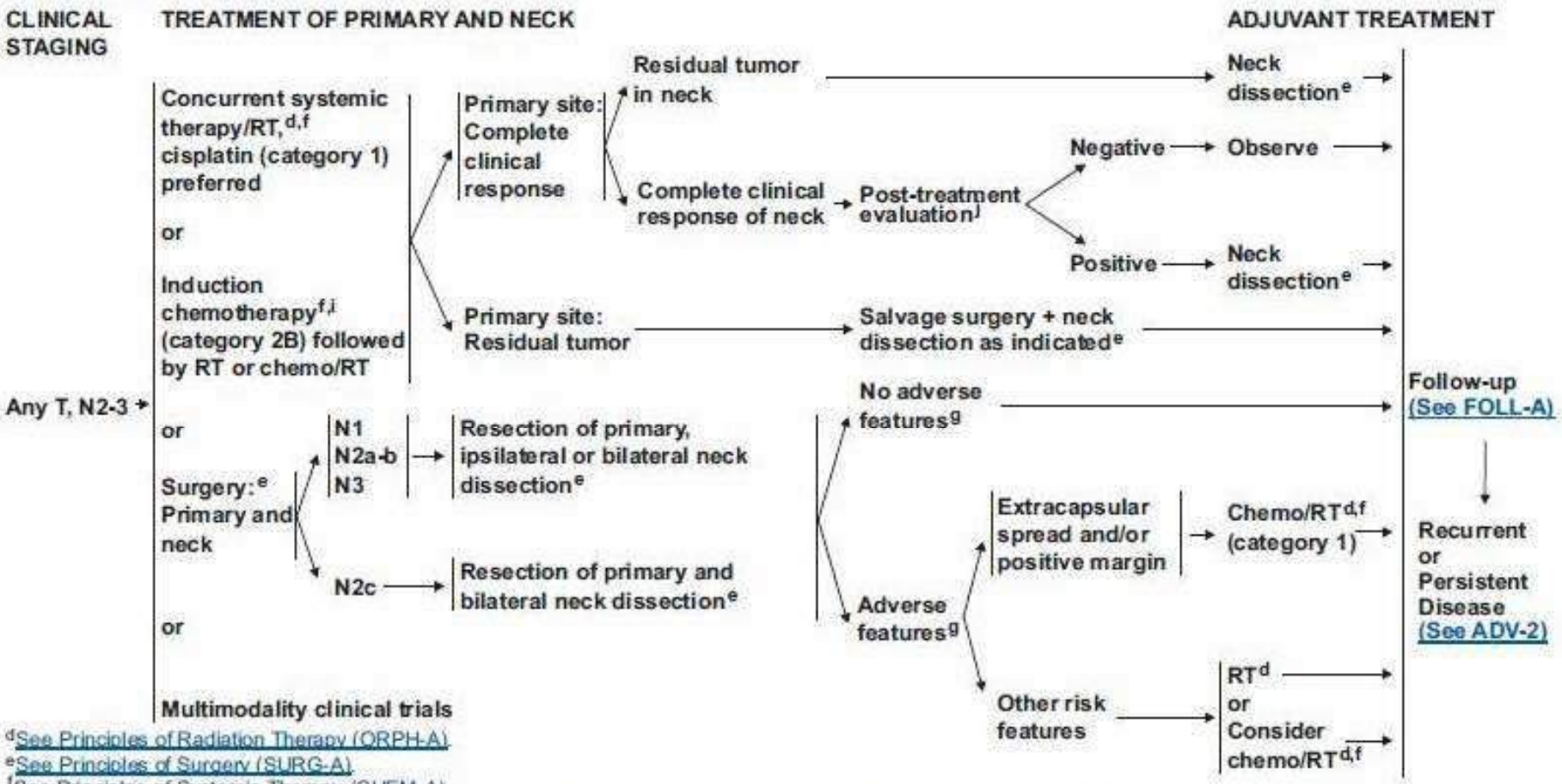
[g] Consider re-resection to achieve negative margins, if feasible.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines Version 1.2012
Cancer of the Oropharynx

NCCN Guidelines Index
Head and Neck Table of Contents
Discussion

Base of tongue/tonsil/posterior pharyngeal wall/soft palate



[d] See Principles of Radiation Therapy (ORPH-A).
[e] See Principles of Surgery (SURG-A).
[f] See Principles of Systemic Therapy (CHEM-A).
[g] Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism (See Discussion).
[i] See Discussion on induction chemotherapy.
[j] See Post Chemoradiation or RT Neck Evaluation (SURG-A 7 of 7).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Conclusions

- Treatment of locally advanced HNC is highly challenging—Loco-regional control, long term morbidity and organ conservation are important considerations.
- Conc RT + CT is superior to Neo Adj CT foll by RT. Role of Induction CT is yet to be defined.
- Tumor HPV status is an independent prognostic factor for OS and PFS

HPV-positive patients are at low risk, therefore may not need to be subjected to the high toxicity of CRT (RTOG 1016: RT + cisplatin vs RT + Erbitux)


Thank You