Role of Radiation Therapy in the Treatment of Head and Neck Cancer: Current Status and Future Directions

Kenneth Hu, MD, FASTRO

Professor

NYU Langone Medical Center

NYU School of Medicine
NYU LANGONE MEDICAL CENTER

Disclosure

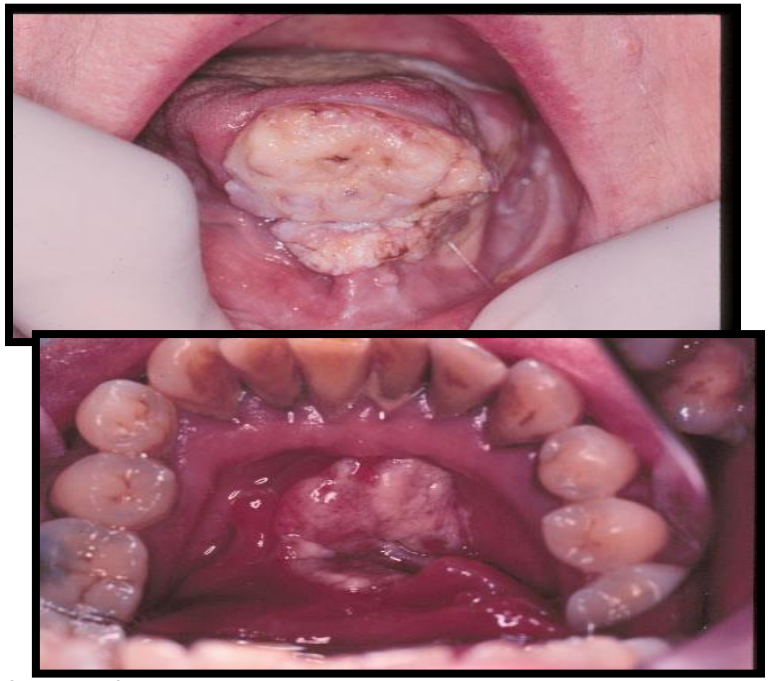
- Full time employee at NYU Langone Medical Center
- No Financial Conflicts of Interest to disclose

Learning Objectives

- Role of radiation therapy to treat the most common head and neck cancers
- Current Role of Altered Fractionation
- Strategies to optimize function preservation/quality of life
- Ongoing trials to improve treatment outcomes

Epidemiology

- Global Incidence 879k
  - Oral cavity—378k
  - Pharynx—316k (133k npx)
  - Larynx—185k
- Risk Factors
  - Tobacco/alcohol 75%
  - Non-Tobacco/alcohol 25%--HPV (opx)/EBV (npx)
- US: 65,630/yr
  - 60% Stage III/IV at diagnosis
  - 14,500 deaths per year

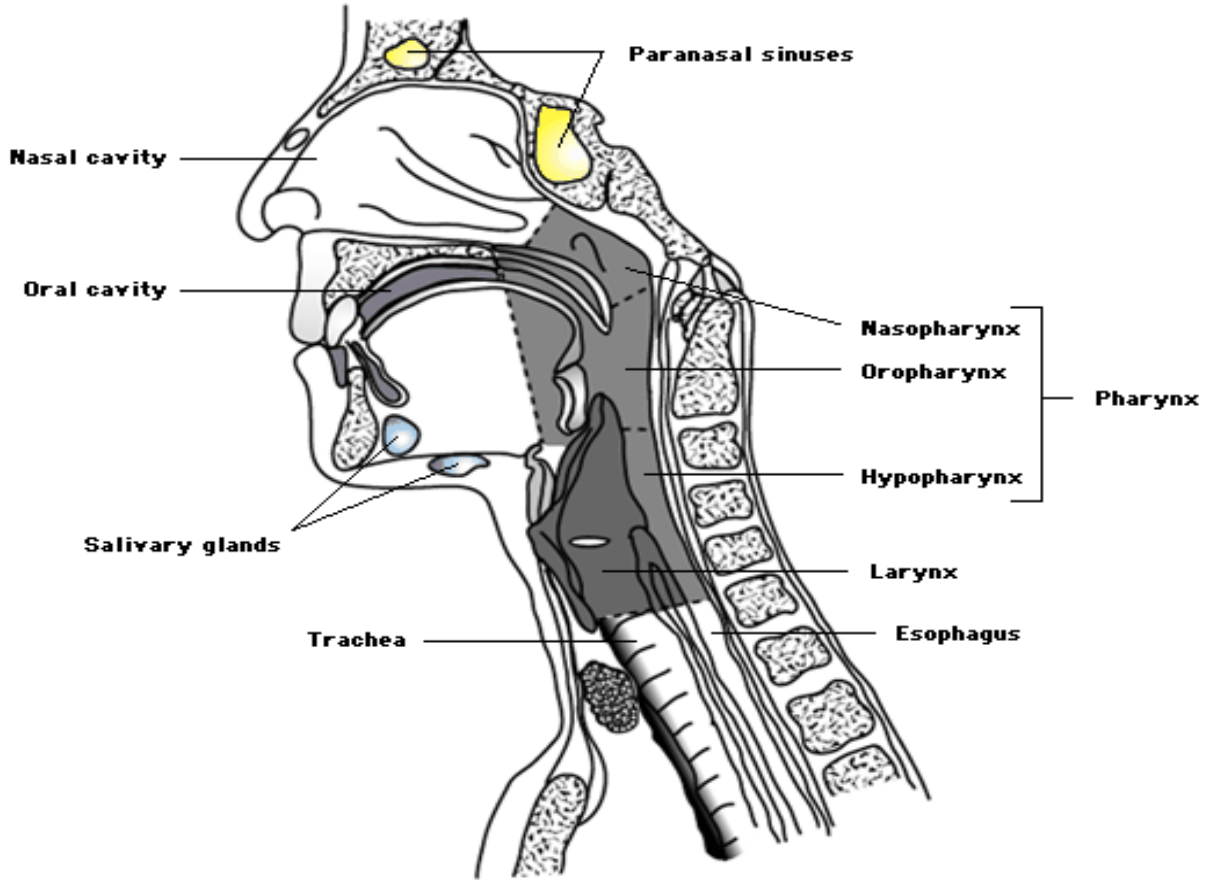


GLOBOCAN Nov, 2020
Curado, et al. Curr Opin Oncol 2013, 25:229-234
American Cancer Society 2020

Head and Neck Cancers

Most Common Sites

- Nasopharynx
- Oropharynx
- Oral Cavity
- Larynx
- Hypopharynx



National Comprehensive Cancer Network. *Clinical Practice Guidelines in Oncology. Head and Neck Cancers.* Vol 1. 2005. Available at: http://www.nccn.org/professionals/physician_gls/PDF/head-and-neck.pdf. Accessed December 14, 2005. Jemal A. *CA Cancer J Clin*. 2005;55:10–30.

General Principles #1

- Multidisciplinary evaluation
- Early Stage-single modality (Surgery or Radiation)
- Advanced Stage—multimodality therapy
- Goals:
  - Maximize Locoregional Control
  - Preserve organ function
  - Minimize toxicity of treatment

General Principles #2

- Oral Cavity/Nasal Cavity/Salivary Gland: Surgery→adjuvant therapy based on pathologic factors
- Nasopharynx, Oropharynx, Hypopharynx, Larynx: Chemoradiation
  - Organ Preservation/Cosmesis/QOL
- Management of neck parallels primary site treatment

General Principles #3

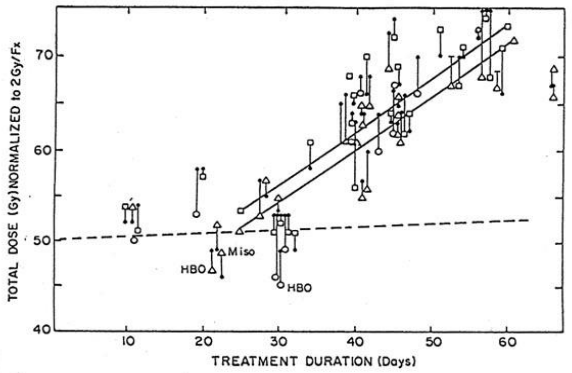
Approaches to improve efficacy radiotherapy

- Altered Fractionation
- Concurrent chemotherapy
- Targeted Biologic
- Immunotherapy

Altered Fractionation

- Hyperfractionation—BID RT for 7 wks to allow dose escalation
- Accelerated Radiation—Shortening Treatment Time to deliver Standard Dose
- Hypofractionation—Decrease overall dose to deliver treatment over 4-5wks

Accelerated Repopulation Begins at Week 4 in H&N Pts Treated Definitively with RT



Overcome Tumor Repopulation During Radiation!

calculated is presented (●) to show the extent of the extrapolation. Rate of increase in TCD_{50} predicted from a 2 month clonogen doubling rate. (– – –). Estimated increase in TCD_{50} (——) with time for 'T3' (□) and mixed T stages (△) from independent scattergram analyses (Tables 2, 3) involving different data sets from those presented in this figure.

Withers, Acta Oncol 1988, 27:145-47

Hyperfractionated or accelerated radiotherapy for head and neck cancer (Review)

Baujat B, Bourhis J, Blanchard P, Overgaard J, Ang KK, Saunders M, Le Maître A, Bernier J, Horiot JC, Maillard E, Pajak TF, Poulsen MG, Bourredjem A, O'Sullivan B, Dobrowsky W, Andrzej H, Skladowski K, Hay JH, Pinto LHJ, Fu KK, Fallai C, Sylvester R, Pignon JP, MARCH Collaborative Group

Figure 9. Locoregional failure by treatment arm according to the type of radiotherapy. The slopes of the broken lines from year 6 to year >= 7 are based on the overall death rates in the seventh and subsequent years. RT = radiotherapyFigure from *Bourhis J, Overgaard J, Audry H, Ang KK, Saunders M, Bernier J et al on behalf of MARCH collaborative group. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. Lancet 2006;368:843-54* **reproduced with permission from Elsevier Ltd.**

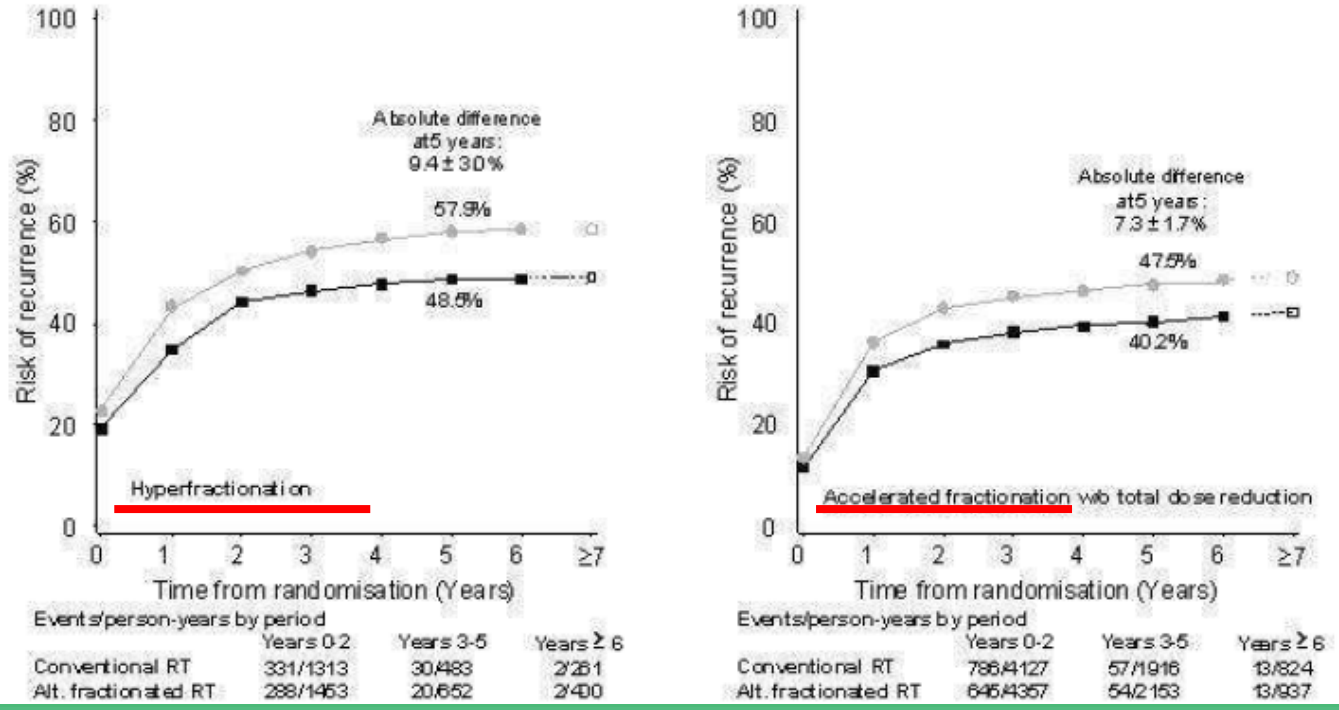
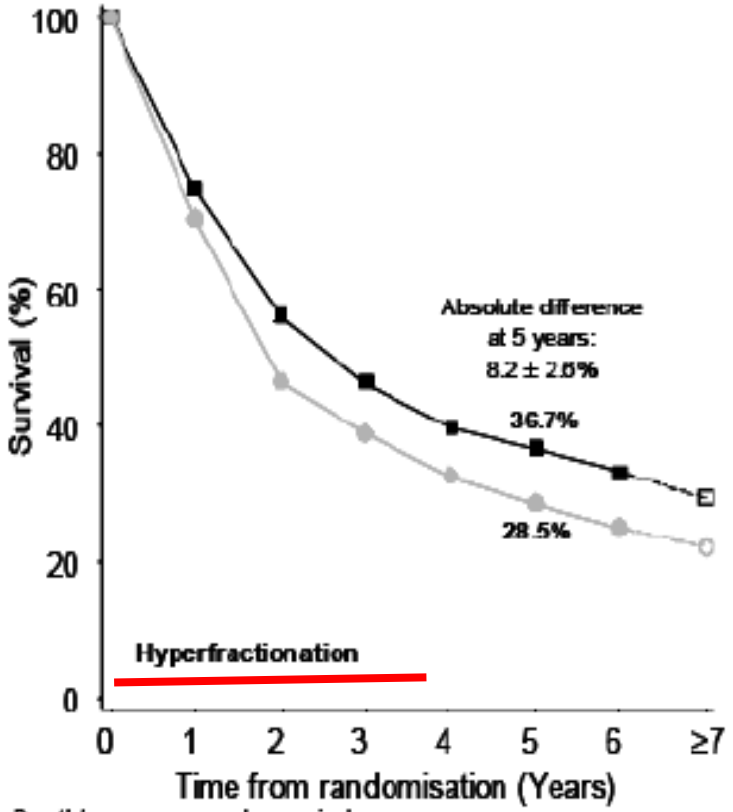
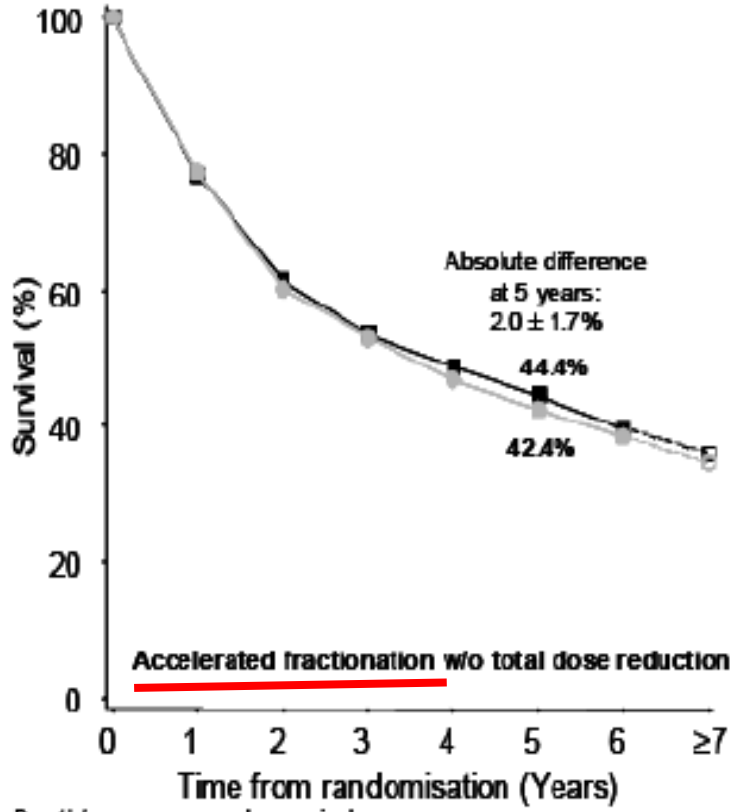


Figure 5. Survival curves by treatment arm for all trials and for the three groups of trials according to the type of altered fractionated radiotherapy. The slopes of the broken lines from year 6 to year >= 7 are based on the overall death rates in the seventh and subsequent years.RT = radiotherapyFigure from *Bourhis J, Overgaard J, Audry H, Ang KK, Saunders M, Bernier J et al on behalf of MARCH collaborative group. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. Lancet 2006;368:843-54*
reproduced with permission from Elsevier Ltd.



Death/person-years by period

	Years 0-2	Years 3-5	Years ≥ 6
Conventional RT	358/929	106/638	45/339
Alt. fractionated RT	290/1019	124/818	56/492



Death/person-years by period

	Years 0-2	Years 3-5	Years ≥ 6
Conventional RT	746/2919	283/2365	99/992
Alt. fractionated RT	734/2977	284/2545	112/1079

Five versus six fractions of radiotherapy per week for squamous-cell carcinoma of the head and neck (IAEA-ACC study): a randomised, multicentre trial

Jens Overgaard, Bidhu Kaylan Mohanti, Naseem Begum, Rubina Ali, Jai Prakash Agarwal, Maire Kuddu, Suman Bhasker, Hideo Tatsuzaki, Cai Grau

Lancet Oncol 2010; 11: 553–60

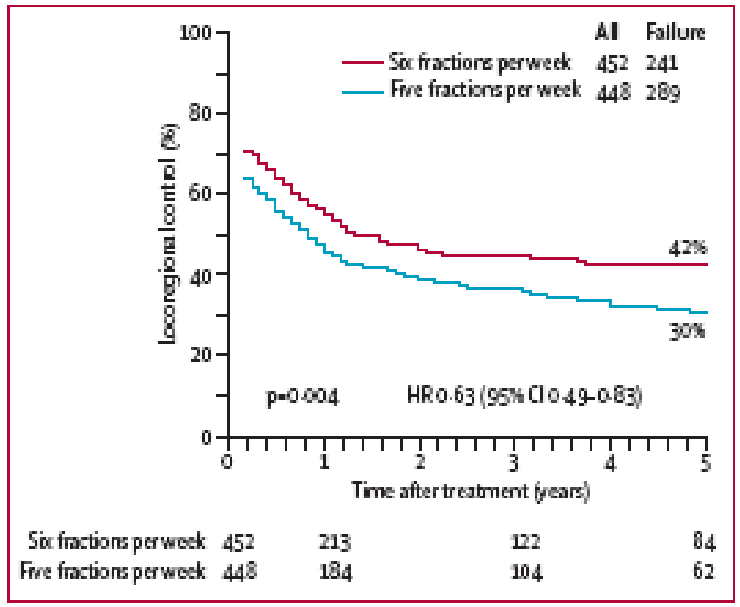


Figure 2: Locoregional tumour control

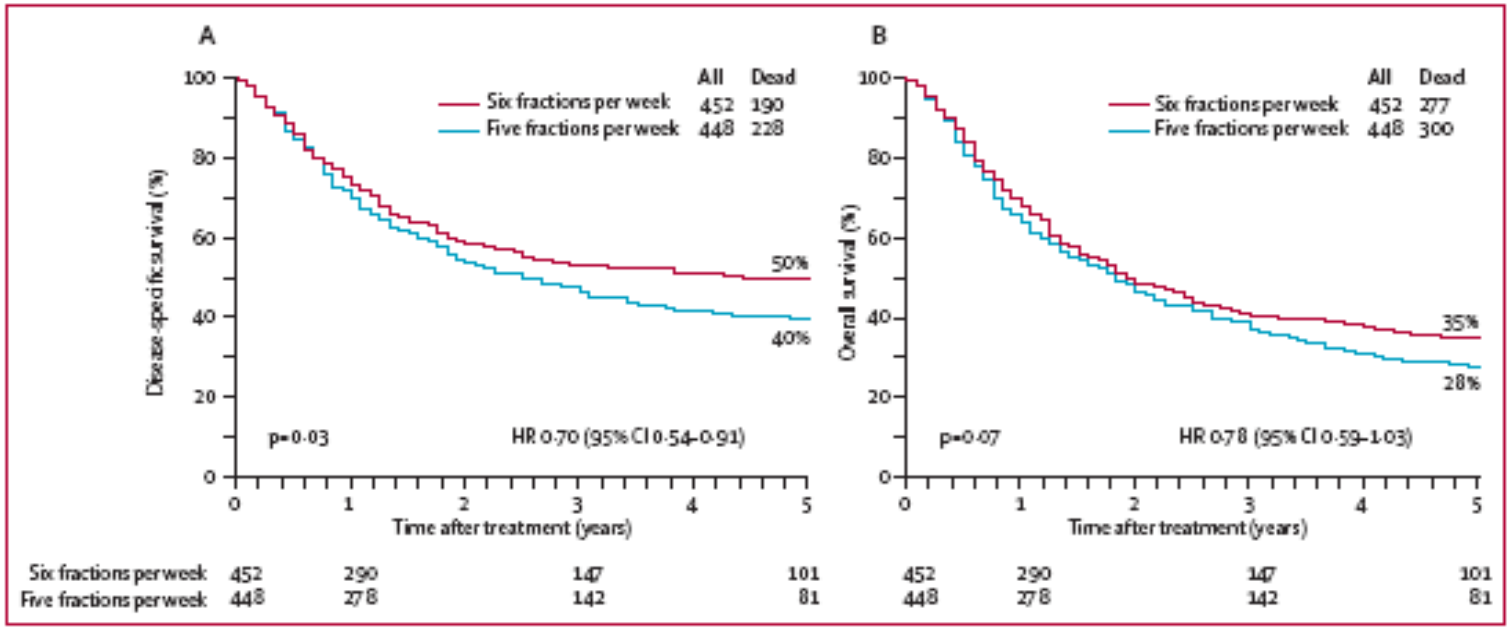


Figure 5: Disease-specific survival (A) and overall survival (B)

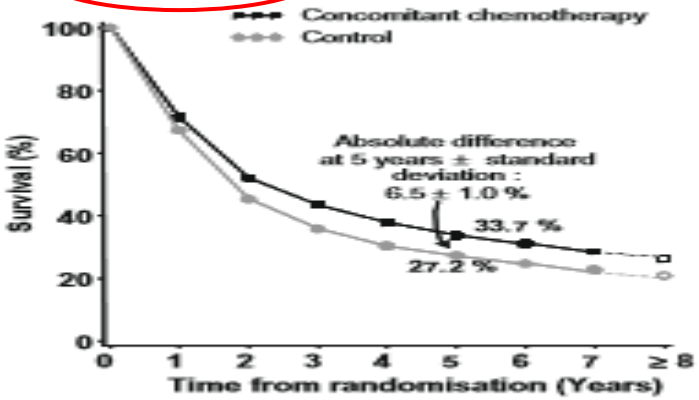
DAHANCA regimen increases 5yr LRC 12% (p=0.004) and 5yr OS by 7% (p=0.07)

Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients

Jean-Pierre Pignon [a,*], Aurélie le Maître [a], Emilie Maillard [a], Jean Bourhis [b], on behalf of the MACH-NC

Radiotherapy and Oncology 92 (2009) 4–14

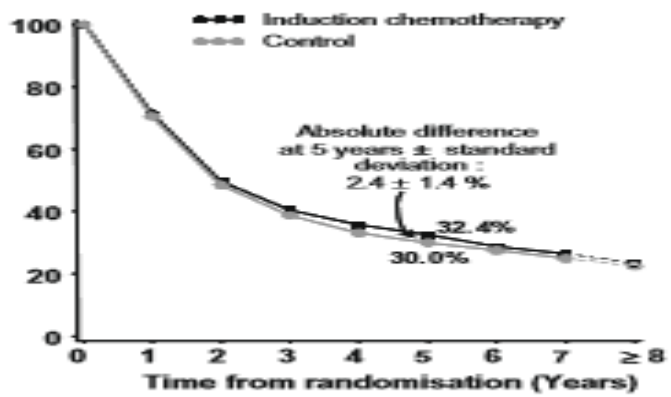
(a) Concomitant chemotherapy.



Death/person-years by period

	Years 0-2	Years 3-5	Years ≥ 6
Control	2500/6298	672/3658	217/2487
Chemotherapy	2187/6647	706/4576	278/3194

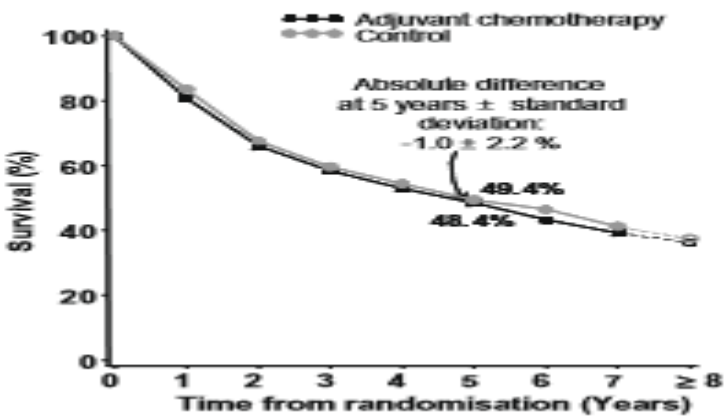
(b) Induction chemotherapy

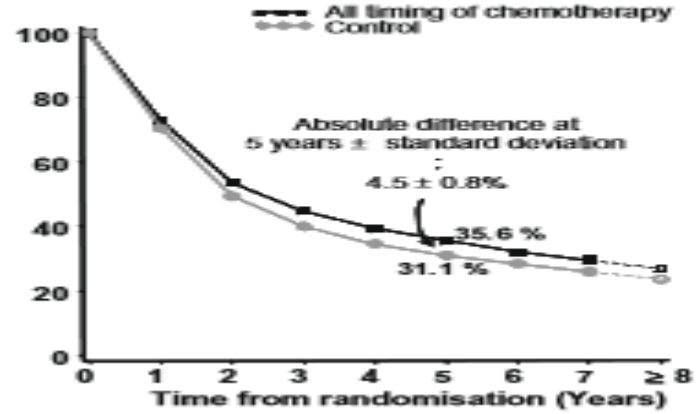


Death/person-years by period

	Years 0-2	Years 3-5	Years ≥ 6
	1283/3535	393/2276	137/1417
	1318/3820	392/2608	167/1530

(c) Adjuvant chemotherapy





Concurrent CT/RT increases 5yr OS by 6.5%

RTOG 0129
Phase III Trial of SF vs AFX-CB with Concurrent CDDP

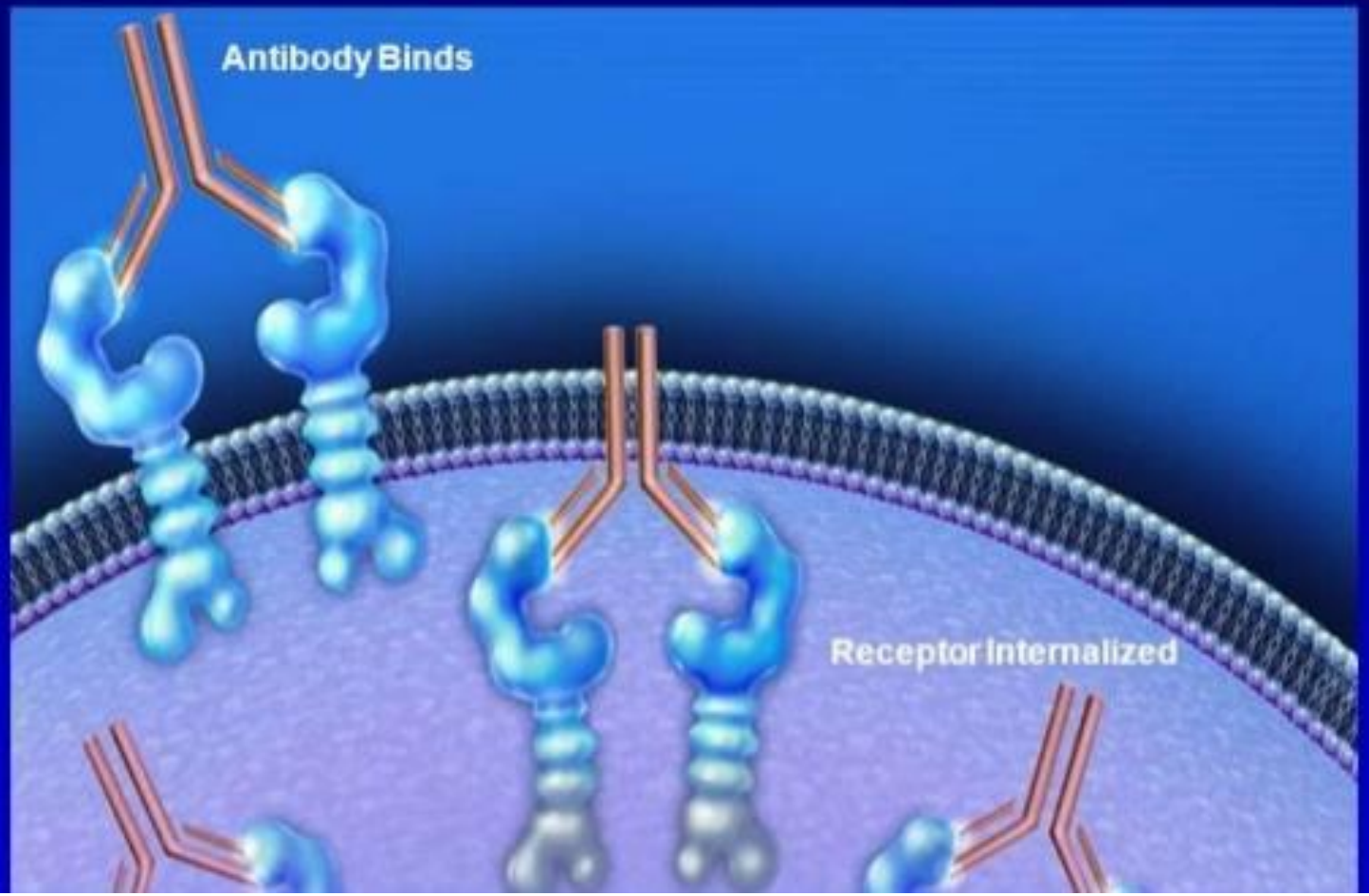
Stage III/IV
Lx, Opx, Hpx

Arm 1 : AFX-CB (72 Gy/6 wks)
+ CDDP 100 mg/m^2 x 2 cycles

Arm 2 : SF (70 Gy/7 wks)
+ CDDP 100 mg/m^2 x 3 cycles

- In setting of concurrent chemoradiation, accelerated radiation with delayed concomitant boost (AFX-CB) **does not improve overall survival or locoregional control** compared to standard fractionation (SF)
- No difference in acute or long-term toxicity
- ASTRO 2009, Ang

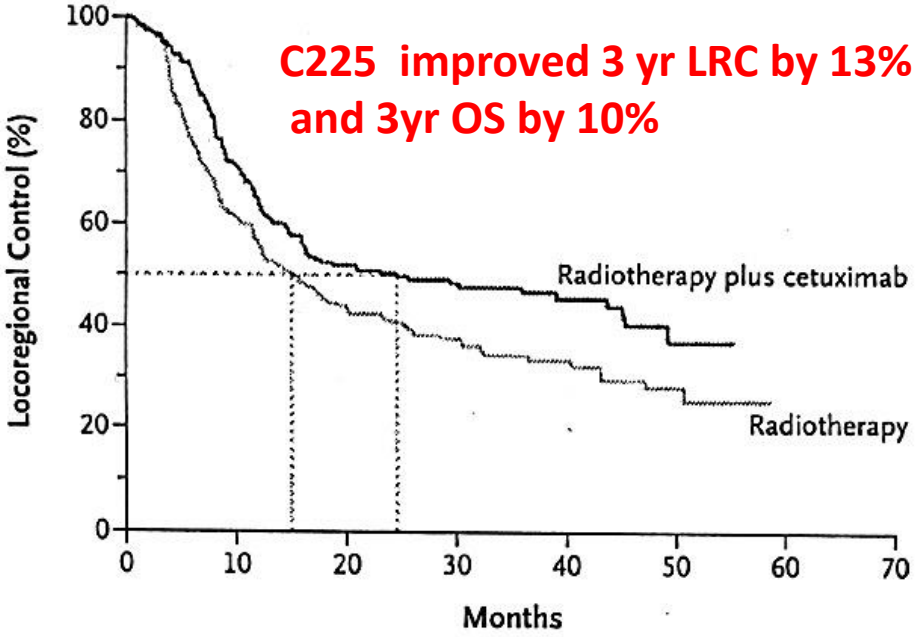
ERBITUX (Cetuximab) Mechanism of Action



Radiotherapy plus Cetuximab for Squamous-Cell Carcinoma of the Head and Neck

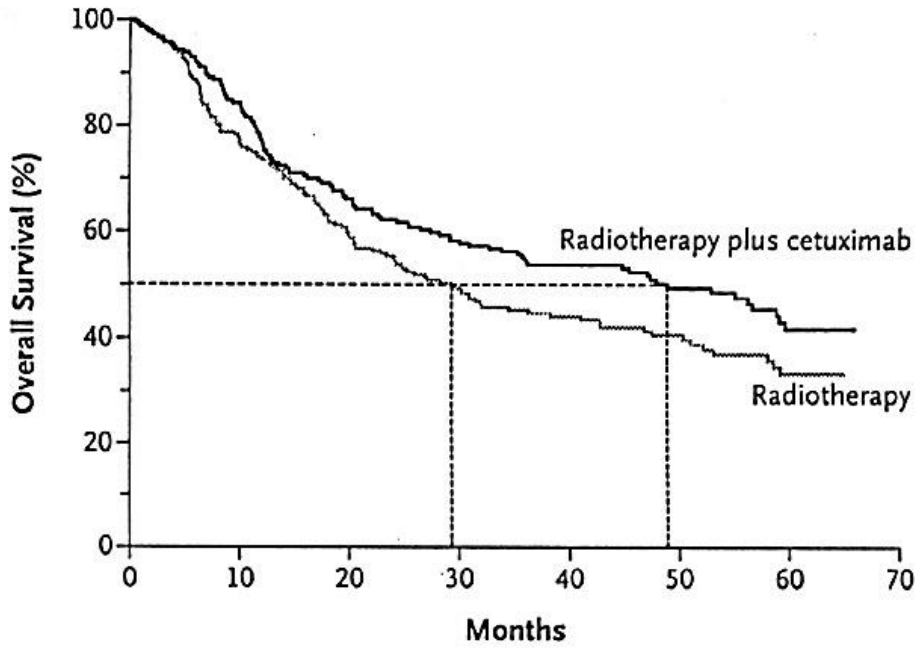
James A. Bonner, M.D., NEJM 354:567-78, Feb 2006

C225 improved 3 yr LRC by 13% and 3yr OS by 10%



No. at Risk						
Radiotherapy	213	122	80	51	30	10
Radiotherapy plus cetuximab	211	143	101	66	35	9

Figure 1. Kaplan–Meier Estimates of Locoregional Control among All Patients Randomly Assigned to Radiotherapy plus Cetuximab or Radiotherapy Alone.



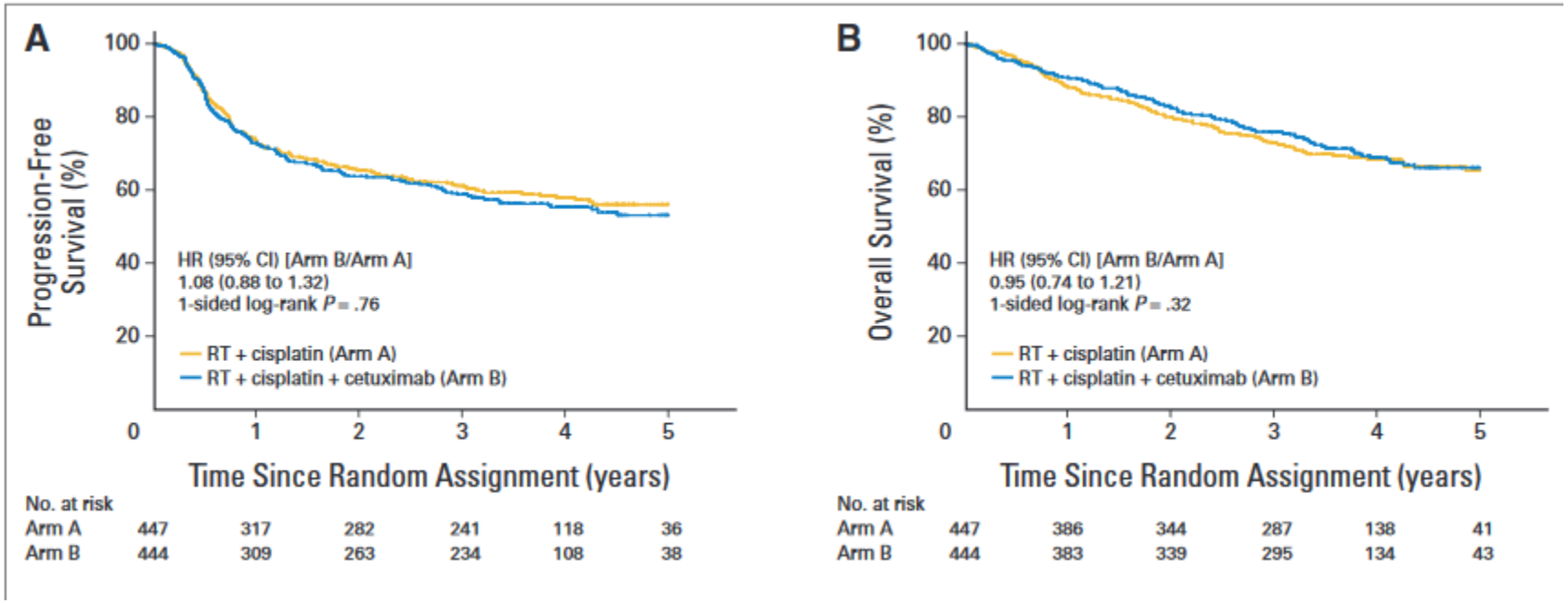
No. at Risk							
Radiotherapy	213	162	122	97	73	47	22
Radiotherapy plus cetuximab	211	177	136	116	98	61	24

Figure 2. Kaplan–Meier Estimates of Overall Survival among All Patients Randomly Assigned to Radiotherapy plus Cetuximab or Radiotherapy Alone.

Randomized Phase III Trial of Concurrent Accelerated Radiation Plus Cisplatin With or Without Cetuximab for Stage III to IV Head and Neck Carcinoma: RTOG 0522

K. Kian Ang,† Qiang Zhang, David I. Rosenthal, Phuc Felix Nguyen-Tan, Eric J. Sherman, Randal S. Weber,

J Clin Oncol 32:2940-2950.



No benefit of addition of C225 to concurrent chemoradiation

Practice Recommendations for Risk-Adapted Head and Neck Cancer Radiation Therapy During the COVID-19 Pandemic: An ASTRO-ESTRO Consensus Statement

Int J Radiation Oncol Biol Phys, Vol. ■, No. ■, pp. 1–10, 2020
0360-3016/$ - see front matter
https://doi.org/10.1016/j.ijrobp.2020.04.016

In scenario 2, risk mitigation with severely reduced radiation therapy capacity:

Use a hypofractionated radiation schedule.	**Strong agreement**
Reserve concomitant chemotherapy for use with conventional or mildly hypofractionated radiation therapy (≤2.4 Gy/f).	Agreement
Do not use induction chemotherapy to delay initiation of treatment.	Majority, near-agreement

Hypofractionation Schedules in Late Pandemic Scenario for Oropharynx

Clinical case	Standard approach: percent agreement and favored schedules*	Scenario 1 Early pandemic: *risk mitigation* Change from standard: percent agreement and favored schedules*	Scenario 2 Late pandemic: *severe shortage of radiation therapy capacity* Change from standard: percent agreement and favored schedules*
1. Oropharynx SCC T2N2bM0, p16 negative (OP−)	2.0-2.2 Gy/f (100%) **(strong agreement)** 70 Gy/35 f (63%) 70 Gy/33 f (17%) 65-66 Gy/30 f (13%)	No change **(strong agreement)**	**Hypofractionated** 2.41-3.0 Gy/f (70%) **(strong agreement)** 55 Gy/20 f (30%) 54 Gy/18 f (7%) 62.5-64 Gy/25 f (7%)

IAEA-HYPNO Phase III Trial

Randomized Multicenter Trial of Accelerated Hypo - vs. Accererated Fractionated Radiotherapy for Head and Neck Squamous Cell Carcinoma

ClinicalTrials.gov Identifier: **NCT02765503**

20 fractions x 275cGy (55Gy/44Gy)/4 wks vs 33 fractions x 200cGy (66Gy)/5 1/2 wks (Dahanca)

Oropharynx, Larynx, Oral Cavity **(Nasopharynx Excluded)**

Concurrent Chemotherapy Permitted

Trial Completed—Analysis Pending

Clinical Oncology 30 (2018) 366–374

Contents lists available at ScienceDirect

Clinical Oncology

64 Gy in 25 fractions/5 wks + platinum

Original Article

Feasibility of Dose-escalated Hypofractionated Chemoradiation in Human Papilloma Virus-negative or Smoking-associated Oropharyngeal Cancer

S. Meade [*], P. Gaunt [†], A. Hartley [*‡], M. Robinson [§], V. Harrop [*], J. Cashmore [*], L. Wagstaff [‡], J. Babrah [†], S.J. Bowden [†], H. Mehanna [‡], P. Sanghera [*‡]

[*] *Hall-Edwards Radiotherapy Research Group, University Hospital Birmingham NHS Foundation Trust, Birmingham, UK*
[†] *CRUK Clinical Trials Unit, University of Birmingham, Birmingham, UK*
[‡] *Institute of Head and Neck Studies and Education (InHANSE), University of Birmingham, Birmingham, UK*
[§] *School of Dental Sciences, Newcastle University, Newcastle, UK*

Radiobiological basis for selection of the trial regimen

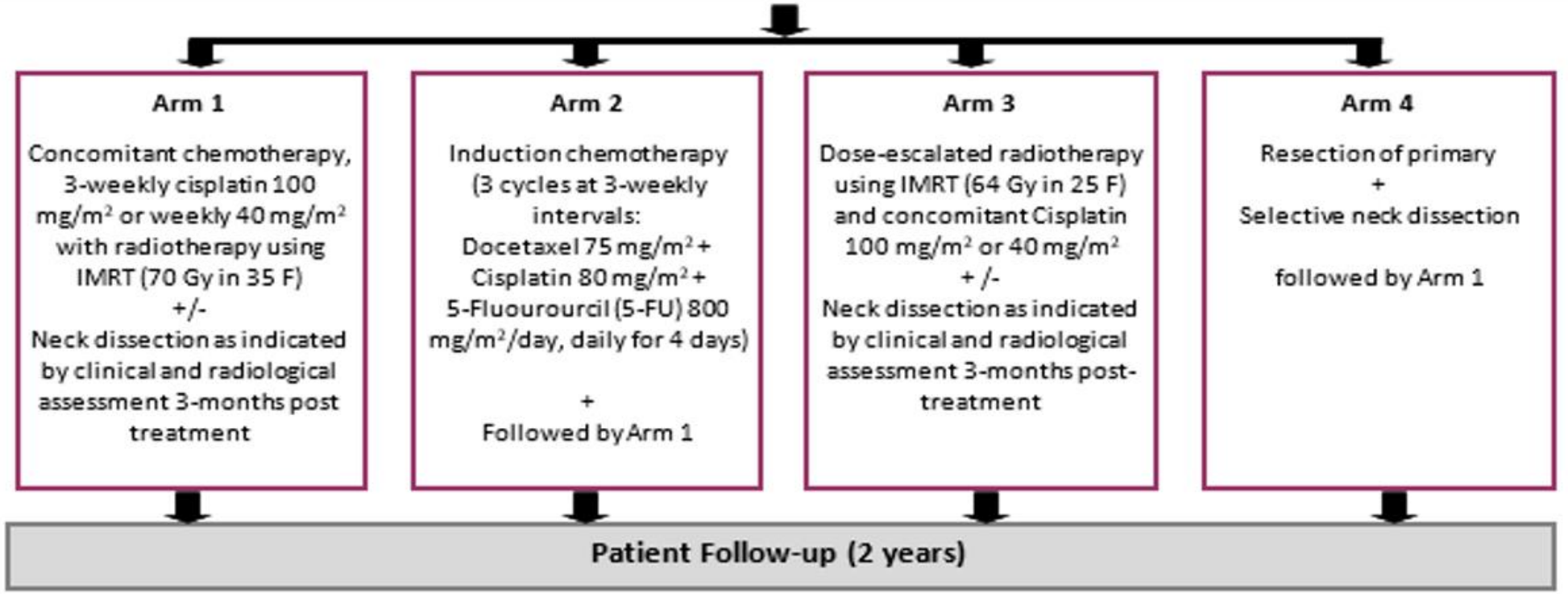
Total dose (Gy)	Fraction number	Overall treatment time (days)	Time corrected BED tumour† (Gy_{10})	Log_{10} cell kill	Time corrected BED mucosa‡ (Gy_{10})	BED late§ (Gy_3)	BED late‖ (Gy_2)
70	35	46	68	10.3	53	117	140
65	30	39	67	10.2	54	112	135
60	30	39	60	9.1	47	100	120
54	30	39	52	7.9	38	86	103
64.5	25	32	74	11.2	61	120	148
64*	25	32	73	11.1	61	119	146
63	25	32	72	10.9	59	116	142
62.5	25	32	71	10.8	58	115	141
56*	25	32	61	9.3	49	98	119
50*	25	32	53	8.0	40	83	100

BED, biologically effective dose; t_k, kick-off time or time of onset of accelerated repopulation; t_p, average doubling time during accelerated repopulation.

Phase III Trial Comparing Alternative Regimens for Escalating Treatment Intermediate and High Risk Oropharynx Cancer

- Definitive:
  - 70Gy/35 + CDDP (weekly or high dose)
  - 64Gy/25 + CDDP (weekly or high dose)
  - Induction TPF→70Gy/35+CDDP (weekly or high dose)
  - Surgery→Adjuvant chemoradiation

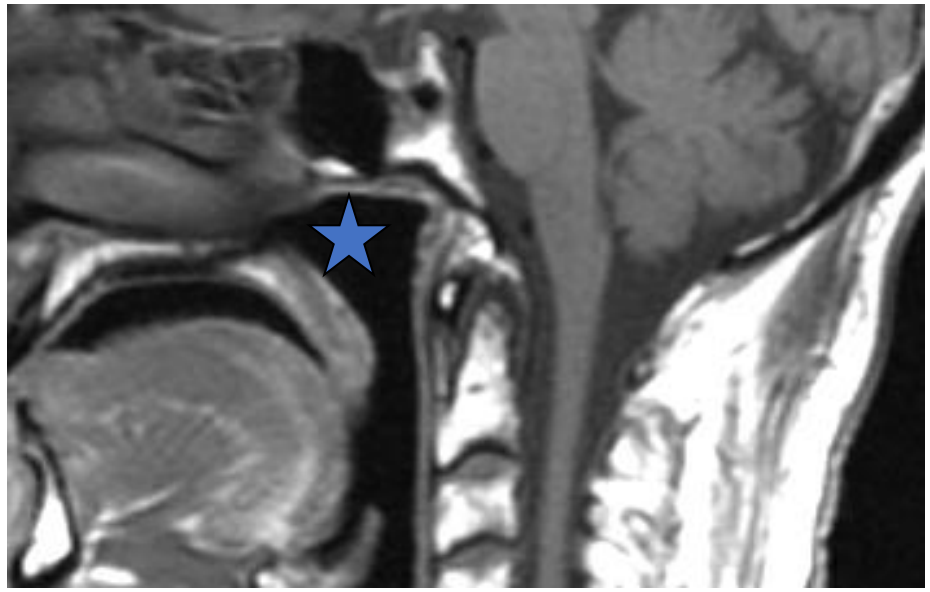
- N=695 Oropharynx Cancer
- Primary Endpoint: Overall Survival
- Secondary: QOL, Toxicity, Swallowing function

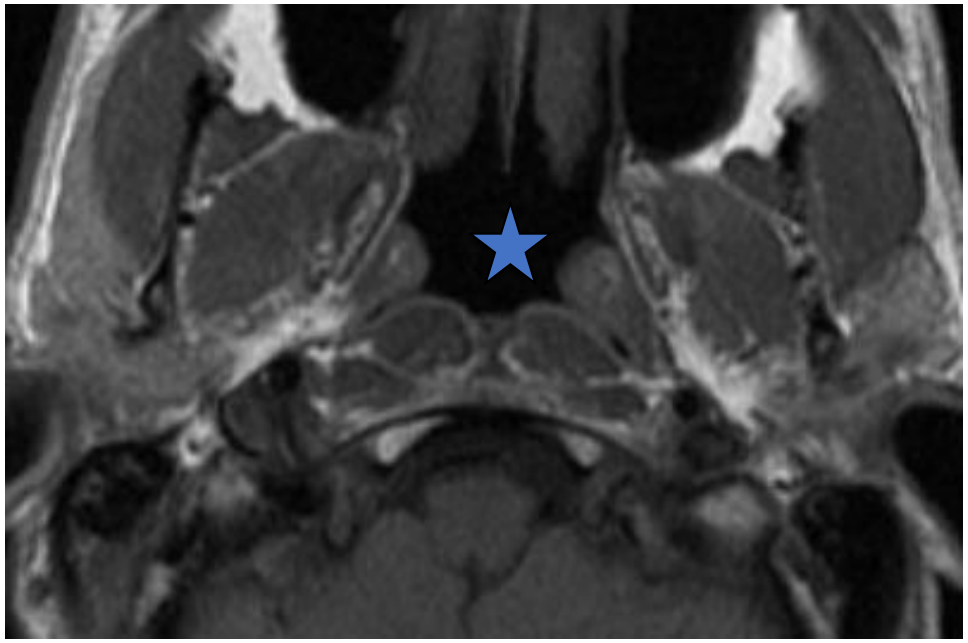


Nasopharynx Cancer

Nasopharynx: Anatomical Boundaries

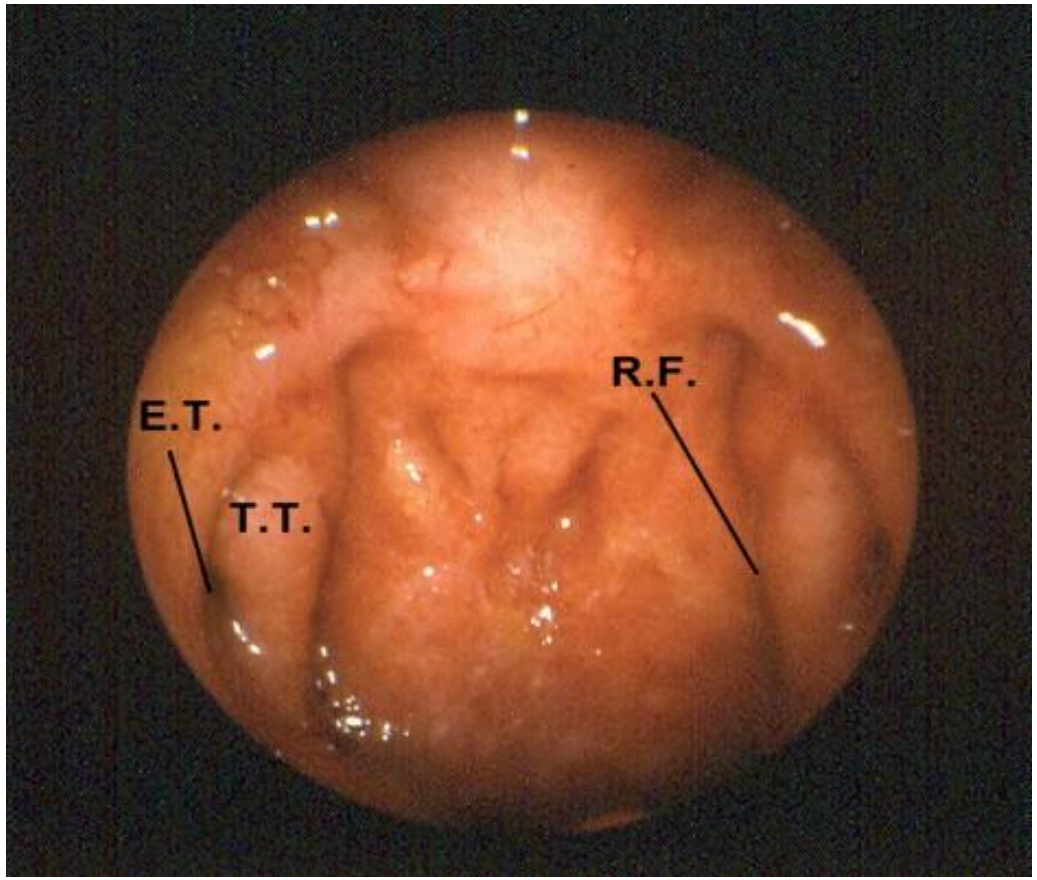
- Upper boundary
  - Sphenoid sinus, clivus
- Lower boundary
  - Superior surface SP
- Posterior boundary
  - Clivus, CVJ, prevertebral muscles
- Anterior boundary
  - Posterior choana
- Lateral boundary
  - Eustachian tube orifice, torus tubarius, fossa of Rosenmuller



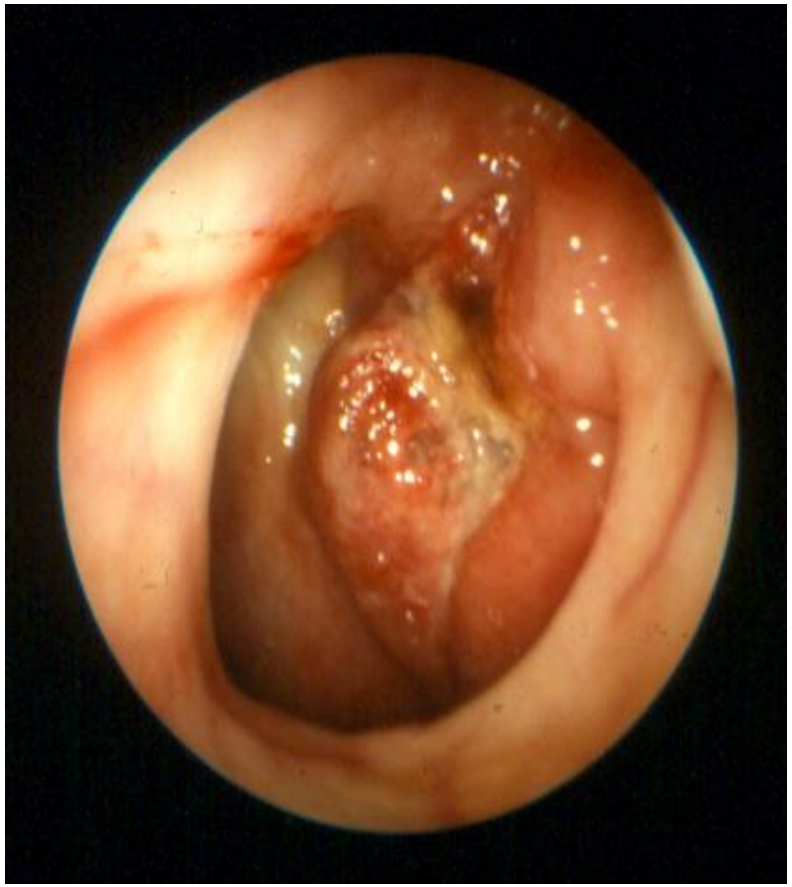


Flexible Endoscopic Images

Endoscopic View of Normal Nasopharynx



Left Nasopharynx Tumor

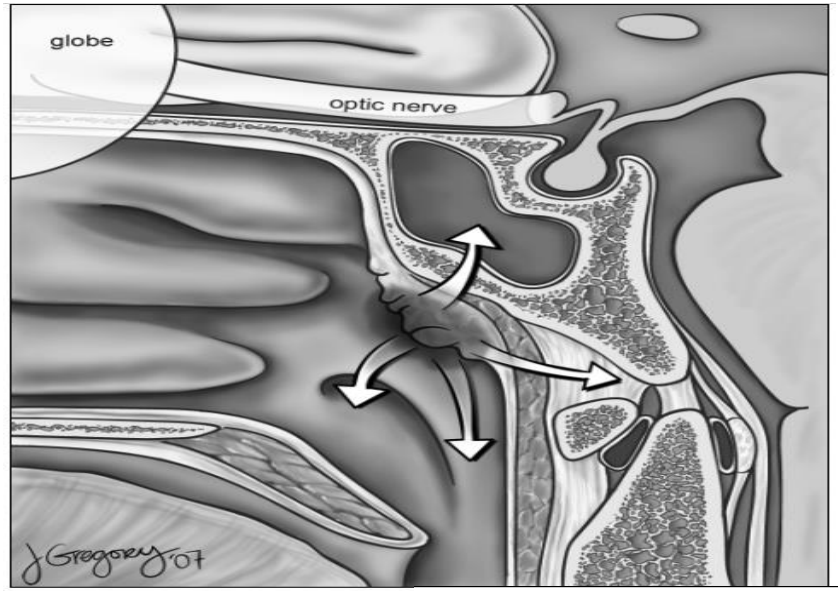


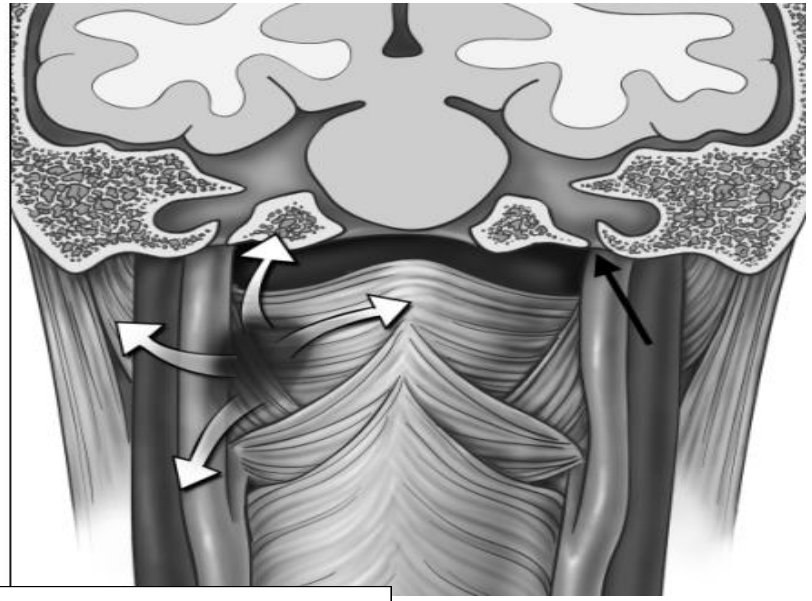
Landmarks: ET – Eustachian Tube opening

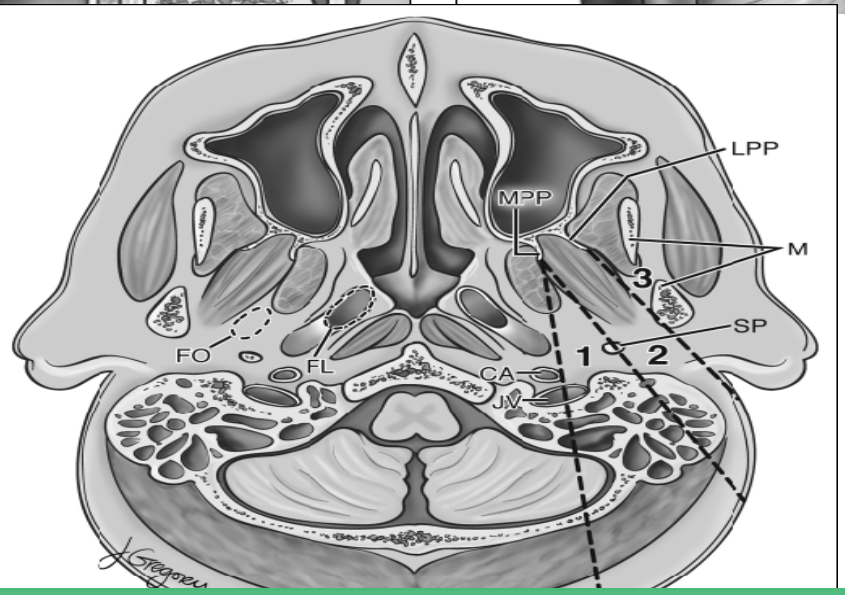
TT – Toru Tubarius

RF – Rosenmuller Fossa

Patterns of Local Spread







Harrison, Head and Neck Cancer 3rd ed

Nasopharynx AJCC Staging 8th Ed

- ❑ T1
- ❑ T2
- ❑ T3
- ❑ T4

Nasopharynx

Tumor confined to the nasopharynx, or extends to oropharynx and/or nasal cavity without parapharyngeal extension*

Tumor with parapharyngeal extension*

Tumor involves bony structures of skull base and/or paranasal sinuses

Tumor with intracranial extension and/or involvement of involvement of cranial nerves, hypopharynx, orbit, or with extension to the infratemporal fossa/ masticator space

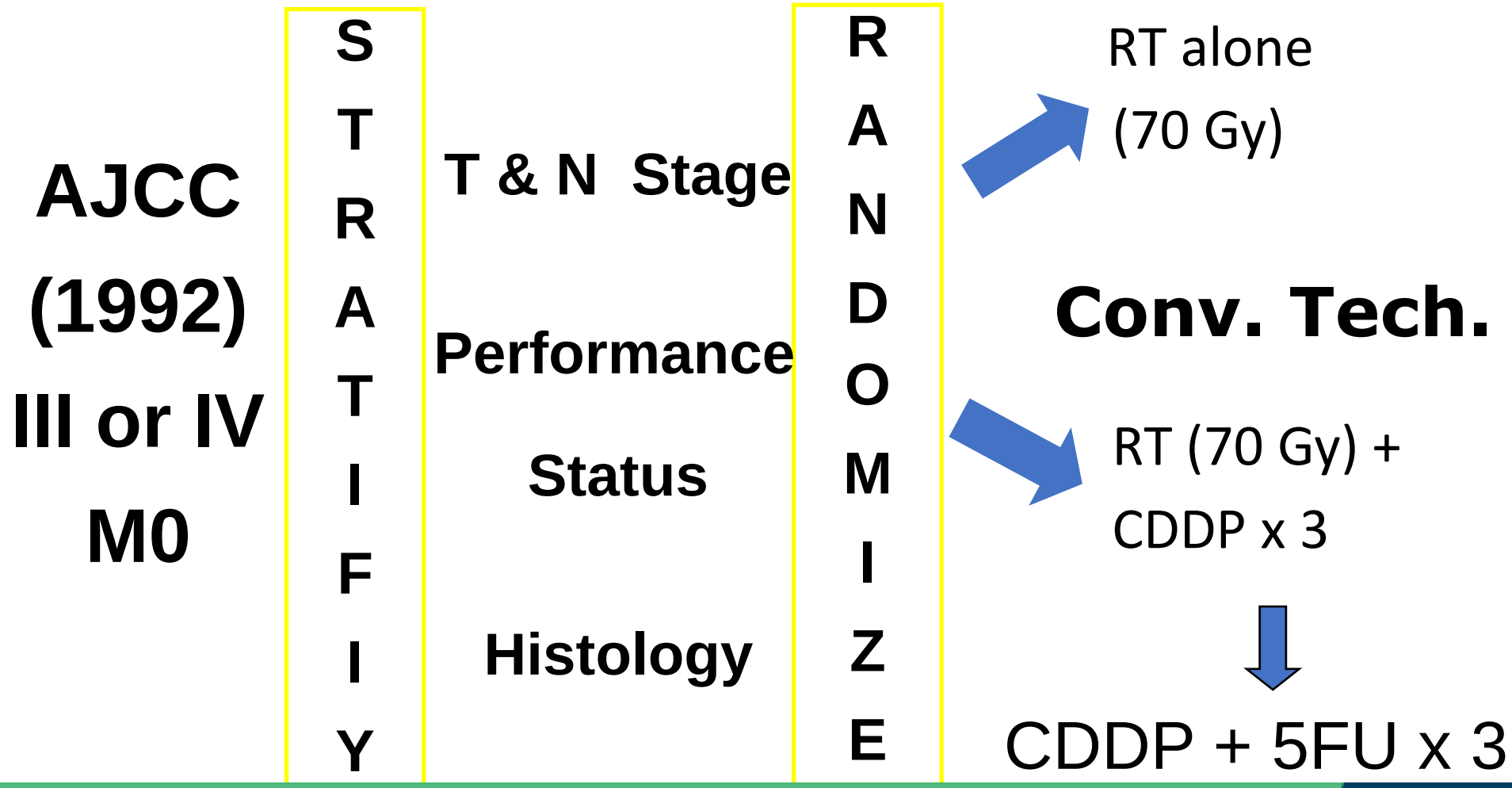
* Parapharyngeal extension denotes posterolateral infiltration of tumor.

N Category	*N Criteria*
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Unilateral metastasis in cervical lymph node(s) and/or unilateral or bilateral metastasis in retropharyngeal lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage
N2	Bilateral metastasis in cervical lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage
N3	Unilateral or bilateral metastasis in cervical lymph node(s), larger than 6 cm in greatest dimension, and/or extension below the caudal border of cricoid cartilage

I	**T1N0**	**III**	**T1-2N2, T3N0-2**	**IVC**	**M1**
II	**T1N1**	**IVA**	**T4N0-2**		
	T2N0-1	**IVB**	**N3**		

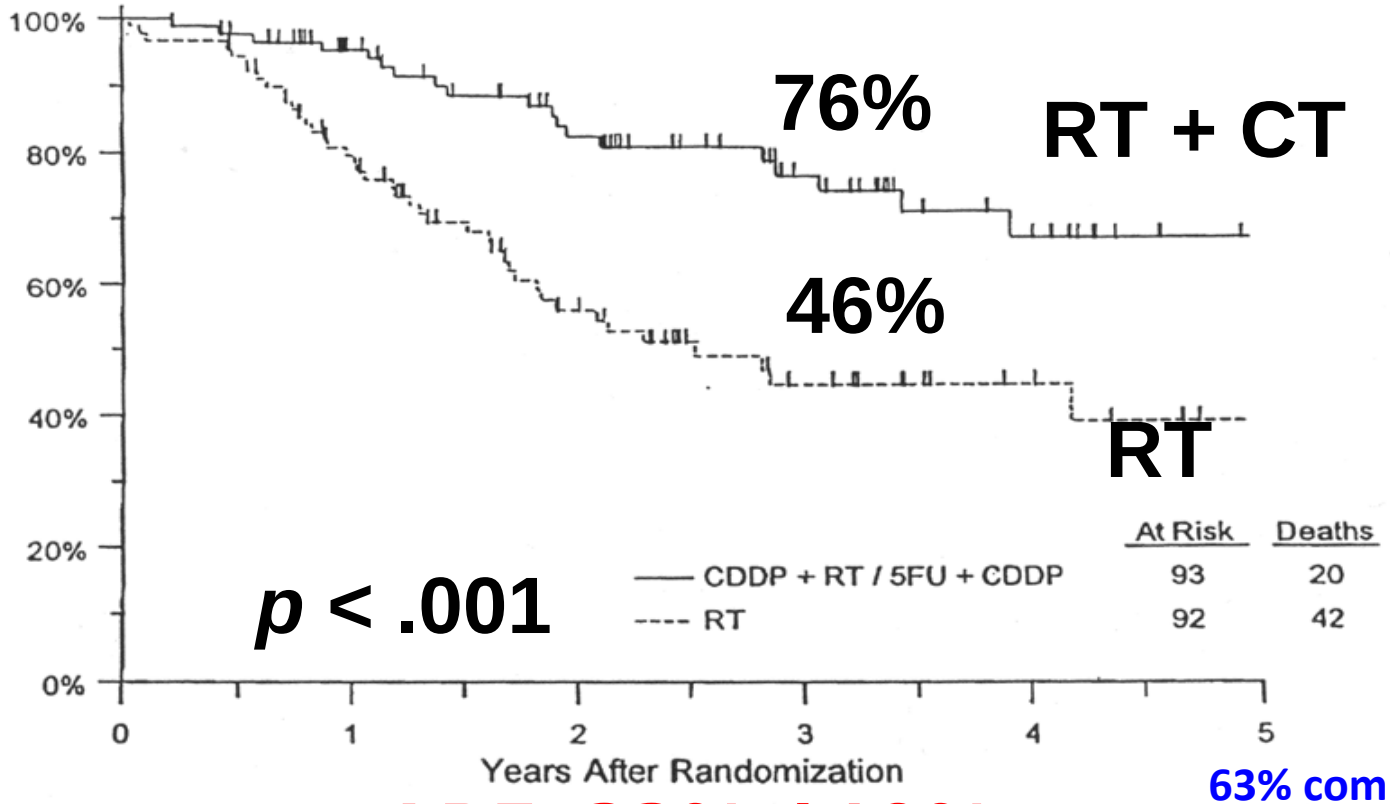
INTERGROUP 99 (RTOG 88-17)

Al-Sarraf et al, JCO, 1998



INTERGROUP 99 (RTOG 88-17) TRIAL OF CHEMOTHERAPY FOR NPC

Overall Survival - All Patients



LRF: 33%→10%

DM: 35%→13%

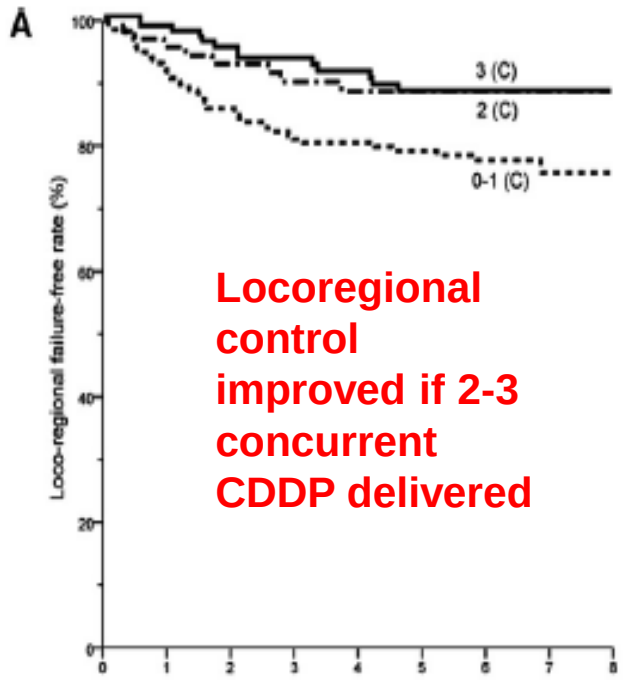
63% completed concurrent CDDPx3

55% completed prescribed adjuvant 5FU/CDDP x 3

Factors contributing to the efficacy of concurrent–adjuvant chemotherapy for locoregionally advanced nasopharyngeal carcinoma: Combined analyses of NPC-9901 and NPC-9902 Trials

Anne W.M. Lee [a,], Stewart Y. Tung [b], Roger K.C. Ngan [c], Rick Chappell [d],*

6–666



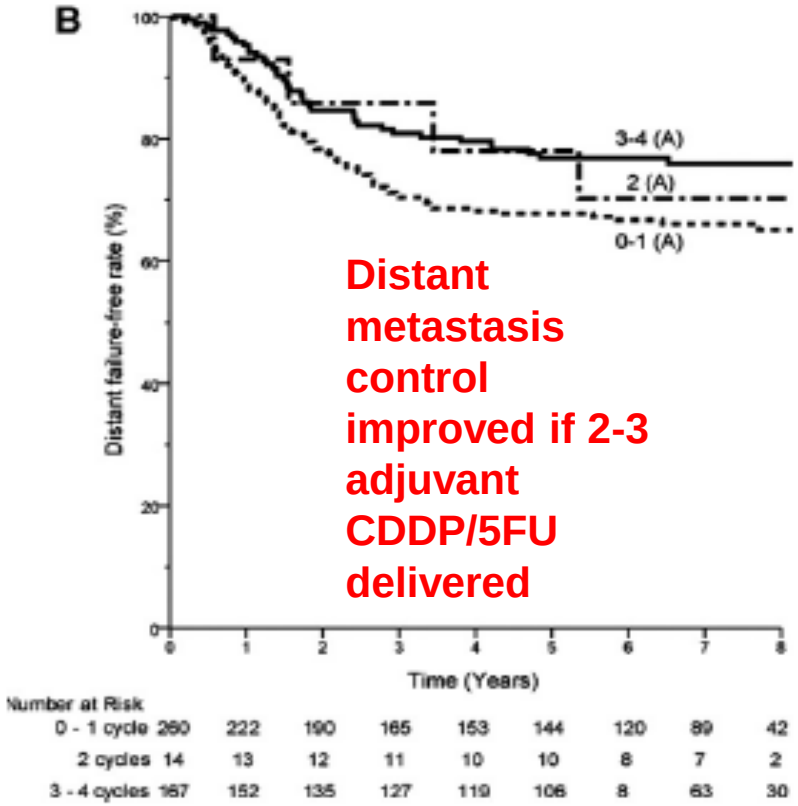


Fig. 5 – Kaplan–Meier estimates of (A) loco-regional failure-free rate and (B) distant failure-free rate. (C) = the number of cycles of concurrent chemotherapy received; (A) = the num-

Can Induction Add Further benefit

To Concurrent Chemoradiotherapy

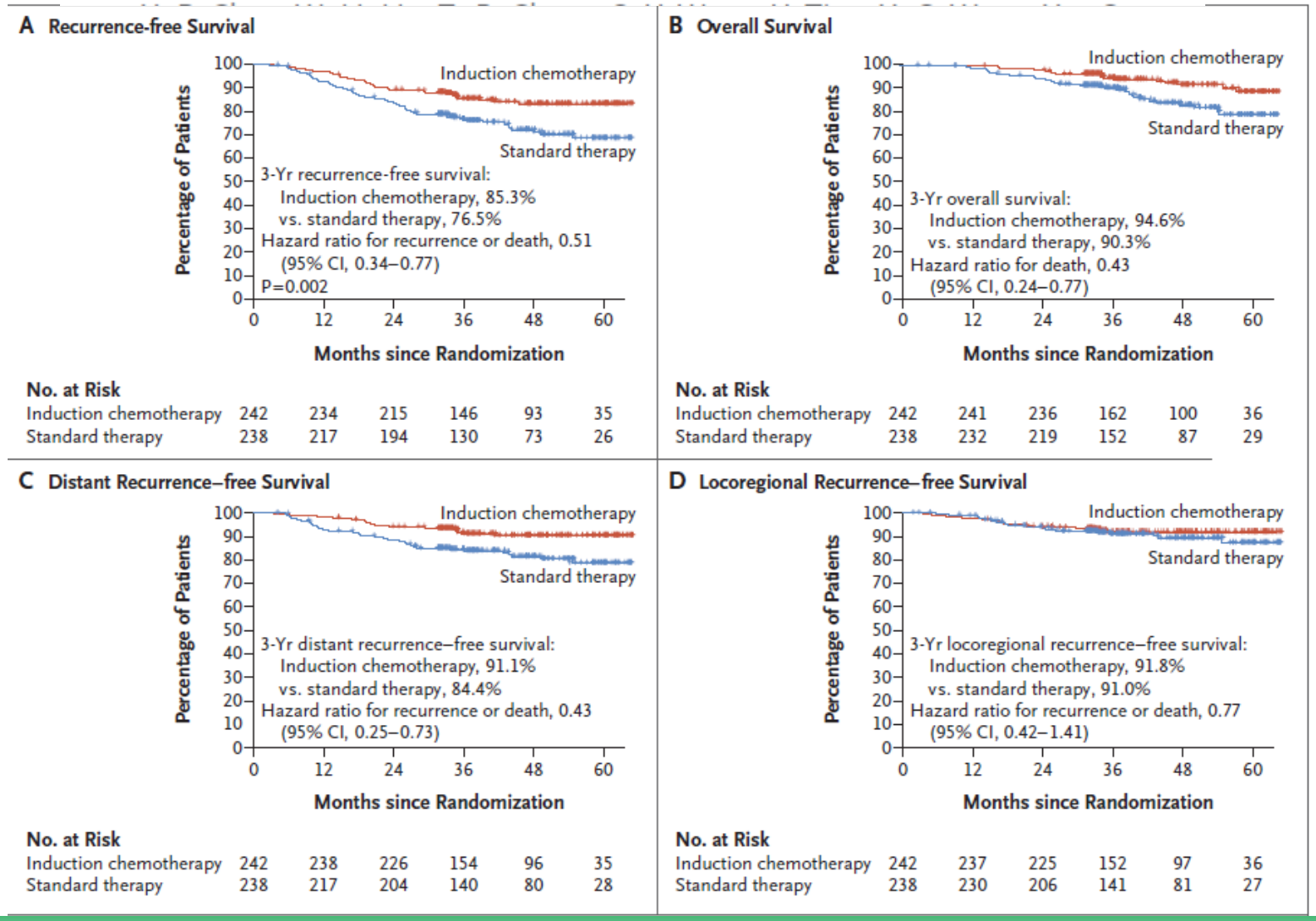
To Improve upon DM rates?

To Improve upon patient compliance?

Gemcitabine and Cisplatin Induction Chemotherapy in Nasopharyngeal Carcinoma

Y. Zhang, L. Chen, G.-Q. Hu, N. Zhang, X.-D. Zhu, K.-Y. Yang, F. Jin, M. Shi,

N ENGL J MED 381;12 NEJM.ORG SEPTEMBER 19, 2019



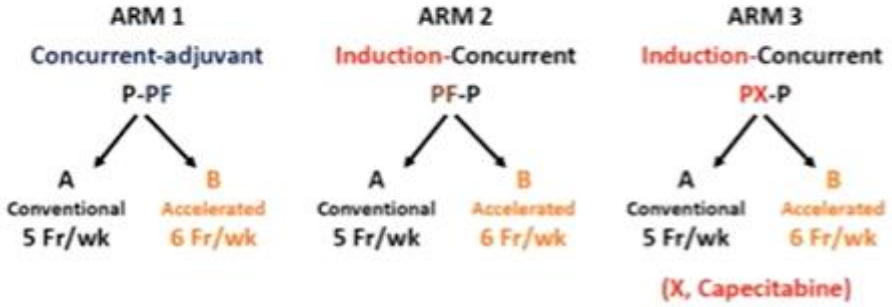
Induction gemcitabine/CDDP x 3 cycles followed by concurrent RT+CDDPx3 had high compliance (97% got 3 cycles induction, 92% got 2-3 cycles of concurrent)

Induction improved 3yr DM (7% Δ)/OS (4% Δ) compared to concurrent RT+CDDPx3 alone (no adjuvant)

Randomized Phase III Trial comparing Induction-Concurrent vs Concurrent-Adjuvant

NPC-0501 Trial

803 Stages III-IVB pt. (IMRT: 93%)



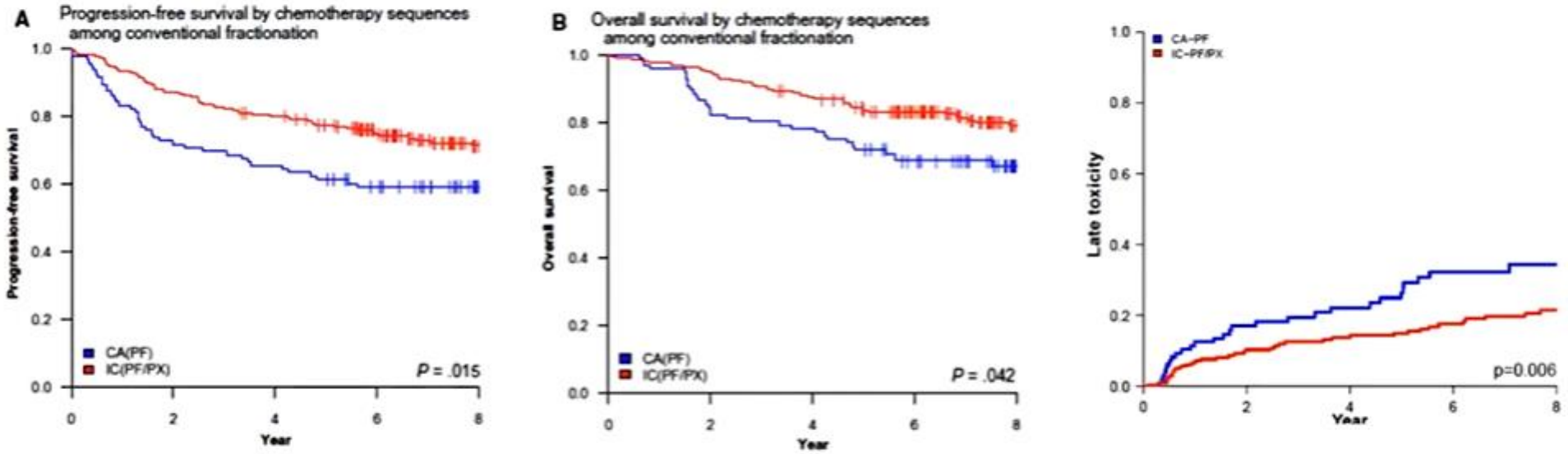
Evaluation of timing, drug and dose

Regimen	Sequence	Concurrent		Non-Concurrent				
		Cisplatin	Cycles	Cisplatin	Drug2		Frequency	Cycles
P-PF	Adjuvant	100 mg/m² Q3 wk	AF: 2 CF: 3	80 mg/m²	5FU	1000 mg/m² IVI x4	Q4 wk	3
PF-P	Induction			100 mg/m²	5FU	1000 mg/m² IVI x5	Q3 wk	
PX-P	Induction			100 mg/m²	Capecitabine	2000 mg/m² Oral x14	Q3 wk	

Hong Kong NPC Study Group - Study PI: A Lee A & R Ngan

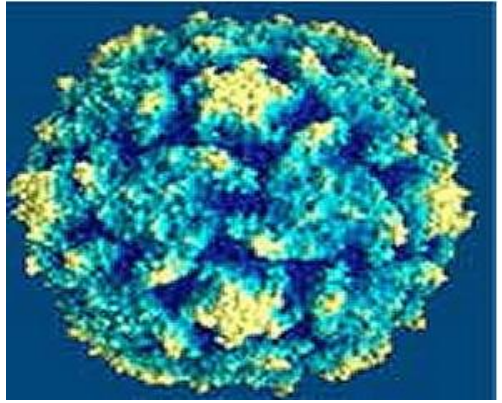
Can Induction-Concurrent Sequence achieve Superior Results For patients irradiated with Conventional Fractionation?

NPC-0501 Trial



Hypothesis-Generating for patients with conventional-fractionated RT
Induction-Concurrent Sequence → better survival without increase in late toxicity

Lee for Hong Kong NPC Study Group, Cancer 2020



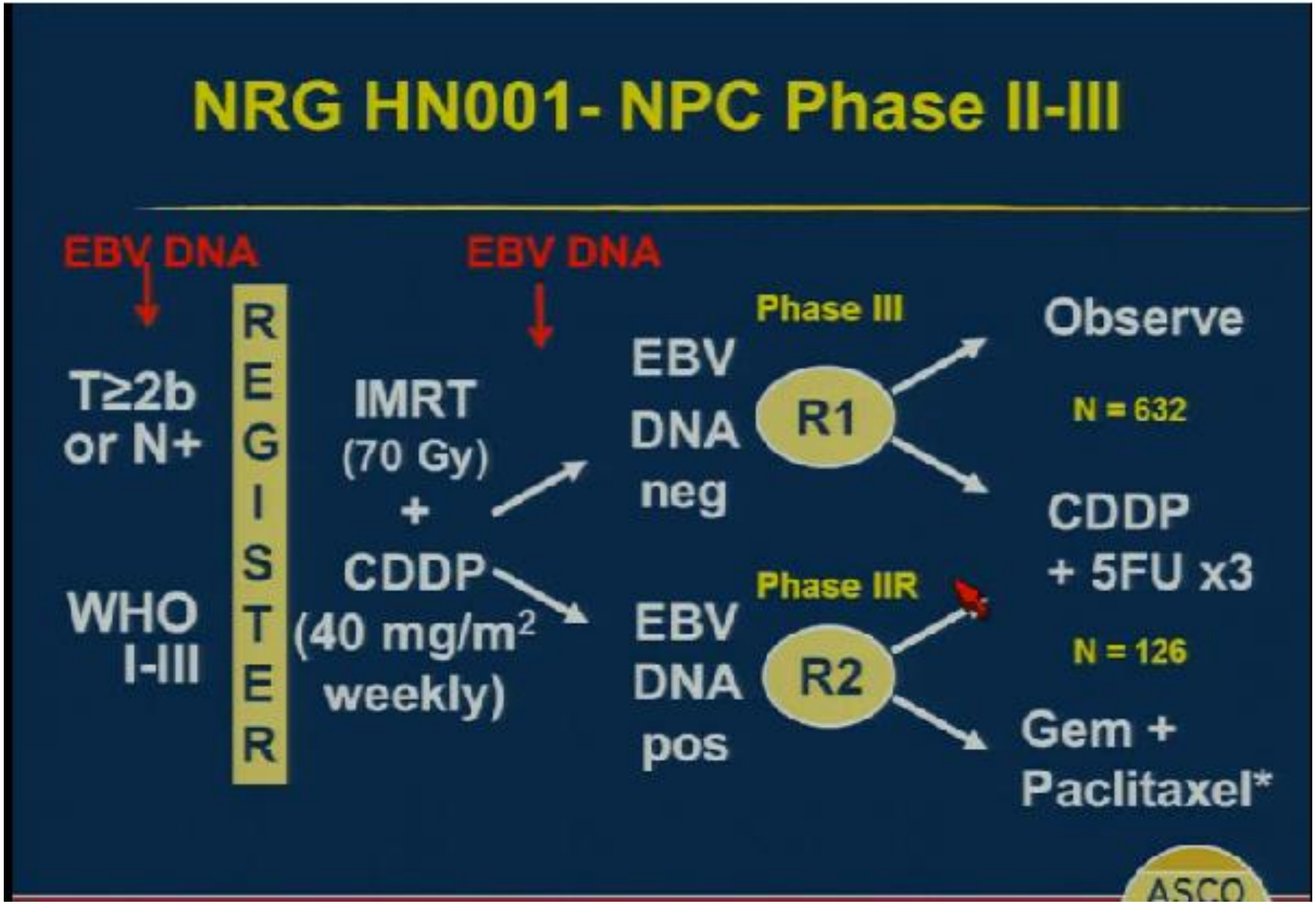
Epstein-Barr Virus in NPC as a Biomarker

- EBV associated with malignant transformation
- EBV Nuclear Antigen and viral DNA can be detected in tumor cells to diagnose NPC and measured in blood by PCR
- Pre-treatment Plasma EBV DNA can prognose survival and predict for distant metastasis (Lo Cancer Res 2000, 60(24) 6878-81)
- Post-treatment Plasma EBV DNA can monitor treatment response and predict recurrence (Lo Cancer Res 1999, 59 (6) 1188-91)

EBV cfDNA 1 week post-CRT for NPC is highly prognostic for disease progression

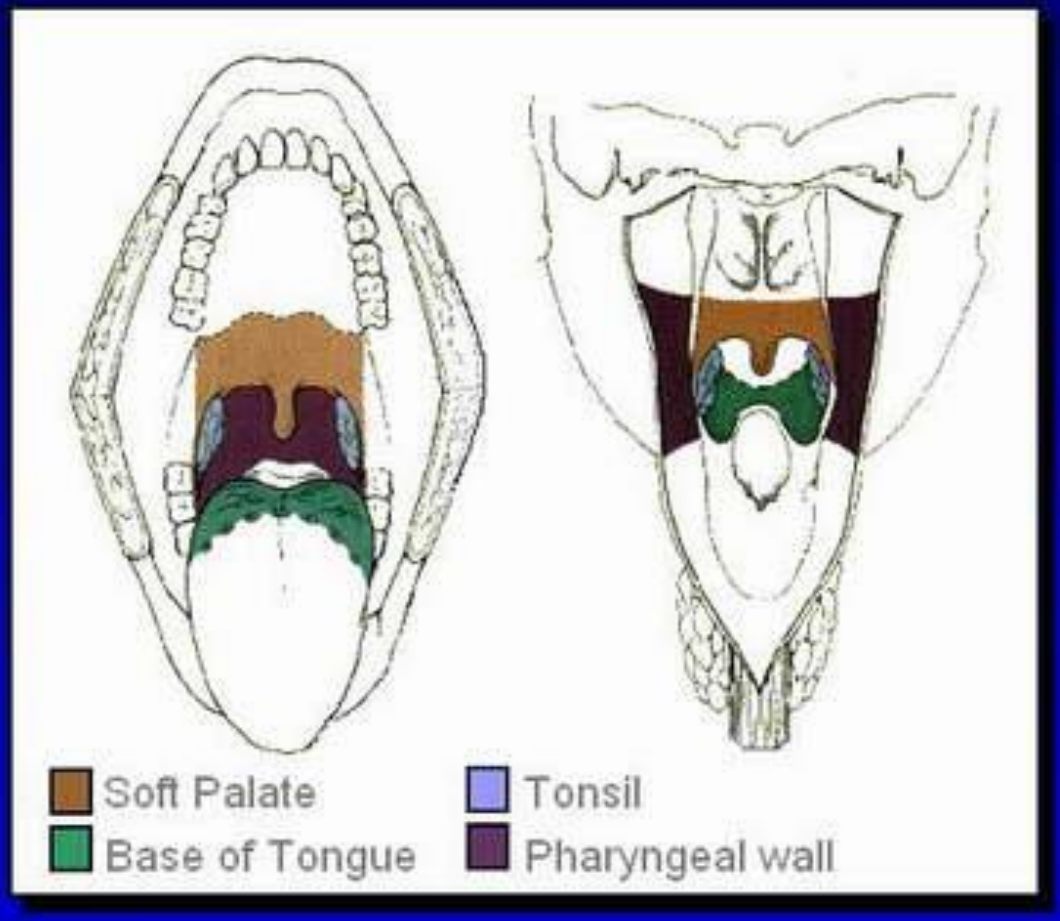
Series	N	Pre-CRT sensitivity	Pre-CRT copies/mL	Post-CRT EBV+ frequency	OS
Chan 2002	170	89%	Median: 2352	29%	1yr 76 vs 97%
Le 2005	46	48%	Range: 0-6600	26%	2yr 55 vs 94%
Lin 2007	152	94%	Median: 573	20%	5yr 39 vs 83%
Hou 2011	69	-	Median: 4000	11%	5yr 50 vs 91%
Lin 2004	99	95%	Median: 1461	10%	2yr 56 vs 97%
Lin 2013	210	-	-	-	5yr 33 vs. 79%

Post-Radiation Plasma EBV levels to Guide Adjuvant CT



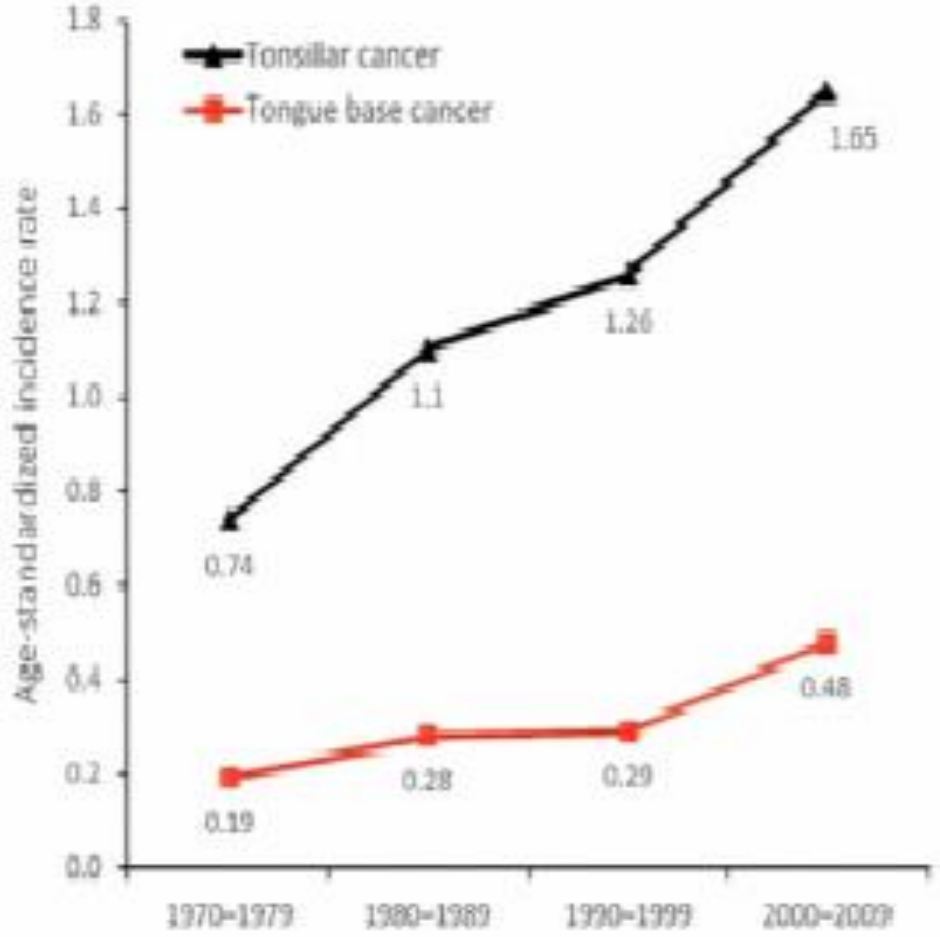
Oropharynx - Sites

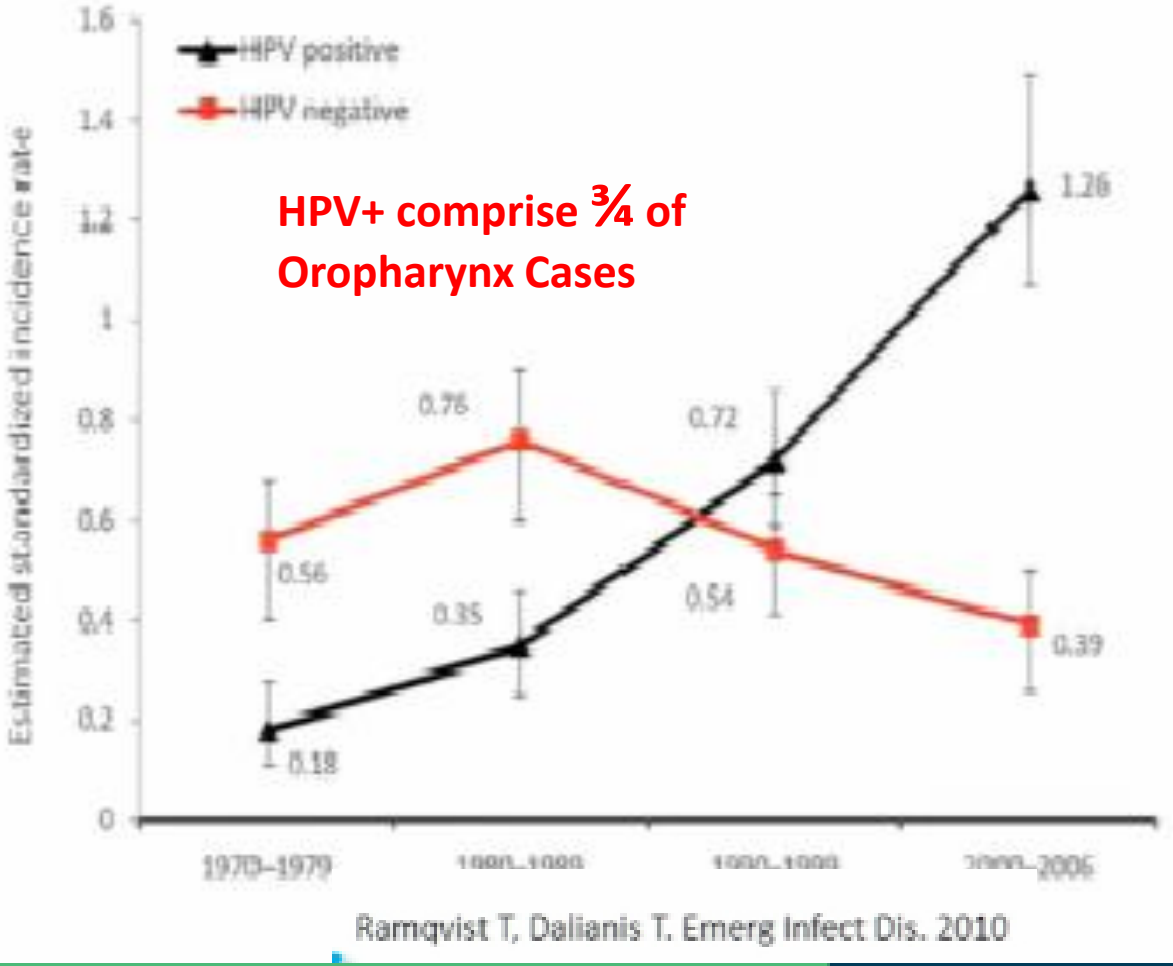
Anterior View



Posterior View

Incidence of Oropharynx Cancer Has Doubled Over Past 30yrs Primarily From HPV+ Tumors especially Tonsil Cancers





HPV+ comprise ¾ of Oropharynx Cases

Ramqvist T, Dalianis T. Emerg Infect Dis. 2010

p16+ Oropharynx Nodal Stage: Clinical vs Pathologic

4.2.1 Clinical N (cN)

✓	*cN Category*	*cN Criteria*
	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1	One or more ipsilateral lymph nodes, none larger than 6 cm
	N2	Contralateral or bilateral lymph nodes, none larger than 6 cm
	N3	Lymph node(s) larger than 6 cm

4.2.2 Pathological N (pN)

✓	*pN Category*	*pN Criteria*
	NX	Regional lymph nodes cannot be assessed
	pN0	No regional lymph node metastasis
	pN1	Metastasis in 4 or fewer lymph nodes
	pN2	Metastasis in more than 4 lymph nodes

6 AJCC Prognostic Stage Groups

Always refer to the specific chapter for rules on clinical and pathological classification of this disease.

6.1 Clinical (cTNM)

✓	*When p16/HPV Status is…*	*And T is…*	*And N is…*	*And M is…*	*Then the stage group is…*
	Positive	T0, T1 or T2	N0 or N1	M0	I
	Positive	T0, T1 or T2	N2	M0	II
	Positive	T3	N0, N1 or N2	M0	II
	Positive	T0, T1, T2, T3 or T4	N3	M0	III
	Positive	T4	N0, N1, N2 or N3	M0	III
	Positive	Any T	Any N	M1	IV

6.2 Pathological (pTNM)

✓	*When p16/HPV Status is…*	*And T is…*	*And N is…*	*And M is…*	*Then the stage group is…*
	Positive	T0, T1 or T2	N0, N1	M0	I
	Positive	T0, T1 or T2	N2	M0	II
	Positive	T3 or T4	N0, N1	M0	II
	Positive	T3 or T4	N2	M0	III
	Positive	Any T	Any N	M1	IV

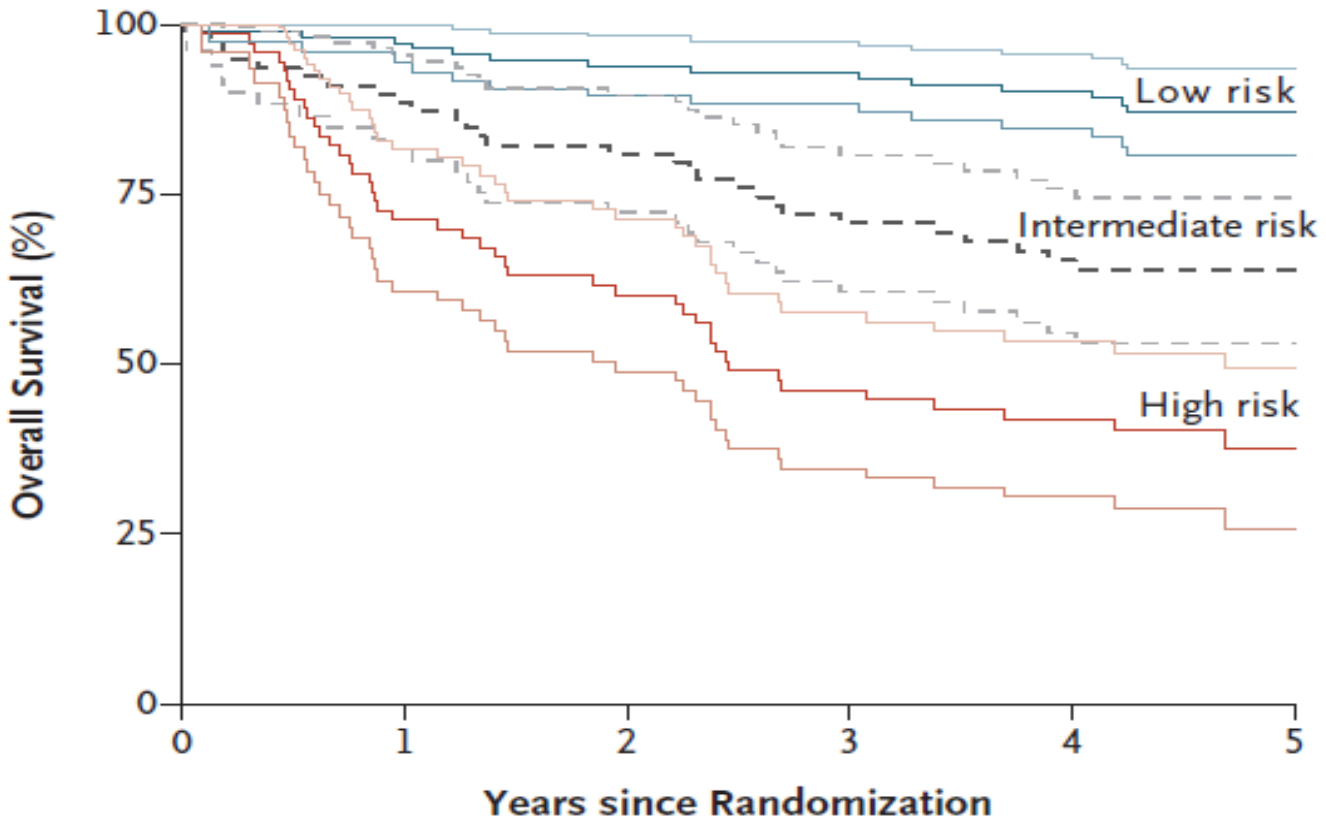
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Subset Analysis of Oropharynx Pts Treated on RTOG 0129

Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer

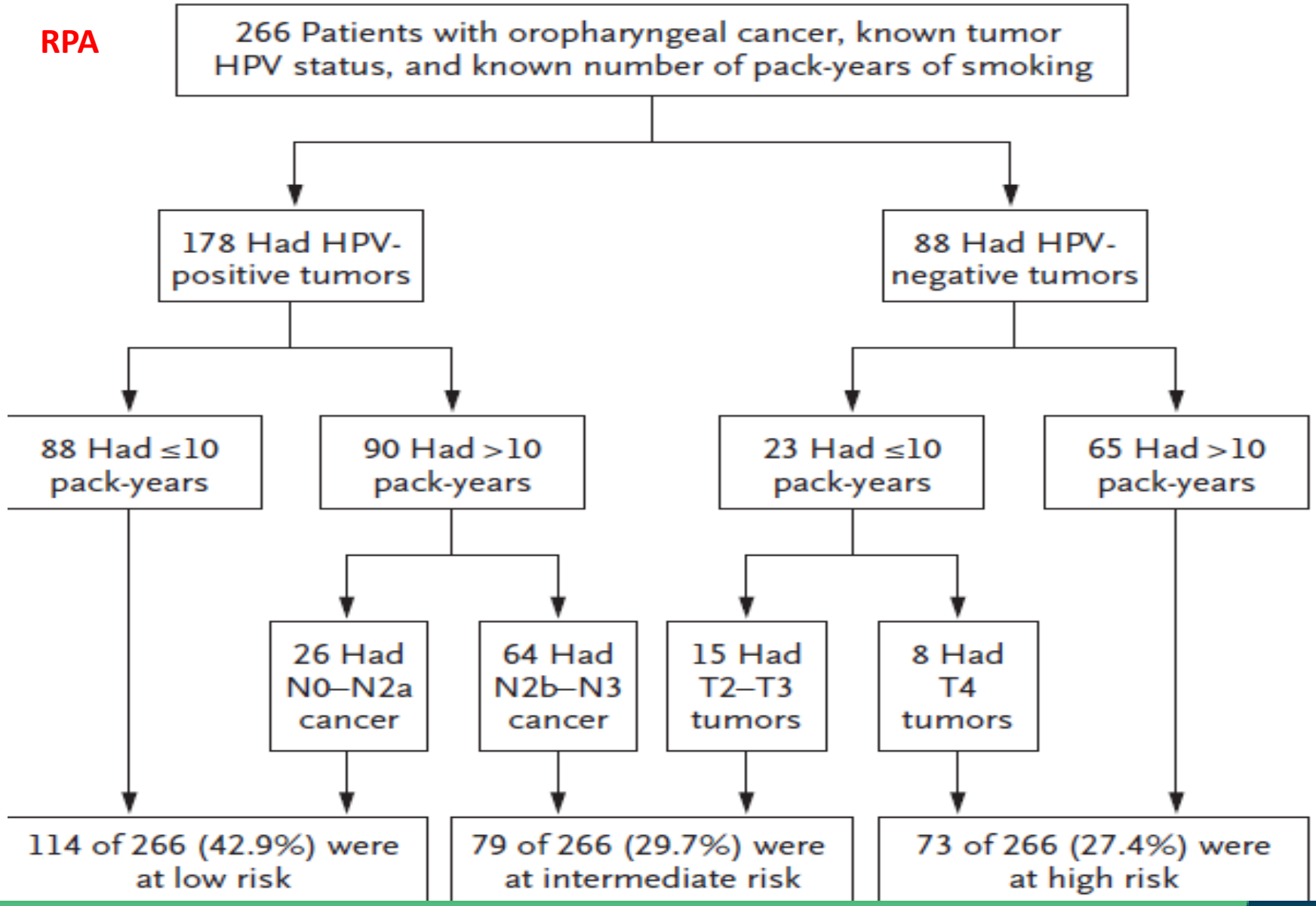
K. Kian Ang, M.D., Ph.D., Jonathan Harris, M.S., Richard Wheeler, M.D.,



No. at Risk						
Low risk	114	111	106	102	95	46
Intermediate risk	79	70	64	54	44	24
High risk	73	52	43	33	28	8

Risk Stratify by HPV, Tobacco and T/N Stage

RPA



Favorable Risk Comprise 43% of all OPX pts

Table 3. Survival Estimates, Causes of Death, and Patterns of Treatment Failure in Patients with Oropharyngeal Cancer, According to Tumor HPV Status.*

Variable	HPV-Positive (N = 206)	HPV-Negative (N = 117)	P Value†
Overall survival at 3 yr — % (95% CI)	82.4 (77.2–87.6)	57.1 (48.1–66.1)	<0.001
Cause of death — no. of patients/total no. (%)			0.67
Primary cancer	25/50 (50.0)	29/58 (50.0)	
Second primary tumor	4/50 (8.0)	8/58 (13.8)	
Protocol treatment	1/50 (2.0)	0/58	
Nonprotocol treatment	1/50 (2.0)	1/58 (1.7)	
Cause unrelated to cancer or treatment	10/50 (20.0)	8/58 (13.8)	
Unknown	9/50 (18.0)	12/58 (20.7)	
Progression-free survival at 3 yr — % (95% CI)	73.7 (67.7–79.8)	43.4 (34.4–52.4)	<0.001
Local–regional relapse at 3 yr — % (95% CI)	13.6 (8.9–18.3)	35.1 (26.4–43.8)	<0.001
Distant metastasis at 3 yr — % (95% CI)	8.7 (4.9–12.6)	14.6 (8.1–21.1)	0.23
Type of first treatment failure — no. of patients/total no. (%)			0.55
Local–regional disease	26/66 (39.4)	33/72 (45.8)	
Distant metastasis	21/66 (31.8)	17/72 (23.6)	
Death, no documented progression	19/66 (28.8)	22/72 (30.6)	
Second primary tumor at 3 yr — % (95% CI)	5.9 (2.6–9.1)	14.6 (8.1–21.0)	0.02

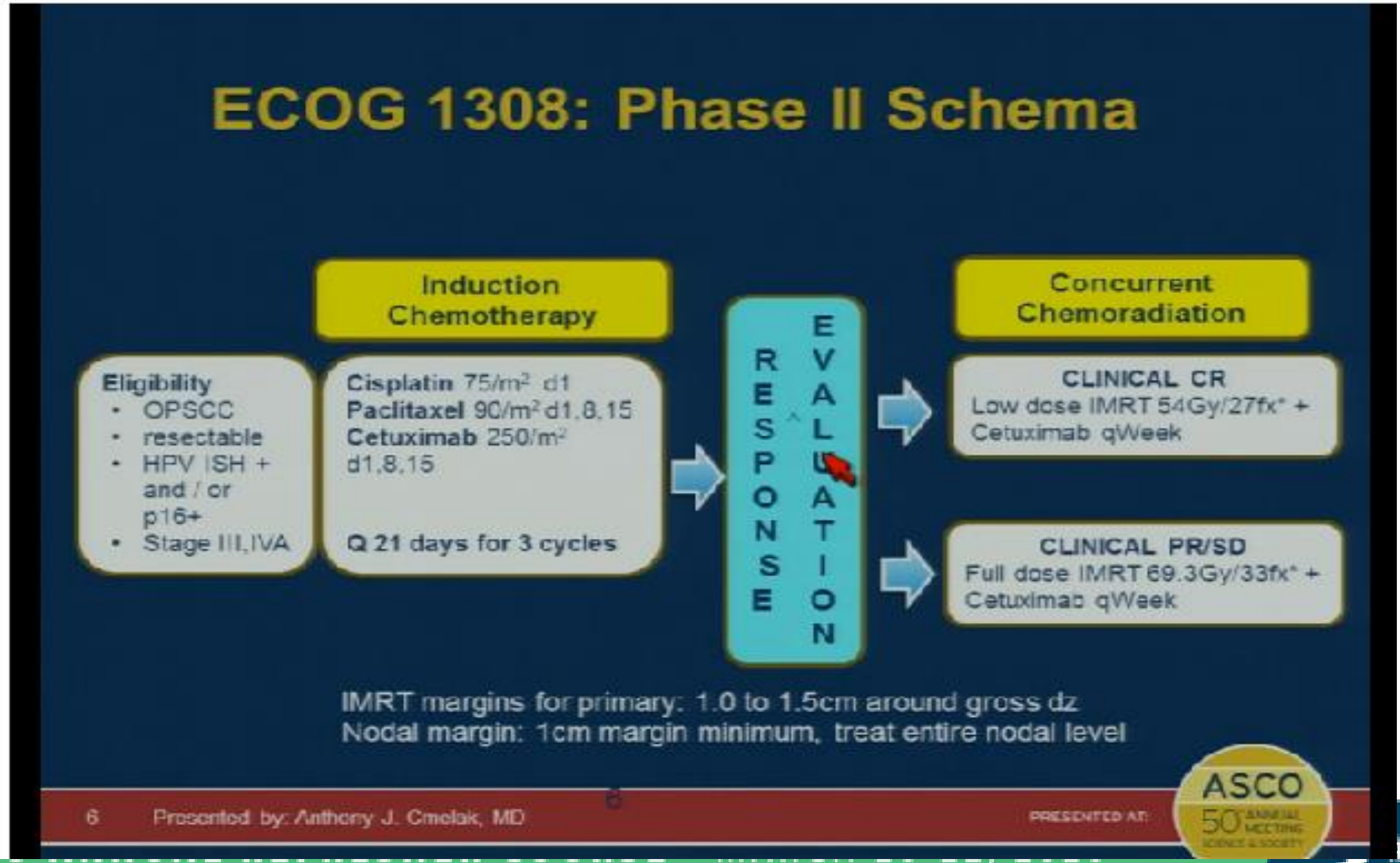
Radiation Dose Deescalation for Favorable Risk HPV+ Oropharynx

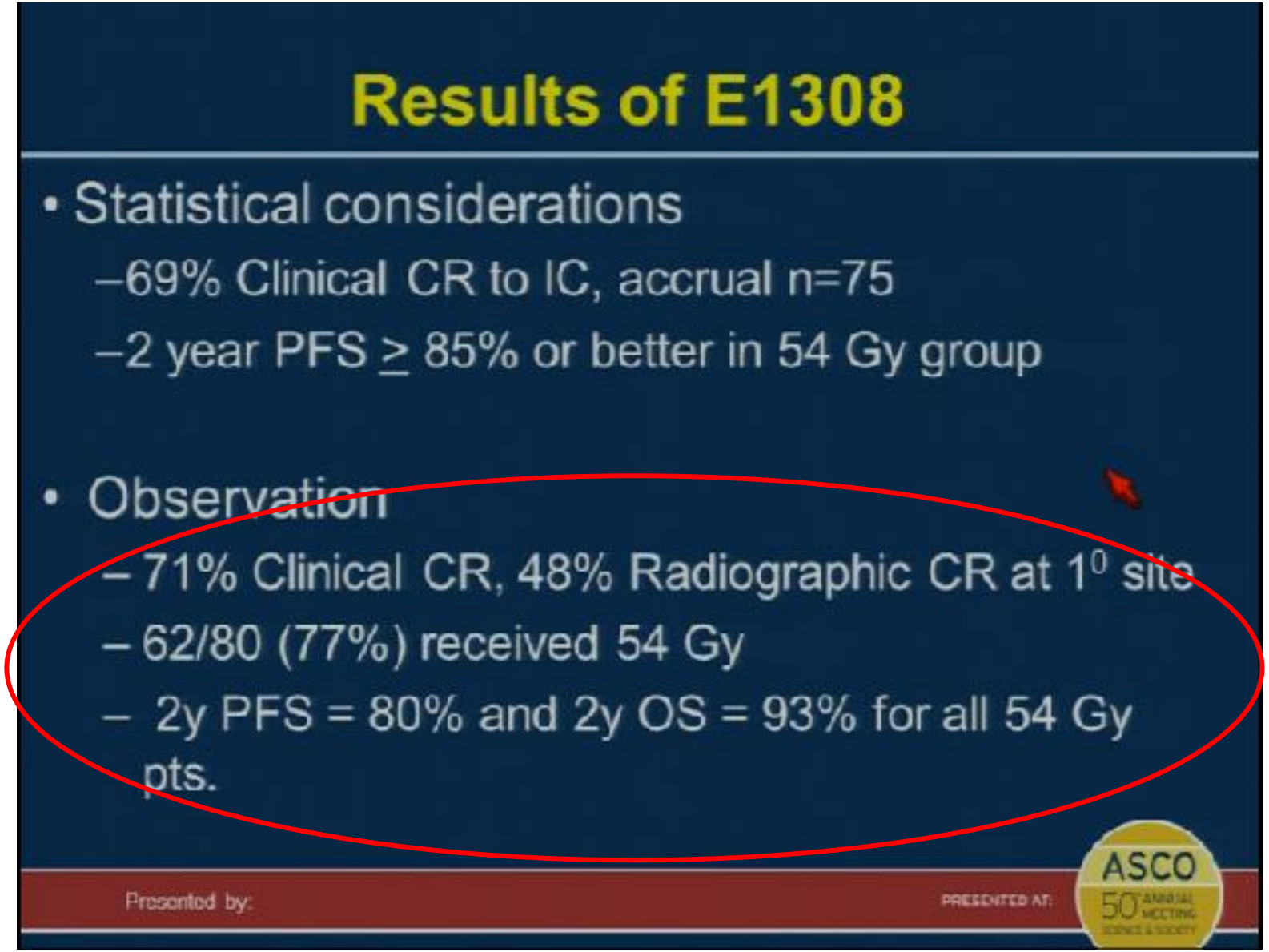
- ECOG 1308: Taxol/Carbo/C225 induction→
  - IF complete response decrease total dose GTV 54Gy+C225
  - IF partial response, standard dose 70Gy + C225

- ECOG3311: TORS Sx followed decreased post-op 50Gy for intermediate risk
- RTOG: Phase III: 70Gy: Cisplatin vs Cetuximab
- NRG: Definitive Radiation Dose Deescalation 60Gy

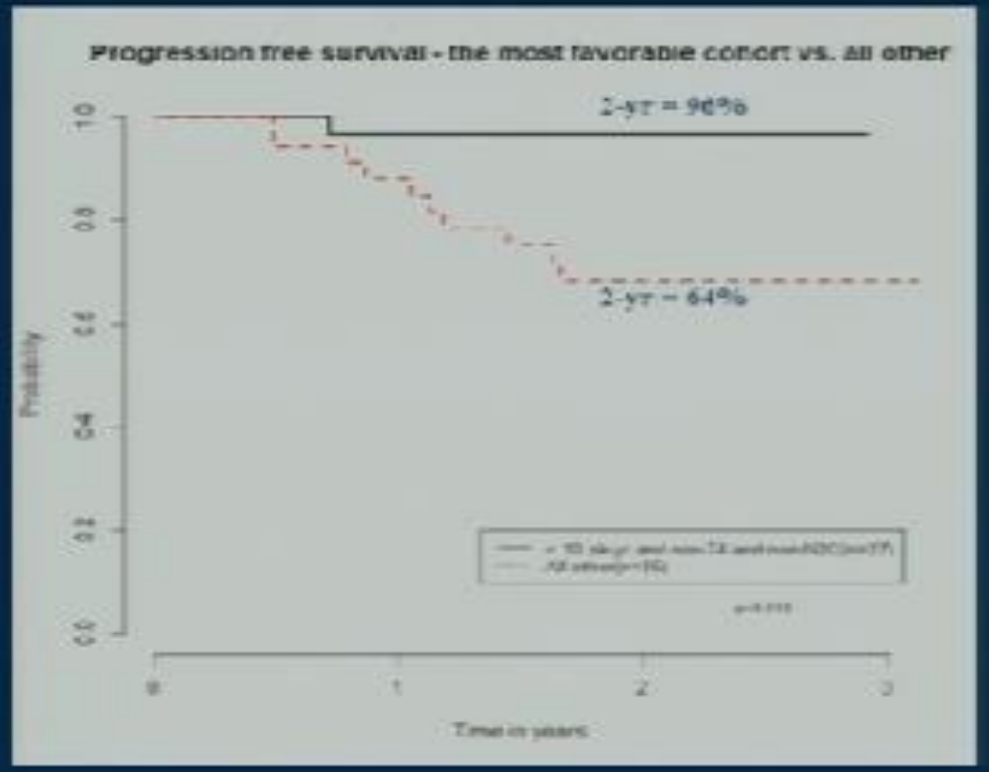
E1308: Reduced-dose IMRT in human papilloma virus (HPV)-associated resectable oropharyngeal squamous carcinomas (OPSCC) after clinical complete response (cCR) to induction chemotherapy (IC).

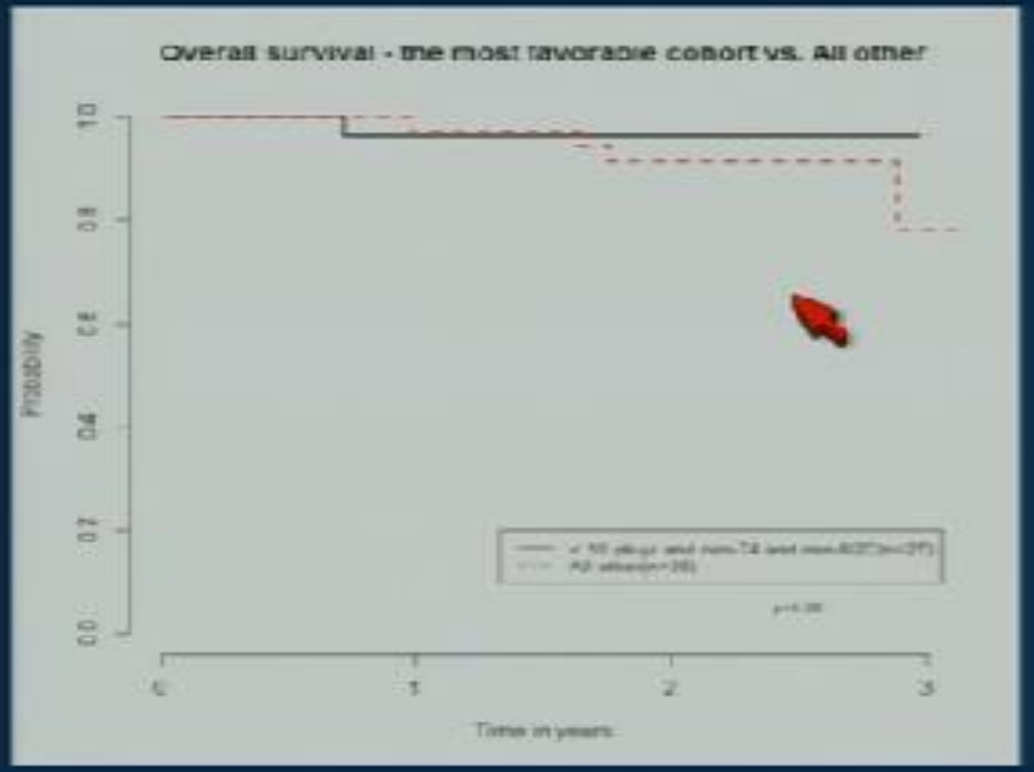
Anthony Cmelak MD
Head and Neck Cancer
Head and Neck Cancer Track



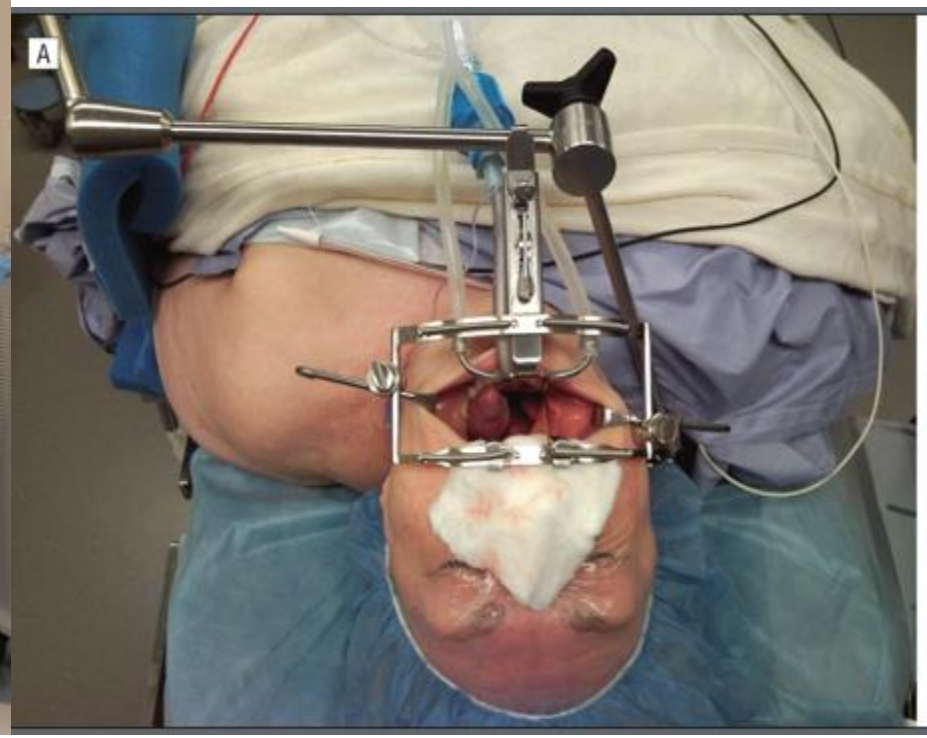

Results of E1308
• Statistical considerations
–69% Clinical CR to IC, accrual n=75
–2 year PFS ≥ 85% or better in 54 Gy group
• Observation
– 71% Clinical CR, 48% Radiographic CR at 1⁰ site
– 62/80 (77%) received 54 Gy
– 2y PFS = 80% and 2y OS = 93% for all 54 Gy pts.
Presented by:
PRESENTED AT:
ASCO
50

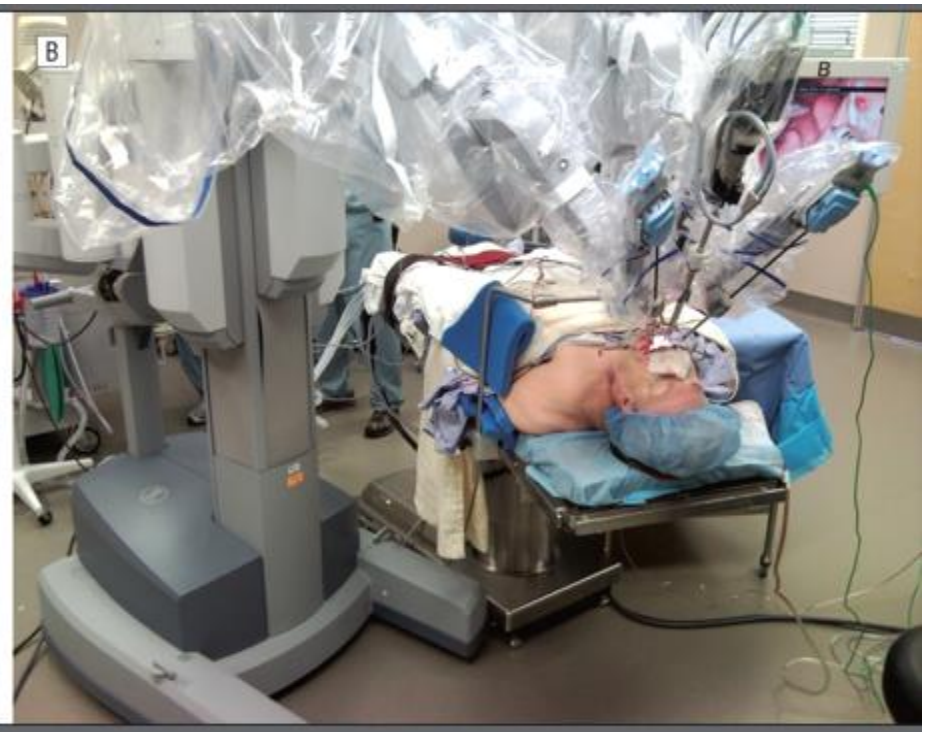
Best Outcome: <T4, T1-N2b, <10 pk-yr





Transoral Robotic Surgery





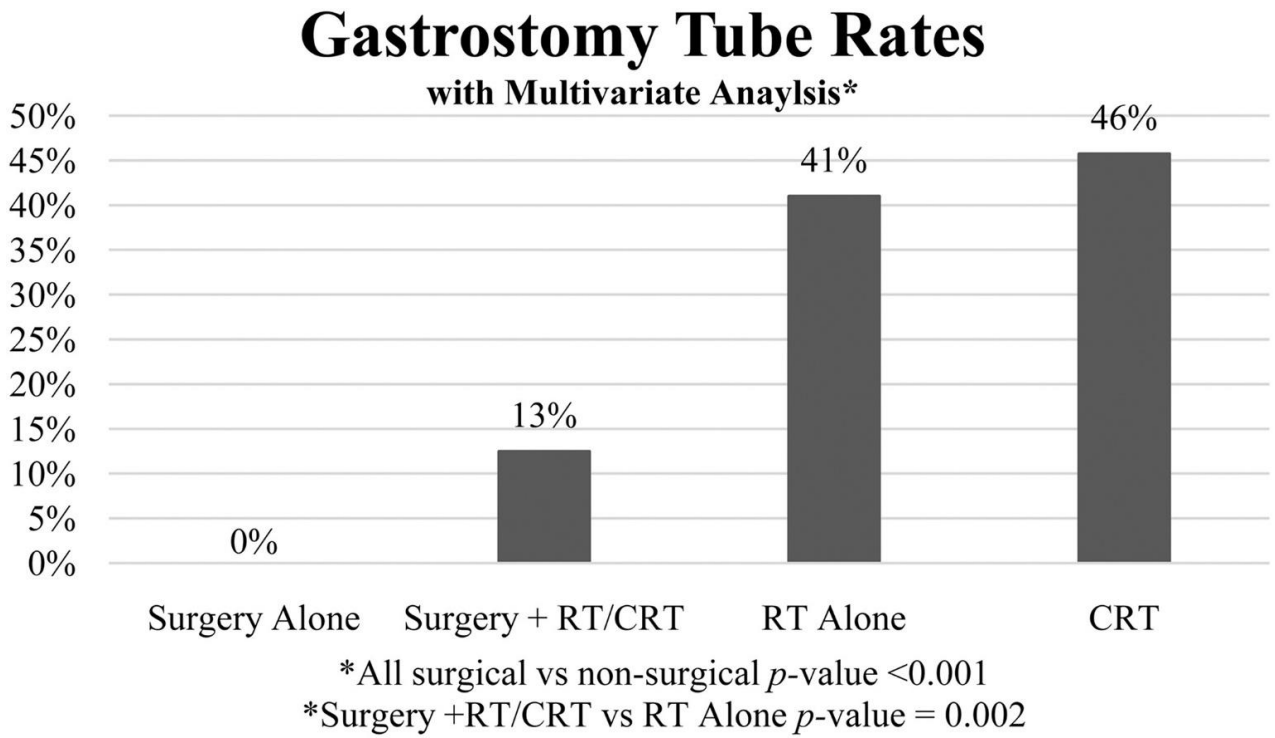
HEAD & NECK
JOURNAL OF THE SCIENCES AND SPECIALTIES OF THE HEAD AND NECK

ORIGINAL ARTICLE | Full Access

Decreased gastrostomy tube incidence and weight loss after transoral robotic surgery for low- to intermediate-risk oropharyngeal squamous cell carcinoma

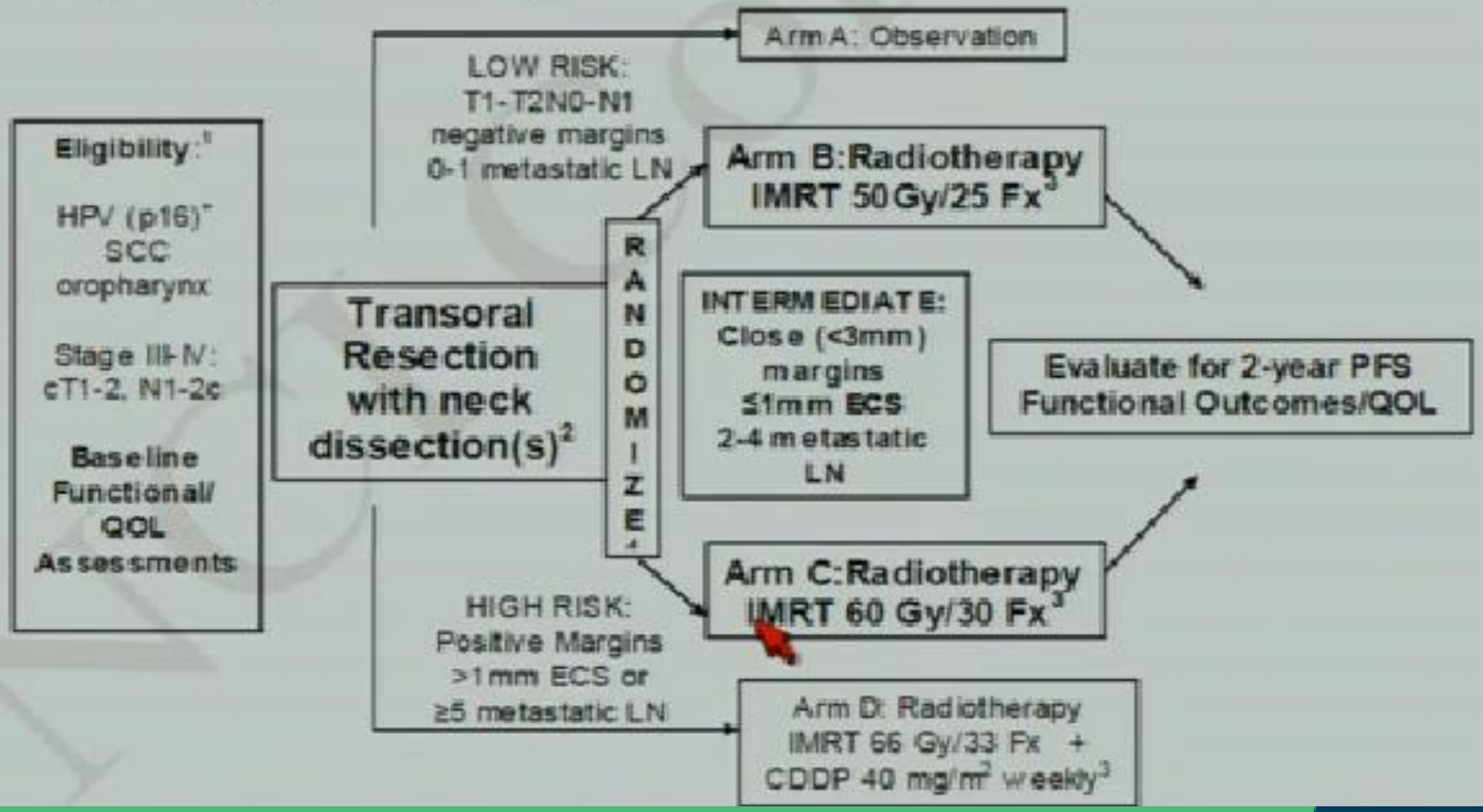
Harold Heah MBBS, MRCS, MMed, Ryan P. Goepfert MD, Katherine A. Hutcheson PhD, Adam S. Garden MD, G. Brandon Gunn MD, Clifton D. Fuller MD, PhD, Jan S. Lewin PhD ... See all authors

- All T1-2 N0-2b
- 66 TORS
  - 48% + RT
  - 21% + CRT
- 157 RT
  - 75% CRT
- Median adjuvant RT 60Gy



E3311 - Phase IIR Trial of Transoral Surgical Resection followed by Low-dose or Standard-dose IMRT in Resectable p16+ Locally OPC

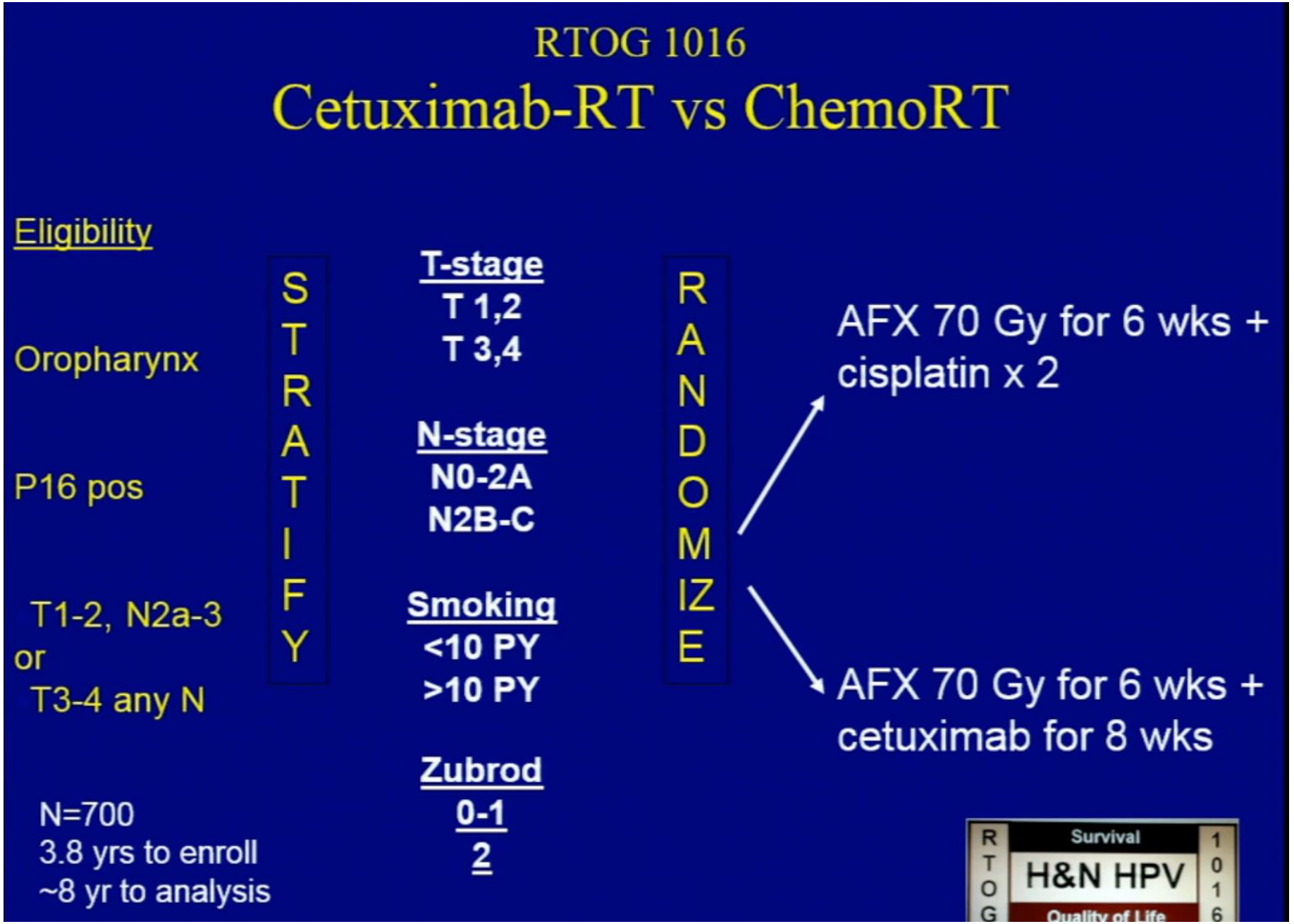
Arms/Regimens (include schema):



Results

	N	2-year PFS	90% CI	Deaths (without recurrence)	Recurrences	LRF	DM
Arm A	37	93.9%	87.3, 100	0	2	1	1
Arm B	102	95.0%	91.4, 98.6	1	4	2	2
Arm C	104	95.9%	92.6, 99.3	0	4	0	4
Arm D	110	90.5%	85.9, 95.3	3	7	4	3

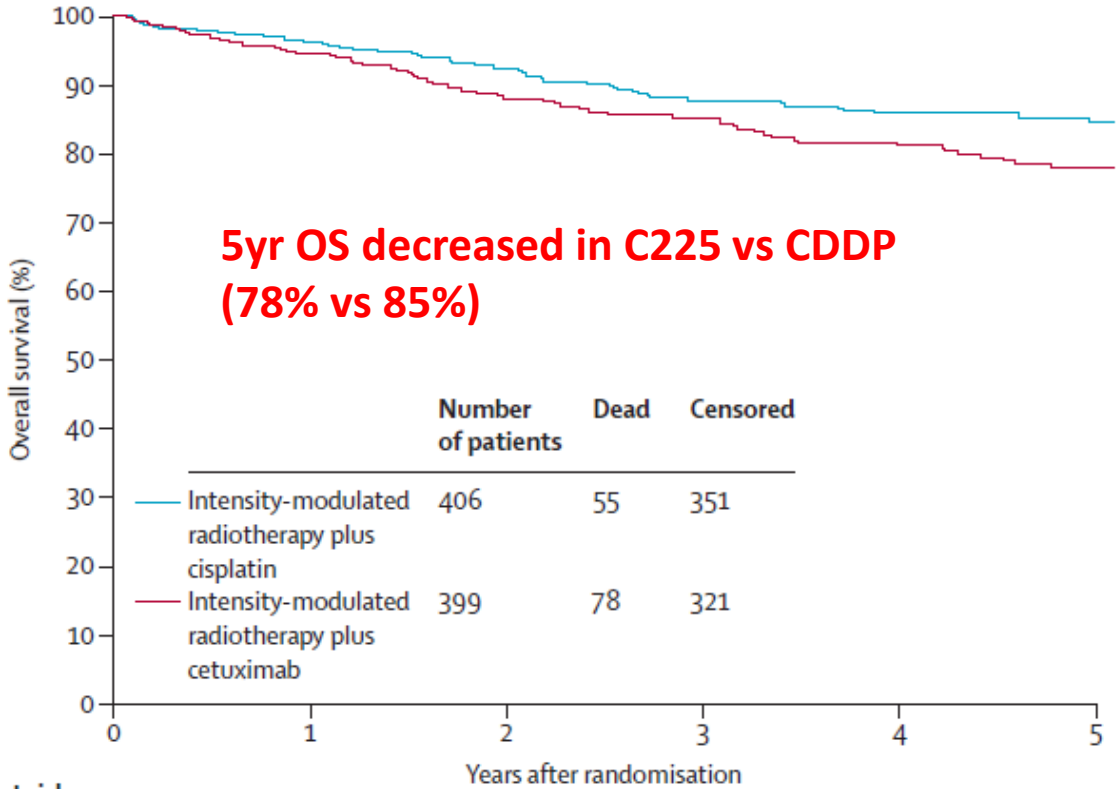
- There were 2 treatment-related deaths (one surgical and one Arm D)
- TOS + low-dose radiation is worthy of further study, since the primary endpoint of the upper bound of the 90% CI (in the intermediate risk group) exceeding 85% was met


RTOG 1016
Cetuximab-RT vs ChemoRT
Eligibility
Oropharynx
P16 pos
T1-2, N2a-3
or
T3-4 any N
N=700
3.8 yrs to enroll
~8 yr to analysis
STRATIFY
T-stage
T 1,2
T 3,4
N-stage
N0-2A
N2B-C
Smoking
<10 PY
>10 PY
Zubrod
0-1
2
RANDOMIZE
AFX 70 Gy for 6 wks + cisplatin x 2
AFX 70 Gy for 6 wks + cetuximab for 8 wks
RTOG
Survival
H&N HPV
Quality of Life
1016

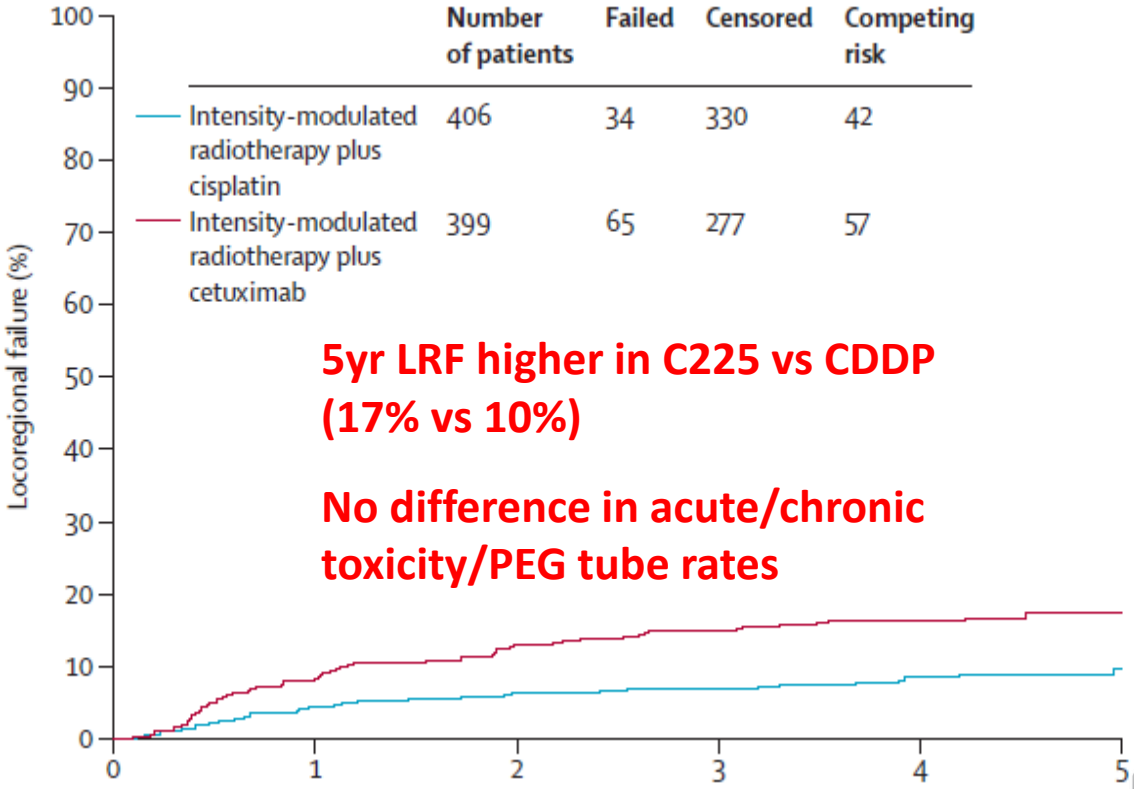
Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial

Maura L Gillison, Andy M Trotti*, Jonathan Harris, Avraham Eisbruch, Paul M Harari, David J Adelstein, Richard C K Jordan, Weiqiang Zhao,*

Lancet 2019; 393: 40–50



5yr OS decreased in C225 vs CDDP (78% vs 85%)



5yr LRF higher in C225 vs CDDP (17% vs 10%)

No difference in acute/chronic toxicity/PEG tube rates

NRG-HN002 (RTOG 1333): A Randomized Phase II Trial for HPV-Positive, Non-Smoking-Associated, Locoregionally Advanced Oropharyngeal Cancer Patients

Eligibility

- Oropharyngeal SCCA
- HPV+
- ≤10 pack-year
- T1-T2 N1-N2b
- T3 N0-N2b

44% of RTOG 1016 population eligible: ~15 patients/month

RANDOMIZE

60 Gy radiation (2.0 Gy/fraction) in 6 weeks + concurrent cisplatin 40 mg/m2 weekly x 6 cycles

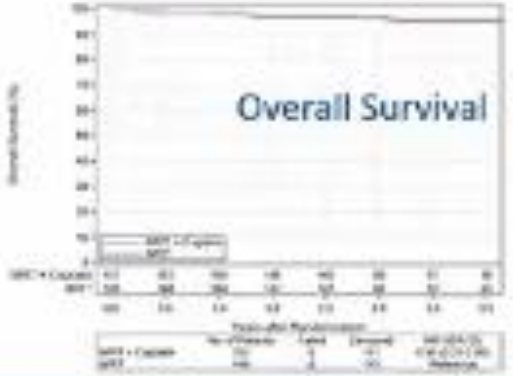
60 Gy radiation (2.0 Gy/fraction, at 6 fractions/week) in 5 weeks

1° end point: Select the arm wit 2y PFS >91% with lower confidence interval > 85% Total sample size: 296 patients randomized, 350 enrolled (2y accrual & 2y follow up); QOL

NRGHN002 Results—ASTRO 2019, Chicago, Sue Yom

Summary of HN002: 2 De-escalation Arms

	IMRT + C	IMRT
2-year PFS	90.5% (84.5-94.7%)	87.6% (81.1-92.5%)
2-year LRF	3.3% (1.2-7.1%)	9.5% (5.5-15.0%)
2-year DM	4.0% (1.6-8.0%)	2.1% (0.6-5.5%)
2-year OS	96.7% (93.9-99.5%)	97.3% (94.6-99.9%)
1-year MDADI	85.3 (82.53-88.07)	81.76 (78.98-84.54)
1-year FT	3.4%	2.1%



#ASTRO19

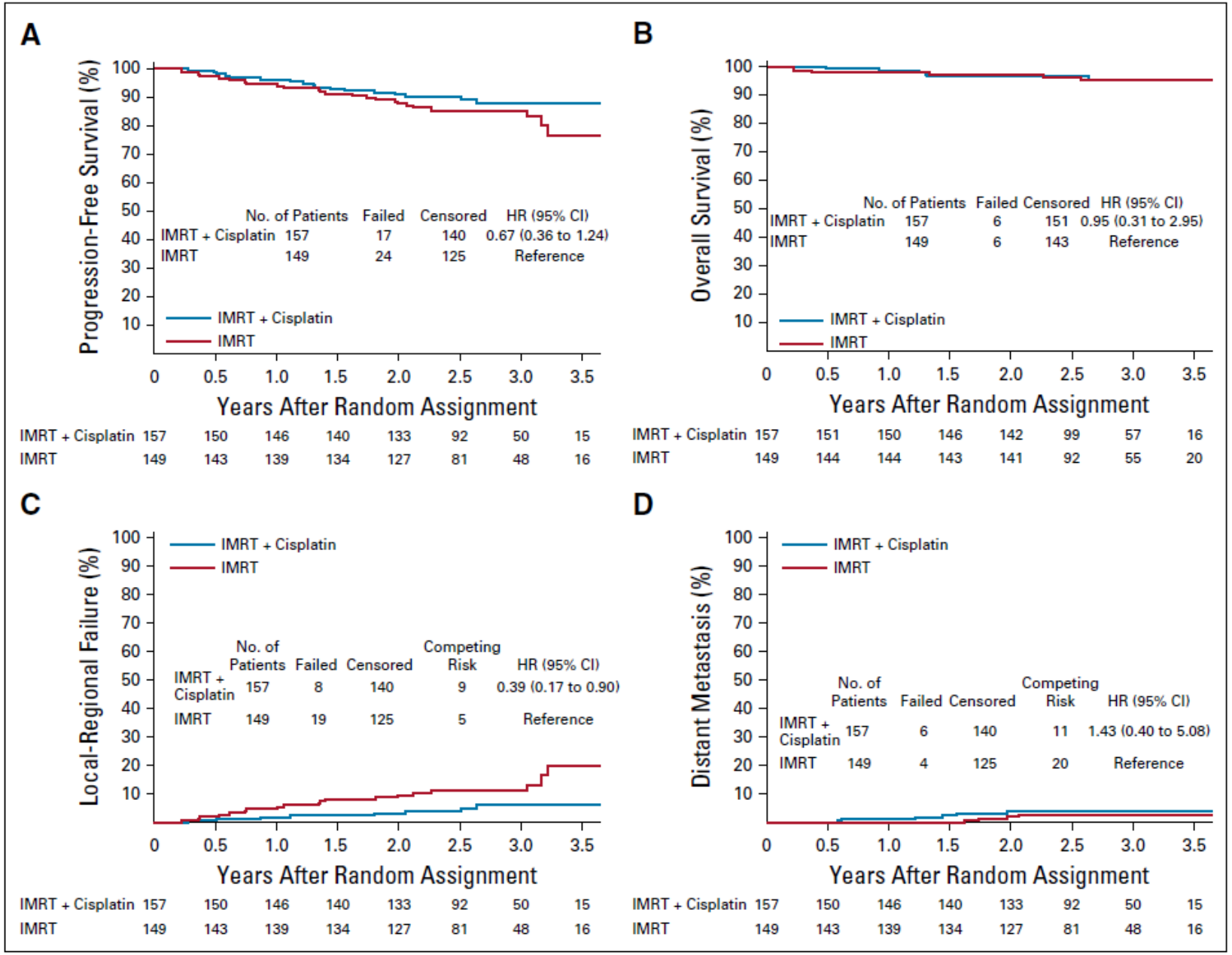
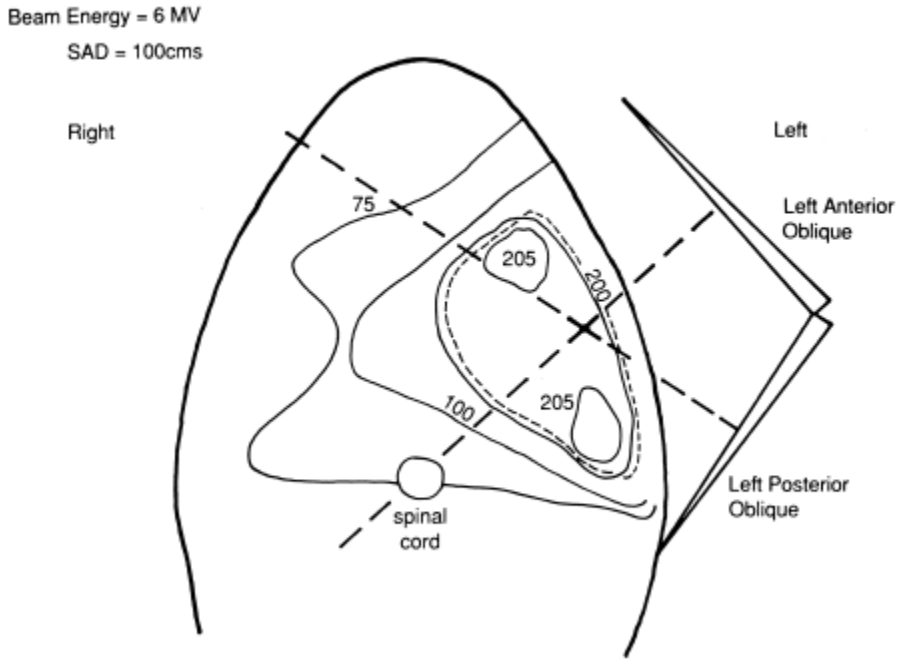


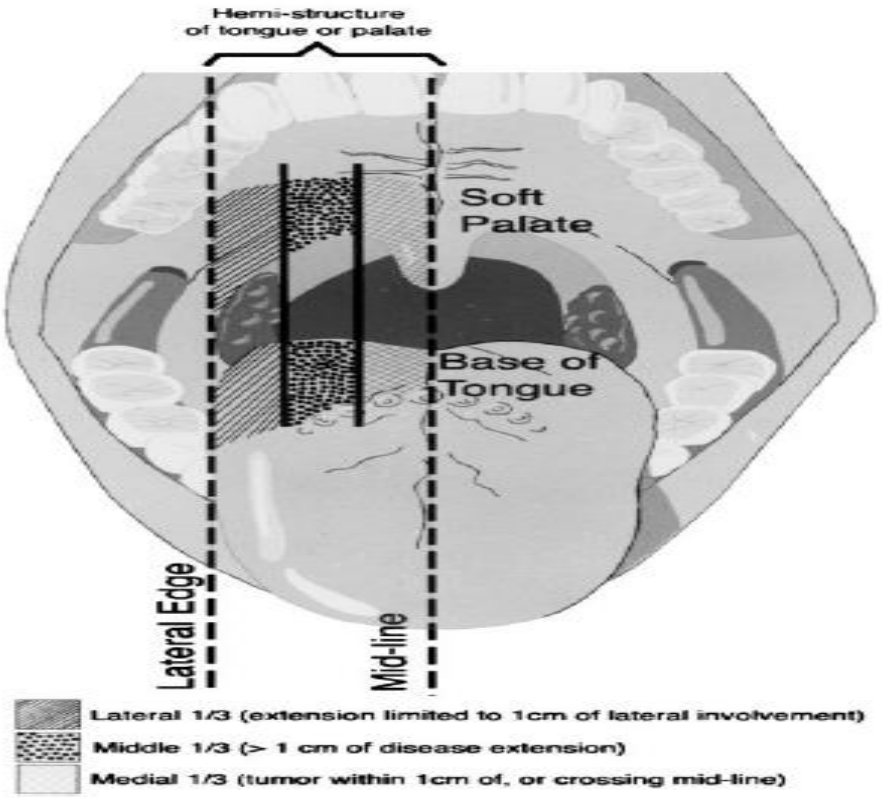
FIG 2. NRG-HN002 progression-free (A) and overall survival (B), local-regional failure (C), and distant metastasis (D). HR, hazard ratio; IMRT, intensity-modulated radiation therapy.

THE BENEFITS AND PITFALLS OF IPSILATERAL RADIOTHERAPY IN CARCINOMA OF THE TONSILLAR REGION

B. O'Sullivan, M.B., F.R.C.P.C.,* P. Warde, M.B., F.R.C.P.C.,* B. Grice, M.R.T.(T).*

Int. J. Radiation Oncology Biol. Phys., Vol. 51, No. 2, pp. 332–343, 2001





Unilateral treatment safe in lateralized T1-2 Tonsil cancer with N0-1

Ipsilateral radiation for squamous cell carcinoma of the tonsil: American Radium Society appropriate use criteria executive summary

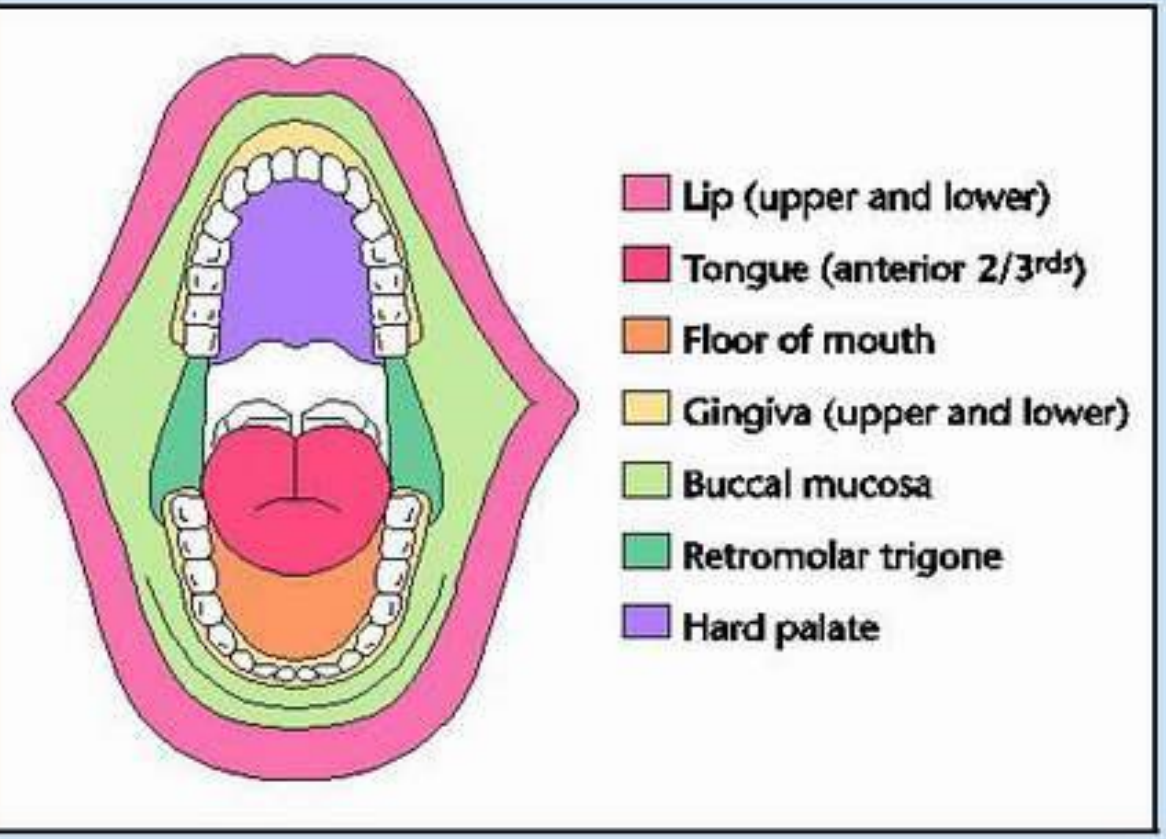
C. Jillian Tsai MD, PhD[1] | Thomas J. Galloway MD[2]

Head & Neck. 2021;43:392–406.

- Tonsil cancers either >1cm from midline or involve ≤1cm of Tongue base/soft palate
- Up to 2 ipsilateral nodes
- No consensus if clinical ECE or >6cm
- In post-op setting, unilateral if lateralized tonsil and single node; consider bilateral RT, if multiple nodes and ECE
- HPV status or concurrent chemotherapy does not impact decision

Treatment Paradigm
Oral Cavity Cancer

Upfront surgical resection followed by radiation +/- chemotherapy
Is the preferred treatment of choice



M32236-06-f01.eps

4 Definitions of AJCC TNM

Always refer to the specific chapter for explicit instructions on clinical and pathological classification for this disease.

4.1 Definition of Primary Tumor (T)

DOI and Tumor Thickness are Not Equivalent
DOI can upstage tumor

✓	*T Category*	*T Criteria*
	TX	Primary tumor cannot be assessed
	Tis	Carcinoma *in situ*
	T1	Tumor ≤ 2 cm with depth of invasion (DOI)* ≤ 5 mm
	T2	Tumor ≤ 2 cm with DOI* > 5 mm *or* tumor > 2 cm and ≤ 4 cm with DOI* ≤ 10 mm
	T3	Tumor > 2 cm and ≤ 4 cm with DOI* > 10 mm *or* tumor > 4 cm with DOI* ≤ 10 mm
	T4	Moderately advanced or very advanced local disease
	T4a	Moderately advanced local disease Tumor > 4 cm with DOI* > 10 mm *or* tumor invades adjacent structures only (e.g., through cortical bone of the mandible or maxilla or involves the maxillary sinus or skin of the face) Note: Superficial erosion of bone/tooth socket (alone) by a gingival primary is not sufficient to classify a tumor as T4.
	T4b	Very advanced local disease Tumor invades masticator space, pterygoid plates, or skull base and/or encases the internal carotid artery
	*DOI is depth of invasion and not tumor thickness.	

Nodal Staging, Clinical:
Oral Cavity, p16- Oropharynx, Larynx and Hypopharynx

4.2.1 Clinical N (cN)

✓	*N Category*	*N Criteria*
	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(–)
	N2	Metastasis in a single ipsilateral node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–); *or* metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–); *or* metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–)
	N2a	Metastasis in a single ipsilateral node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–)
	N2b	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(–)
	N2c	Metastases in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–)
	N3	Metastasis in a lymph node, larger than 6 cm in greatest dimension and ENE(–); *or* metastasis in any lymph node(s) with clinically overt ENE(+)
	N3a	Metastasis in a lymph node, larger than 6 cm in greatest dimension and ENE(–)
	N3b	Metastasis in any lymph node(s) with clinically overt ENE(+)
Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE(–) or ENE(+).		

Nodal Staging, Pathologic:
Oral Cavity, p16- Oropharynx, Larynx and Hypopharynx

4.2.2 Pathological N (pN)

✓	*pN Category*	*pN Criteria*
	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(–)
	N2	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+); *or* larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–); *or* metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–); *or* in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension, ENE(–)
	N2a	Metastasis in single ipsilateral node 3 cm or smaller in greatest dimension and ENE(+); *or* a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–)
	N2b	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(–)
	N2c	Metastases in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(–)
	N3	N3: Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(–); *or* metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral, or bilateral nodes, any with ENE(+); *or* a single contralateral node of any size and ENE(+)
	N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(–)
	N3b	Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral or bilateral nodes any with ENE(+); *or* a single contralateral node of any size and ENE(+)

ECE will upstage single LN <3cm to N2a
Any other nodal scenario with ECE upstaged to N3b

Role of Post-op RT in SCC of Head and Neck

- Complex patterns of failure
  - Local tumor spread
  - Perineural invasion
  - Regional nodes and In transit lymphatics
  - Distant Metastasis
  - Second Primary

Pathologic Risk Factors

- Local: PNI/LVI/primary site/margin status/depth of invasion (oral cavity)
- Regional: extracapsular extension (ECE)/multiple LN/LN level/nodal size
- Snow et al. 405 pts, ECE: higher regional failure, lower OS
  - Node >3cm: 75% ECE positive
  - Node <1cm: 20% ECE positive

- Cachin, Y., et al., Otolaryngol Clin North Am, 1979. **12**(1): p. 145-54
- Snow, G.B., et al., Clin Otolaryngol Allied Sci, 1982. **7**(3): p. 185-92.
- Carter, R.L., et al., Clin Otolaryngol Allied Sci, 1979. **4**(4): p. 271-81.
- Kalnins, I.K., et al.,. Am J Surg, 1977. **134**(4): p. 450-4.
- Pfreundner, L., et al., Int J Radiat Oncol Biol Phys, 2000. **47**(5): p. 1287-97.
- Kramer, S., et al.,. Head Neck Surg, 1987. **10**(1): p. 19-30.

EVALUATION OF THE DOSE FOR POSTOPERATIVE RADIATION THERAPY OF HEAD AND NECK CANCER: FIRST REPORT OF A PROSPECTIVE RANDOMIZED TRIAL

LESTER J. PETERS, M.D.,* HELMUTH GOEPFERT, M.D.,† K. KIAN ANG, M.D., PH.D.,*

- 240 pts
- Risk factors: ECE, oral cavity, close/positive margins, PNI, multiple LN+, node >3cm, treatment delay >6wks, poor performance status
- Risk stratification:
  - High: if ECE or 2 others
  - Lower: No ECE and 0-1 of other risk factors

Results: 2yr LC and RC

Table 6. 2-year actuarial control rates at the primary site and neck by dose

Risk	Primary site: Dose (Gy)	Primary site: No. pts.	Primary site: Control rate %	Neck: No. pts.	Neck: Control rate %
Lower (Intermediate)	≤ 54.0	17	63[1]	9	89
	57.6	66	92[2]	65	86
	63.0	51	89	54	89
Higher	63.0	51	89	61	84
	68.4	54	81	51	77

1 vs. 2 $p = 2.34$.

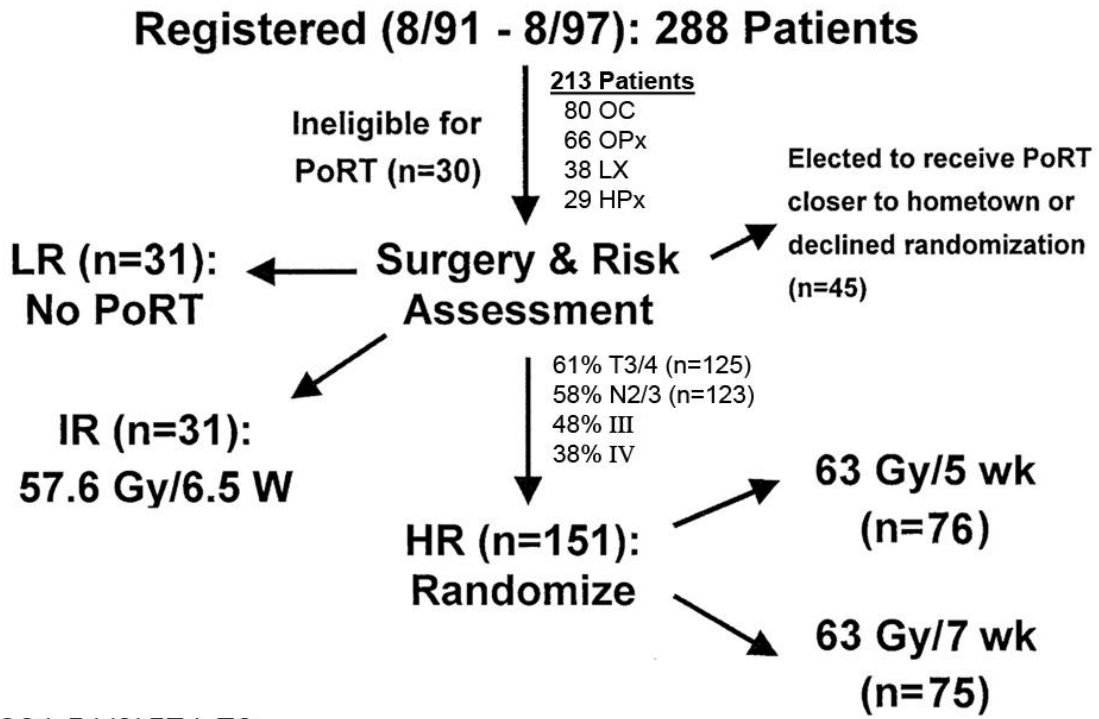
In patients with ECE, the 2yr control rate was dose dependent, 52% at 57.6Gy vs 74% at 63Gy vs 72% at 68.4Gy, p=0.03

Intermediate risk: 5760 High risk 63Gy

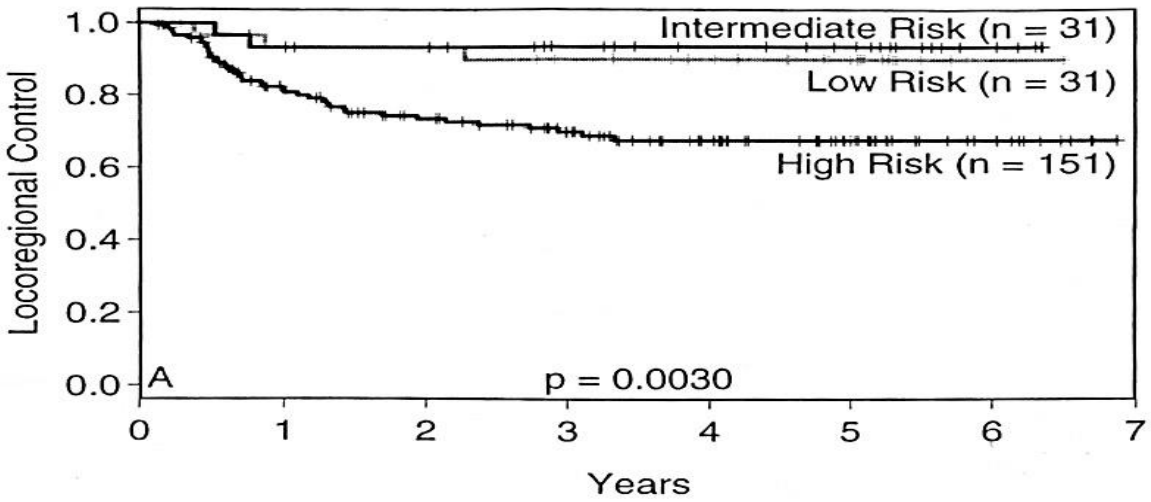
RANDOMIZED TRIAL ADDRESSING RISK FEATURES AND TIME FACTORS OF SURGERY PLUS RADIOTHERAPY IN ADVANCED HEAD-AND-NECK CANCER

K. Kian Ang, M.D.,* Andy Trotti, M.D.,† Barry W. Brown, Ph.D.,‡ Adam S. Garden, M.D.,* Robert L. Foote, M.D.,§ William H. Morrison, M.D.,* Fady B. Geara, M.D.,*[1] Douglas W. Klotch, M.D.,‖ Helmuth Goepfert, M.D.,¶ and Lester J. Peters, M.D.*

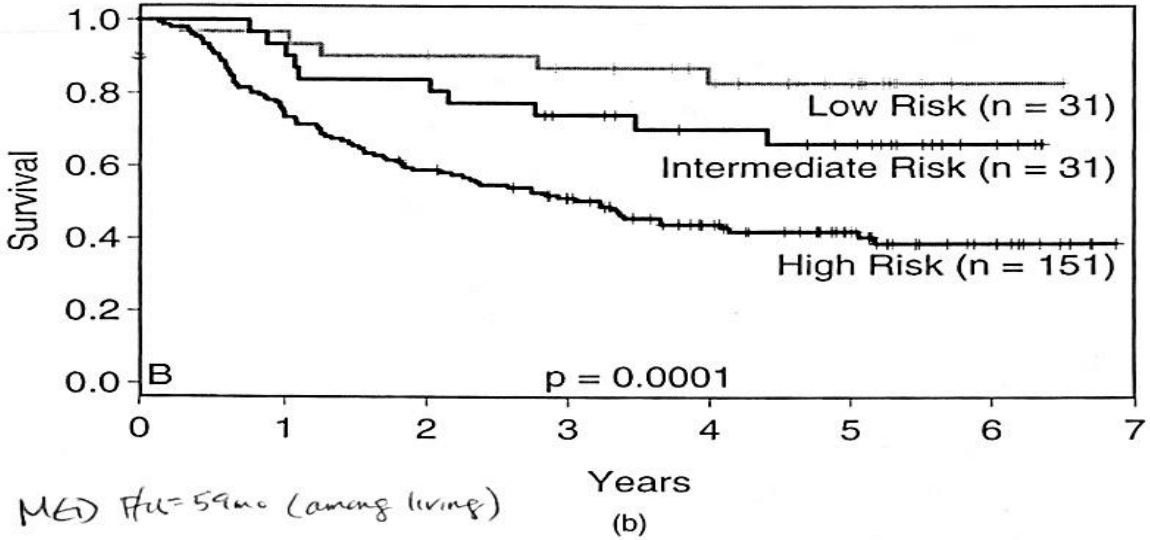
Study Design and Population



IJROBP 2001;51(3)571-78.



(a)



(b)

Fig. 2. Actuarial (A) LRC and (B) survival curves by risk grouping.

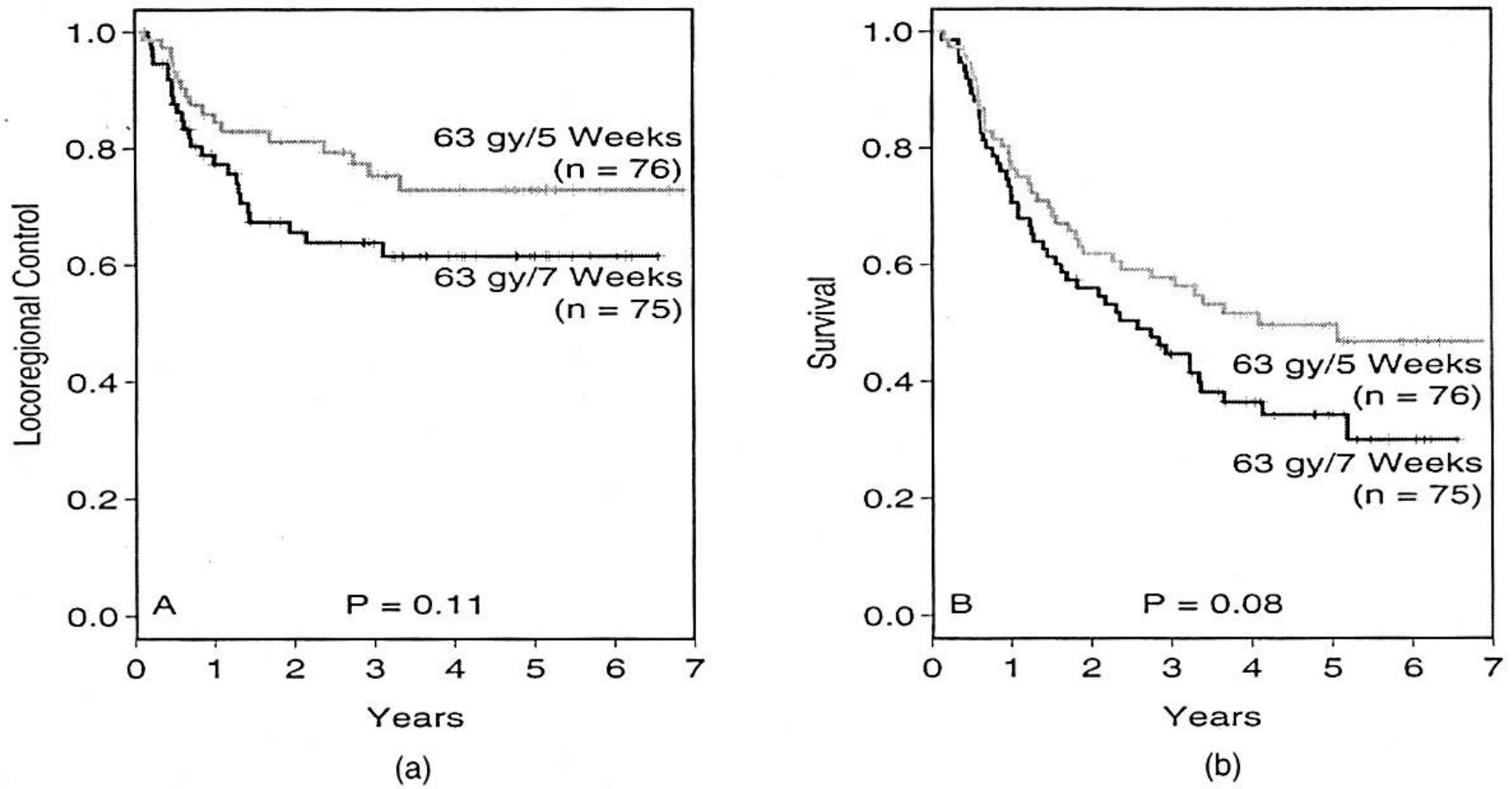
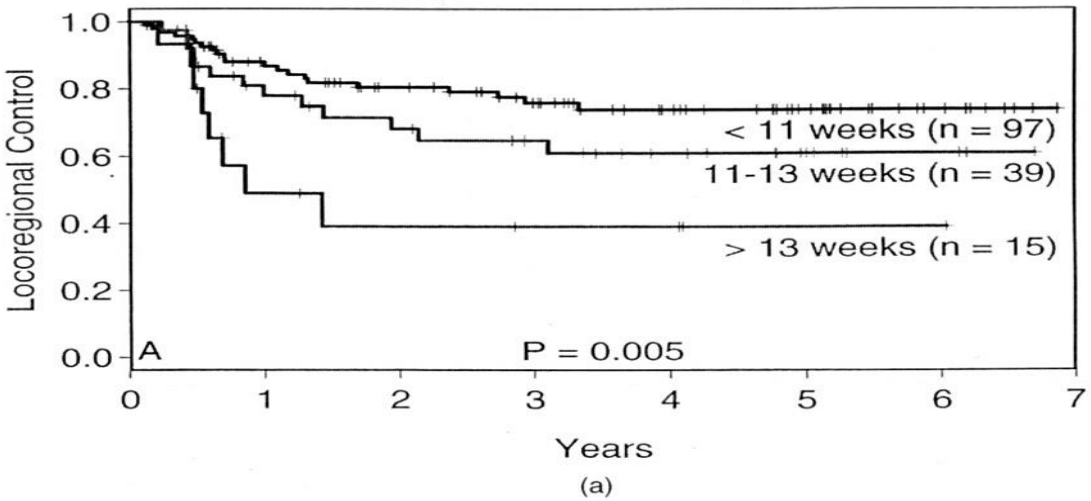
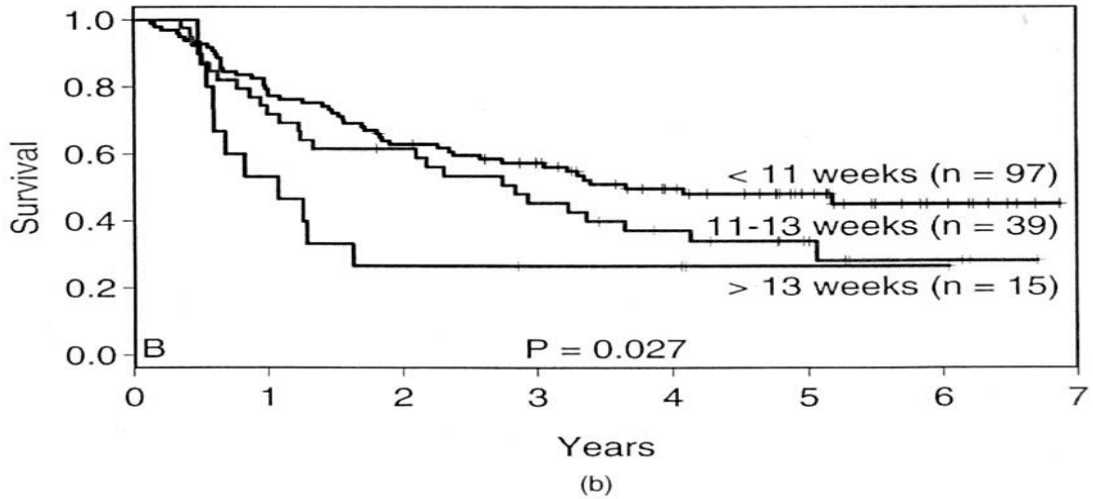


Fig. 3. Actuarial (A) LRC and (B) survival curves for high-risk patients as a function of the fractionation schedule of PORT.



(a)



(b)

High Risk: Keep Tx Package Time <11wks

EORTC and RTOG Phase III Studies
CDDP + RT vs RT for High Risk Post-op

High Risk Post-op:

EORTC 22931 : ECE, + margin, LVI, PNI, Level IV/V if OC,OPX, Stage III/IV

RTOG 95-01 : ECE, + margin, multiple nodes

→ 60-66Gy in 2Gy fractions

→ 60-66Gy in 2Gy fractions
+
CDDP 100mg/m2 wk 1,4,7

Post-operative Chemoradiation vs Radiation: Phase III Trials

	RTOG95-01	EORTC22931
# patients	459	334
OPX /OC/ /LX/HPX	42%/27%/21%/10%	30%/26%/22%/20%
% T3-4	61%	66%
% N2-3	94%	57%
% with ECE and/or + margins	**59%**	**70%**
RT: %receiving 66Gy	13%	91%

Post-op CT/RT vs RT: Results of EORTC/RTOG Phase III Trials

	RTOG95-01	EORTC22931
Median follow up	46mo	60 months
Locoregional failure	**Outcomes(CT/RTvs RT)** 3yr: 22% vs 33% (p=0.01)	**Outcomes(CT/RTvs RT)** 5yr: 18%vs 31% (p=0.007)
Disease-free Survival	3yr: 47% vs 36% (p=0.04)	5yr: 47% vs 36% (p=0.04)
Overall Survival	3yr: 56% vs 47% (p=0.09)	5yr: 53% vs 40% (p=0.02)
Distant Metastases	3yr: 20% vs 23% (P=0.46)	5yr: 21% vs 24% (p=0.61)
≥Grade 3 acute toxicity	77% vs 34% (p<0.0001)	44% vs 21% (p=0.001)
All late toxicity	21% vs 17% (p=0.29)	38% vs 41% (p=0.25)

JCOG
Japan Clinical Oncology Group

Phase II/III Trial of Post-operative Chemoradiotherapy Comparing 3-Weekly Cisplatin with Weekly Cisplatin in High-risk Patients with Squamous Cell Carcinoma of the Head and Neck（JCOG1008）

Naomi Kiyota, Makoto Tahara, Hirofumi Fujii, Tomoko Yamazaki, Hiroki Mitani, Shigemichi Iwae, Yasushi Fujimoto, Yusuke Onozawa, Nobuhiro Hanai, Takenori Ogawa, Hiroki Hara, Nobuya Monden, Eiji Shimura, Shujiro Minami, Takashi Fujii, Kaoru Tanaka, Takeshi Kodaira, Junki Mizusawa, Kenichi Nakamura, Ryuichi Hayashi

Head and Neck Cancer Study Group of the Japan Clinical Oncology Group (JCOG-HNCSG)

Japan Registry of Clinical Trials Registry Number: jRCTs031180135

PRESENTED BY: Naomi Kiyota, MD, PhD, Kobe University Hospital, Japan, E-mail: nkiyota@med.kobe-u.ac.jp

Trial Design

Multi-institutional randomized phase II/III Trial
28 institutions from JCOG-HNCSG

Post-operative high-risk SCCHN
- Pathological Stage III/IV
- Microscopically positive margin and/or ENE
- oral cavity, larynx, oropharynx, hypopharynx

Randomization 1:1

Arm A: 3-Weeky CDDP+RT
- CDDP 100 mg/m^2, q3wks
- RT* 66 Gy/33Fr

Arm B: Weekly CDDP+RT
- CDDP 40 mg/m^2, qwk
- RT* 66 Gy/33 Fr

Adjustment factors
- Microscopically positive margin and/or ENE
- Institution

* 3D conformal RT or IMRT was allowed at institutional discretion

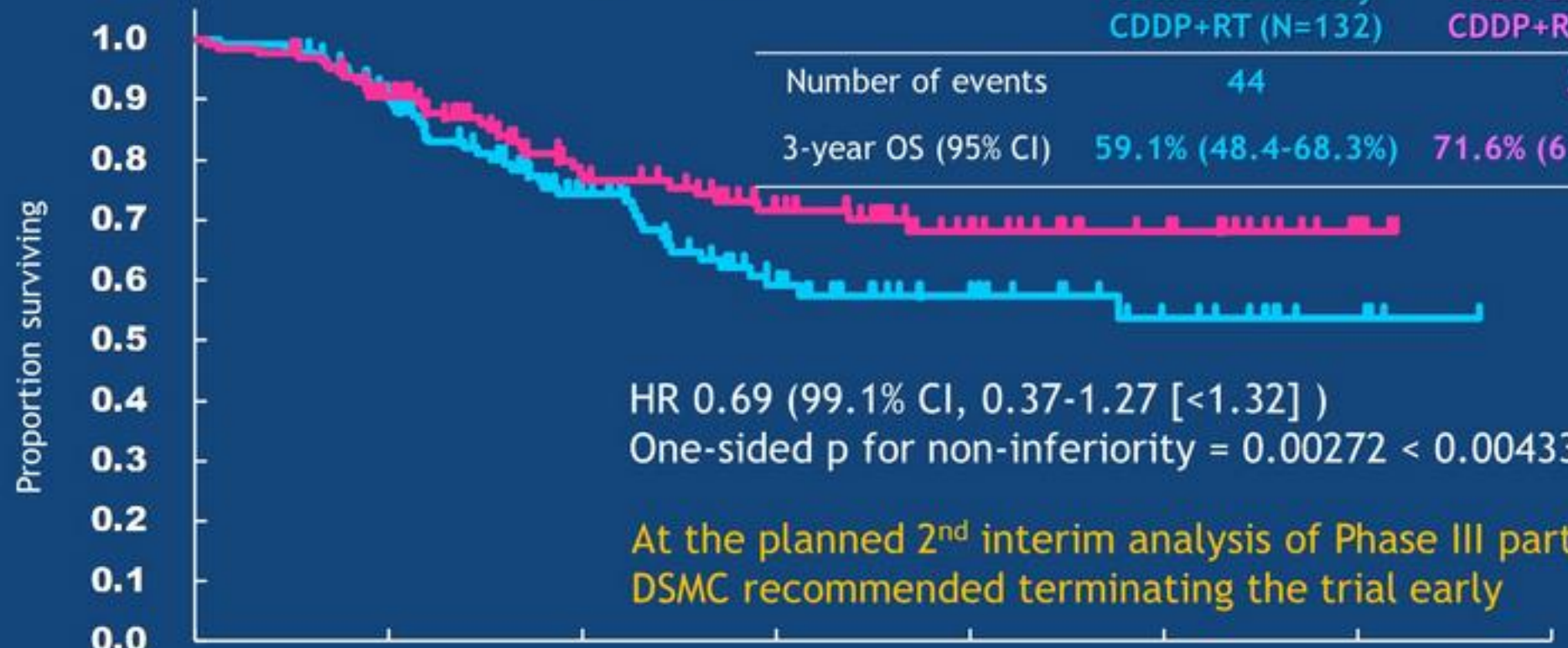
ENE: extra-nodal extension
RT: radiation therapy, IMRT: intensity modulated RT

Overall Survival: OS (ITT)

JCOG Japan Clinical Oncology Group

Median follow-up period: 2.2 years

	Arm A: 3-Weekly CDDP+RT (N=132)	Arm B: Weekly CDDP+RT (N=129)
Number of events	44	32
3-year OS (95% CI)	59.1% (48.4-68.3%)	71.6% (61.7-79.4%)



HR 0.69 (99.1% CI, 0.37-1.27 [<1.32])
One-sided p for non-inferiority = 0.00272 < 0.00433

At the planned 2nd interim analysis of Phase III part, DSMC recommended terminating the trial early

Patients at risk (censored)								
Arm A	132 (0)	110 (10)	67 (25)	39 (16)	23 (15)	12 (10)	4 (8)	0 (4)
Arm B	129 (0)	108 (9)	70 (25)	50 (15)	31 (17)	19 (12)	5 (14)	0 (5)

PRESENTED BY: Naomi Kiyota, MD, PhD, Kobe University Hospital, Japan, E-mail: nkiyota@med.kobe-u.ac.jp

Acute Non-hematological Toxicities*

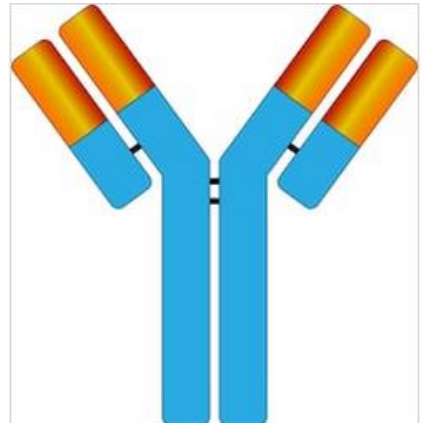
Non-hematological	Arm A: 3-Weekly CDDP+RT (N=129)		Arm B: Weekly CDDP+RT (N=122)	
	Any grade	Grade3-4(%)	Any grade	Grade3-4
Mucositis	118 (91.5%)	30 (23.3%)	113 (92.6%)	34 (27.9%)
Dysphagia	75 (58.1%)	24 (18.6%)	59 (48.4%)	14 (11.5%)
Dermatitis	118 (91.4%)	19 (14.7%)	112 (91.8%)	14 (11.5%)
Nausea	87 (67.4%)	17 (13.2%)	57 (46.7%)	6 (4.9%)
Infection	25 (19.4%)	15 (11.6%)	18 (14.8%)	8 (6.6%)
Hyponatremia	119 (92.2%)	13 (10.1%)	100 (82.0%)	13 (10.7%)
Renal impairment	51 (39.5%)	0 (0%)	36 (29.5%)	0 (0.0%)
Hearing impairment	22 (17.1%)	5 (3.9%)	9 (7.4%)	2 (1.6%)
Peripheral neuropathy	7 (5.4%)	0 (0.0%)	2 (1.6%)	0 (0.0%)

- *Grade 3 or more toxicities which occurred in ≥10% patients or toxicities of special interest

Postoperative Chemoradiotherapy and Cetuximab for High-Risk Squamous Cell Carcinoma of the Head and Neck: Radiation Therapy Oncology Group RTOG-0234

Paul M. Harari, Jonathan Harris, Merrill S. Kies, Jeffrey N. Myers, Richard C. Jordan, Maura L. Gillison,

- Kies, ASTRO 2009
- 203 pts with ECE (59%),+ margin (41%), or ≥2LN+
- 60Gy: C225+cddp vs C225+taxotere
- Median f/u 2.5yrs



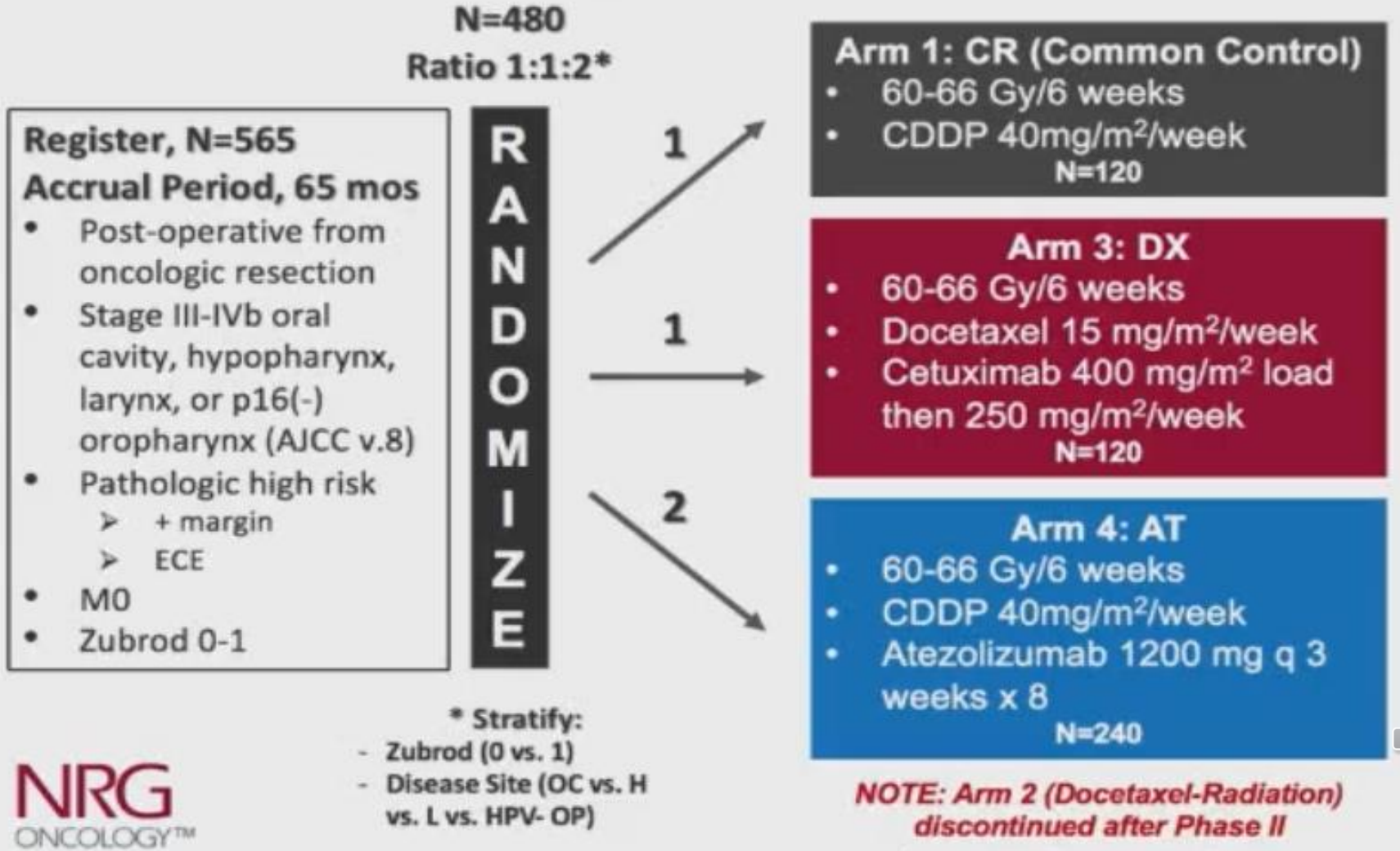
J Clin Oncol 32:2486-2495. © 2014 by American Society of Clinical Oncology

Results: RTOG 0234

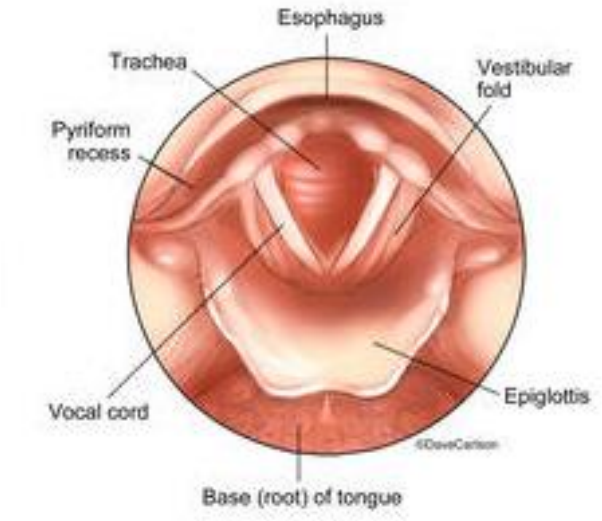
	CDDP/C225	Taxotere/C225
Locoregional failure	2yr: 21%	2yr: 20%
Disease-free Survival	2yr: 57%	2yr: 66%
Compared to 95-01	HR 0.85 p=0.19	HR 0.72 p=0.031
Overall Survival	2yr: 69%	2yr: 79%
Distant Metastases	2yr: 26%	2yr: 13%
≥Grade 3 acute heme/derm/mucositis	28%/39%/37%	14%/39%/33%

RTOG 1216 continued (PIs – Bauman, Harari, Rosenthal)

Schema



Cancers of the Larynx/Hypopharynx

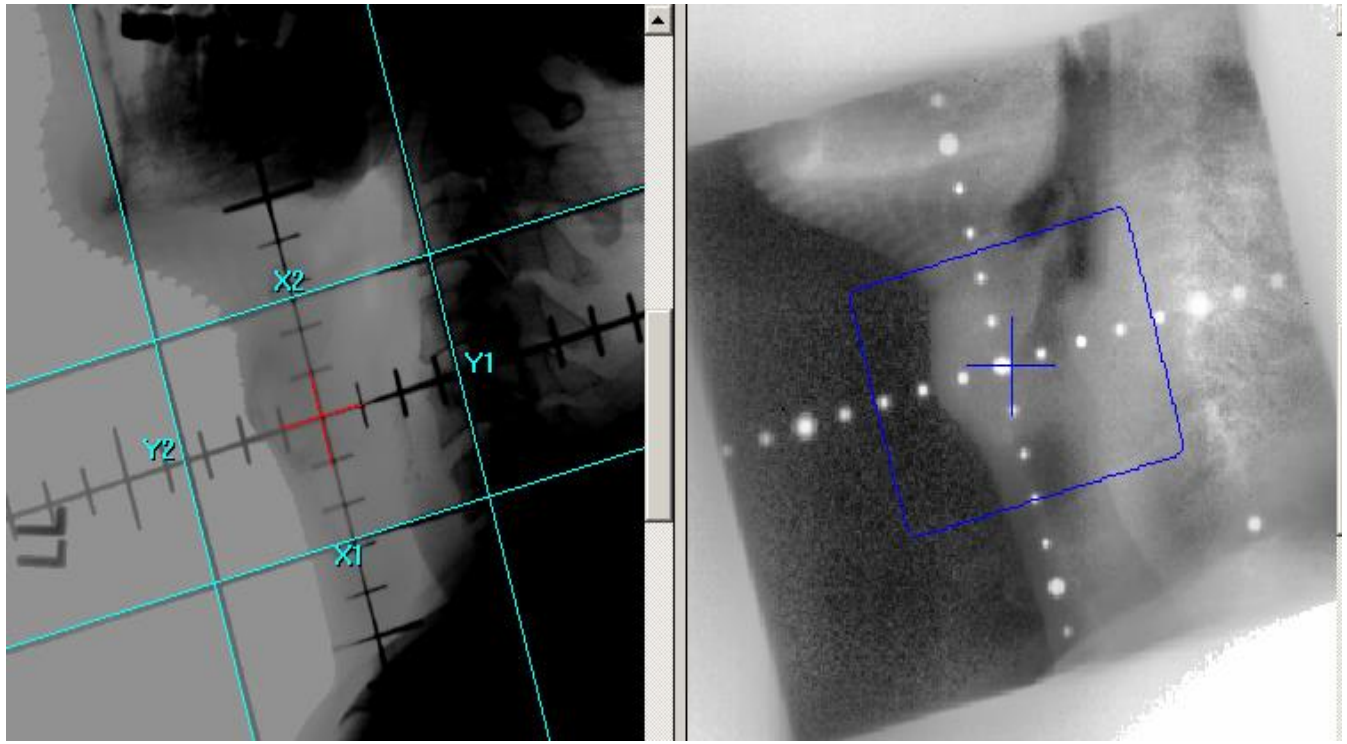


CARCINOMA OF THE LARYNX

INCIDENCE OF LYMPH NODE METASTASES

Site	Incidence
Supraglottis	
Positive Nodes	55 %
Bilateral Nodes	16 %
Glottis	
T1	≤ 2 %
T2	3-7 %
T3	15-20 %
T4	20-30 %
Subglottis	10-30 %

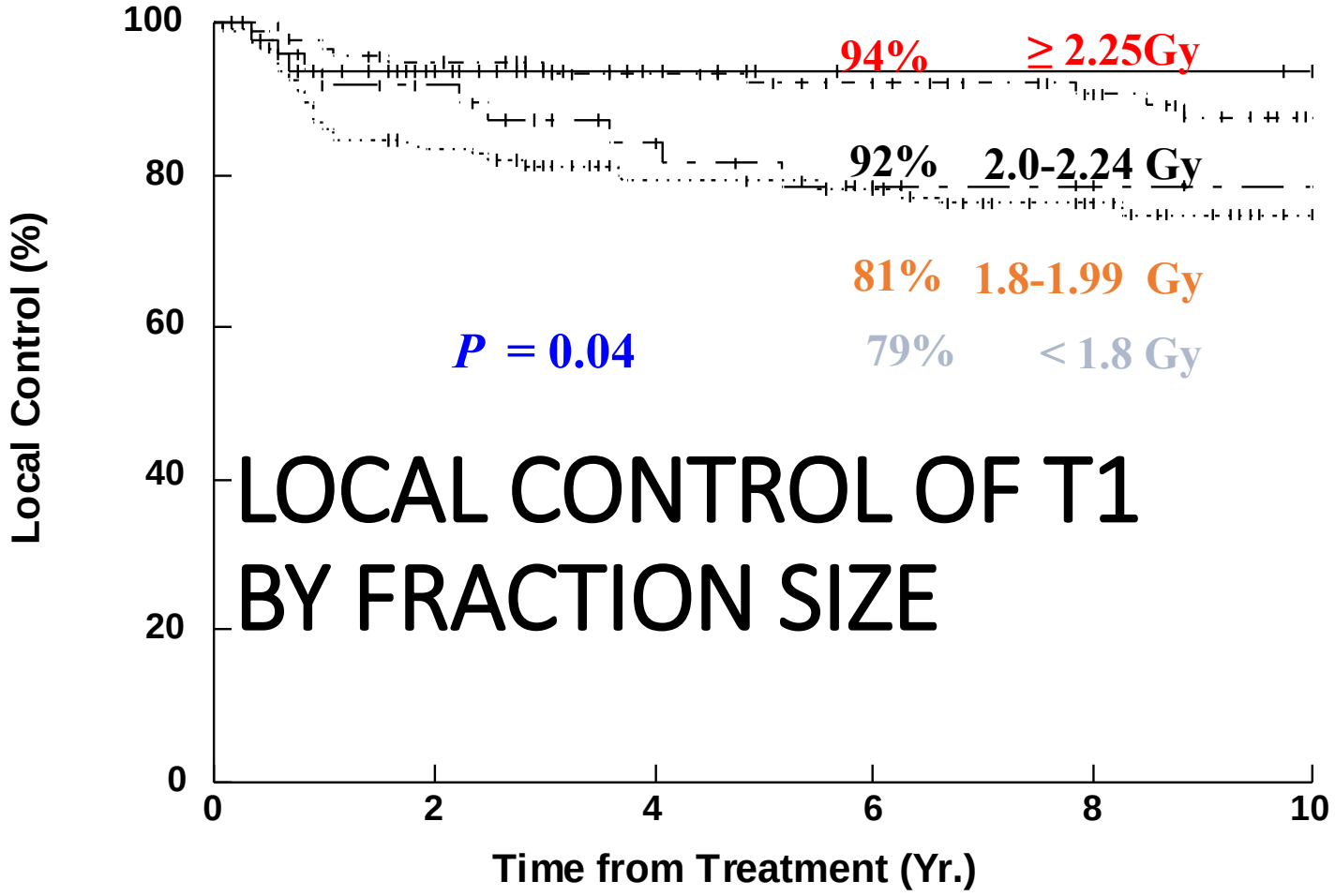
T1-2NO Glottic Treatment Technique



INFLUENCE OF FRACTION SIZE, TOTAL DOSE, AND OVERALL TIME ON LOCAL CONTROL OF T1–T2 GLOTTIC CARCINOMA

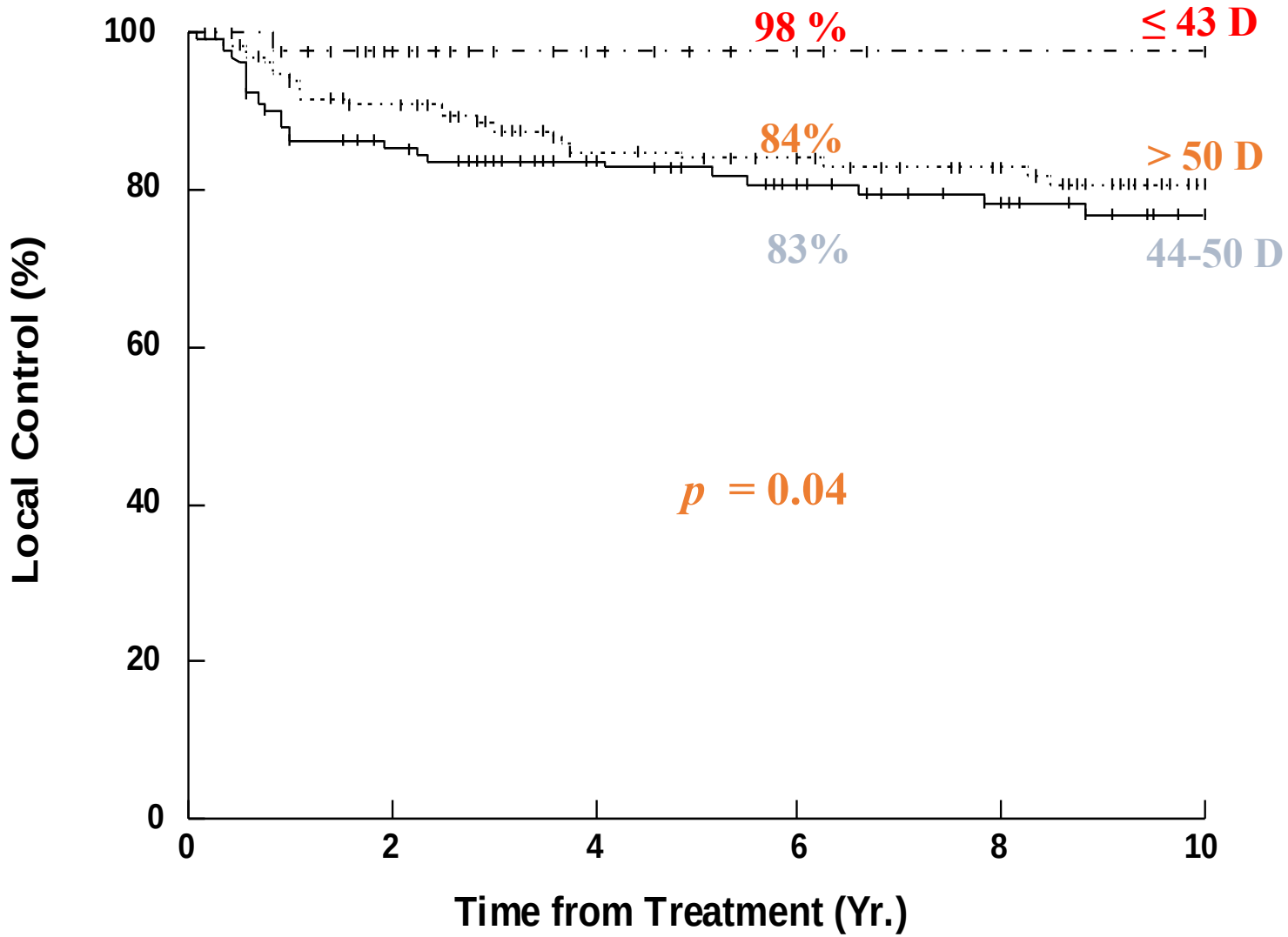
QUYNH-THU X. LE, M.D.,* KAREN K. FU, M.D.,* STEWARD KROLL, M.A.,*

Int. J. Radiation Oncology Biol. Phys., Vol. 39, No. 1, pp. 115–126, 1997

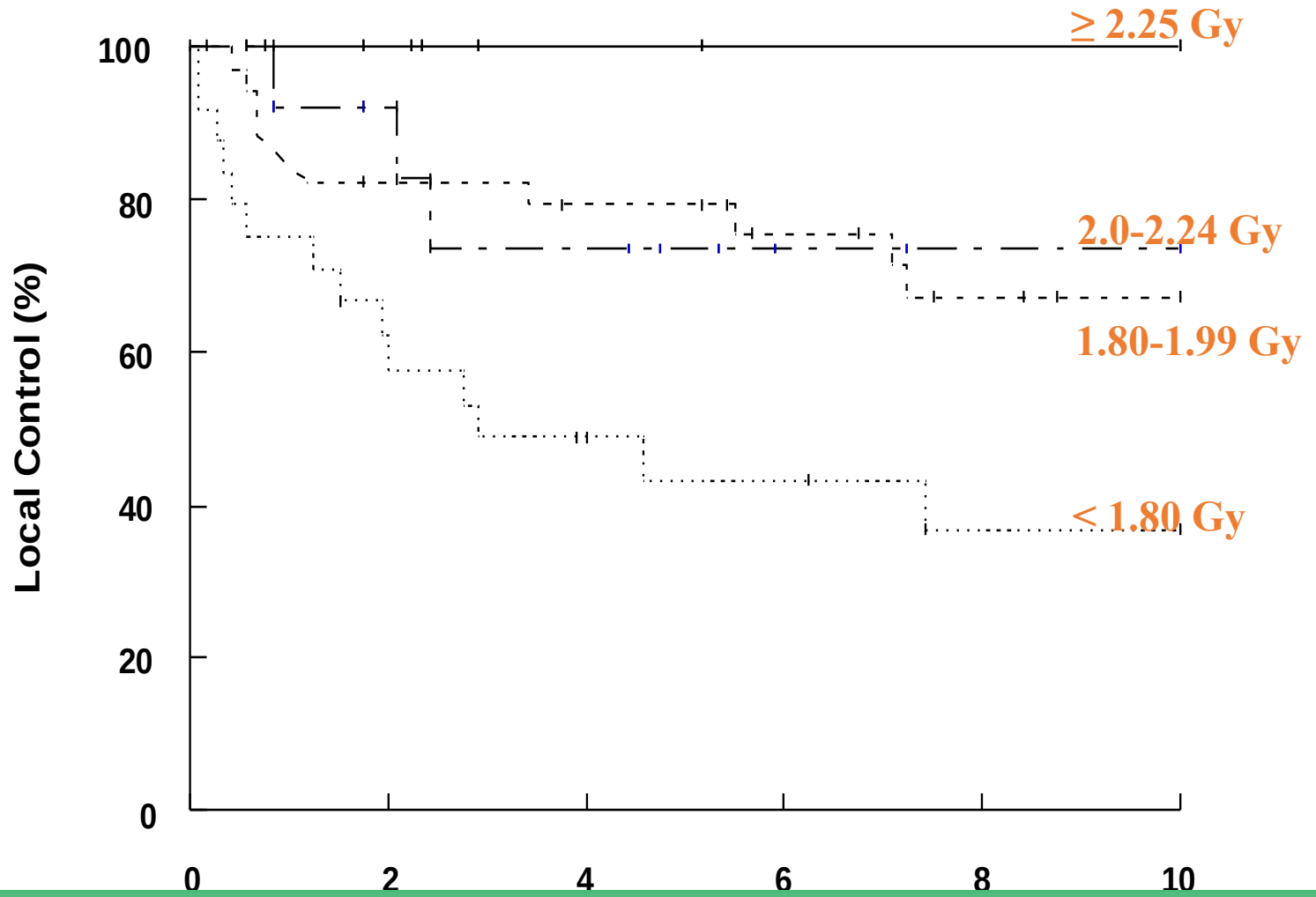


LOCAL CONTROL OF T1 BY FRACTION SIZE

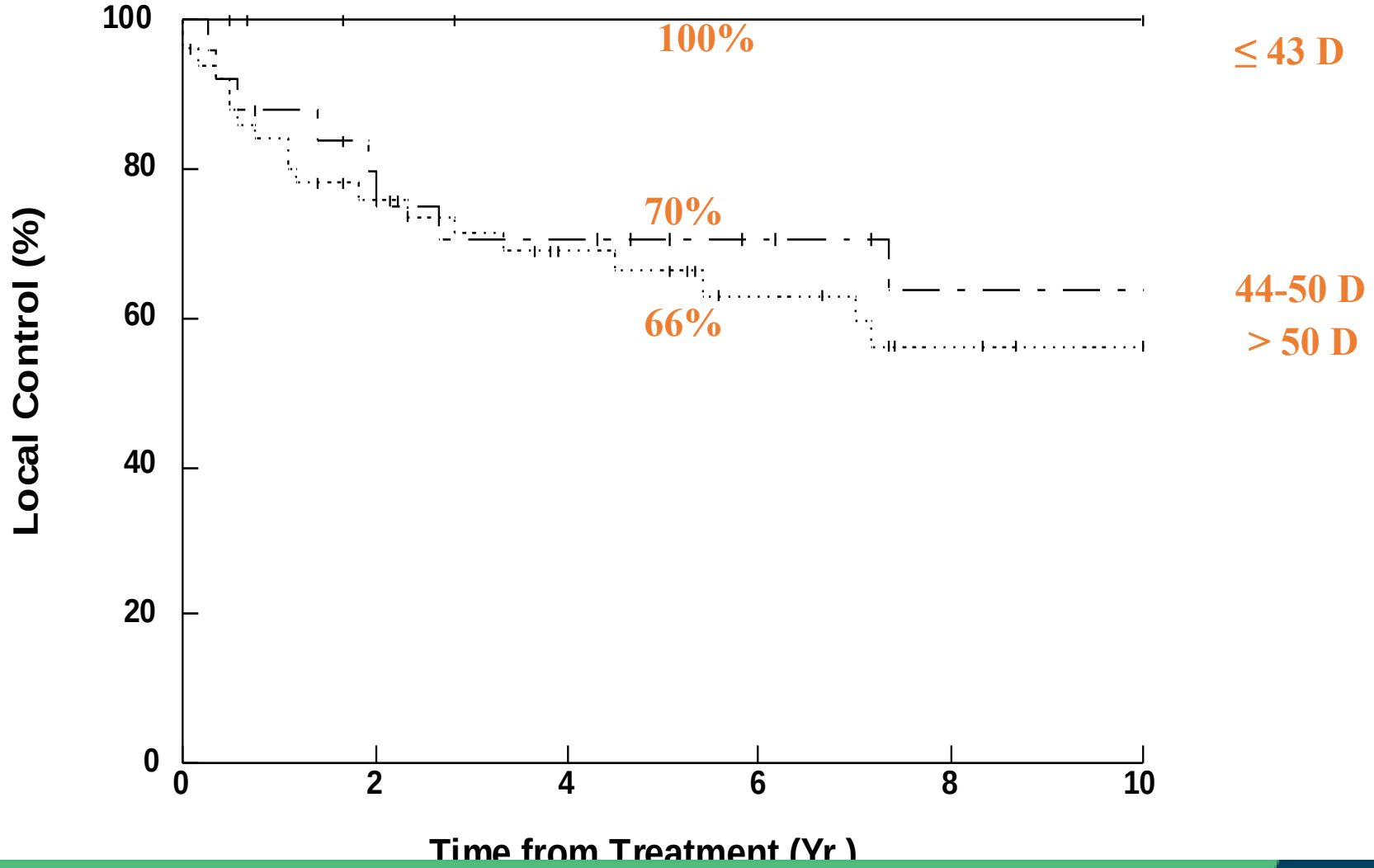
LOCAL CONTROL OF T1 LESIONS BY OVERALL TIME



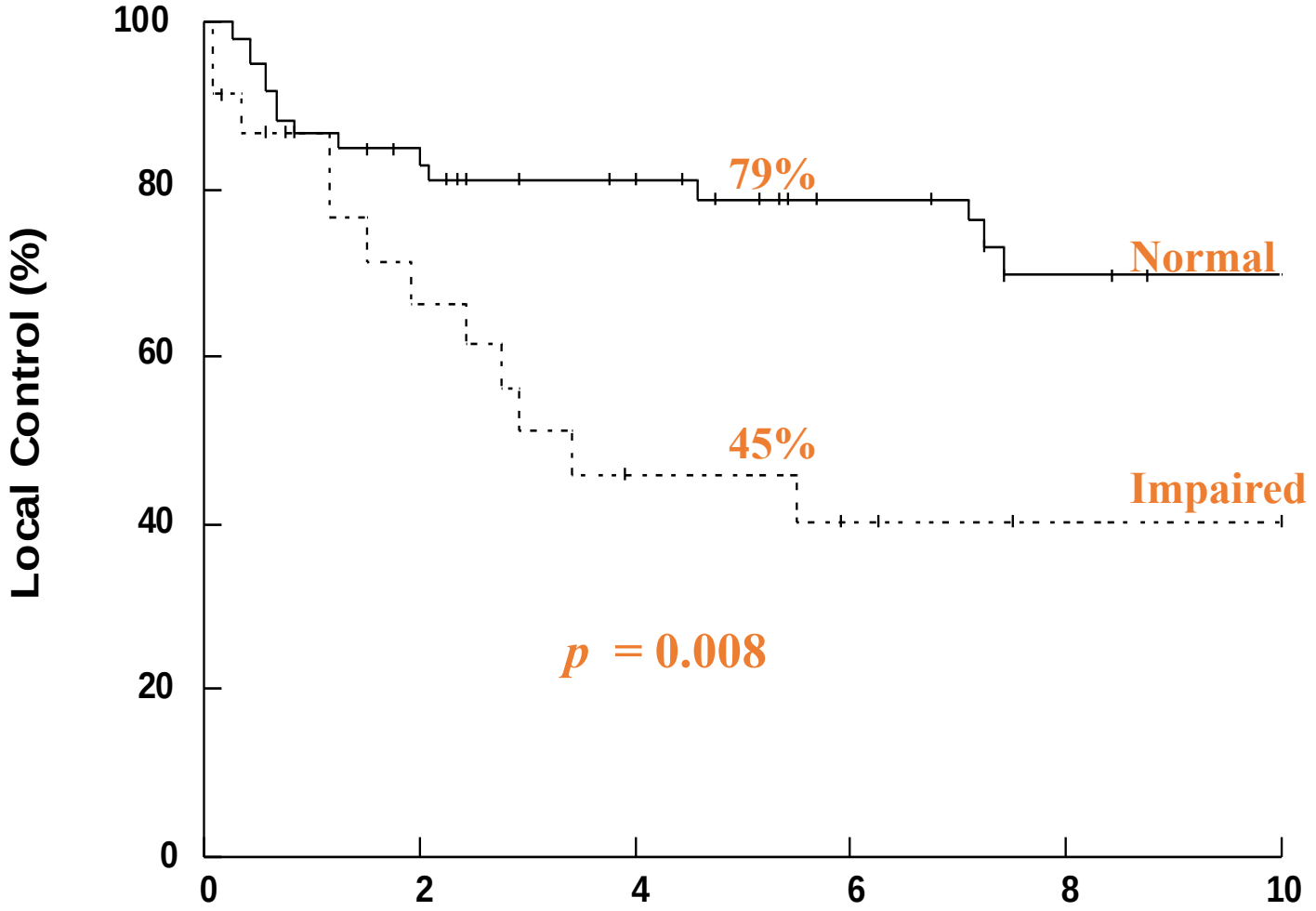
LOCAL CONTROL OF T2 LESIONS BY FRACTION SIZE



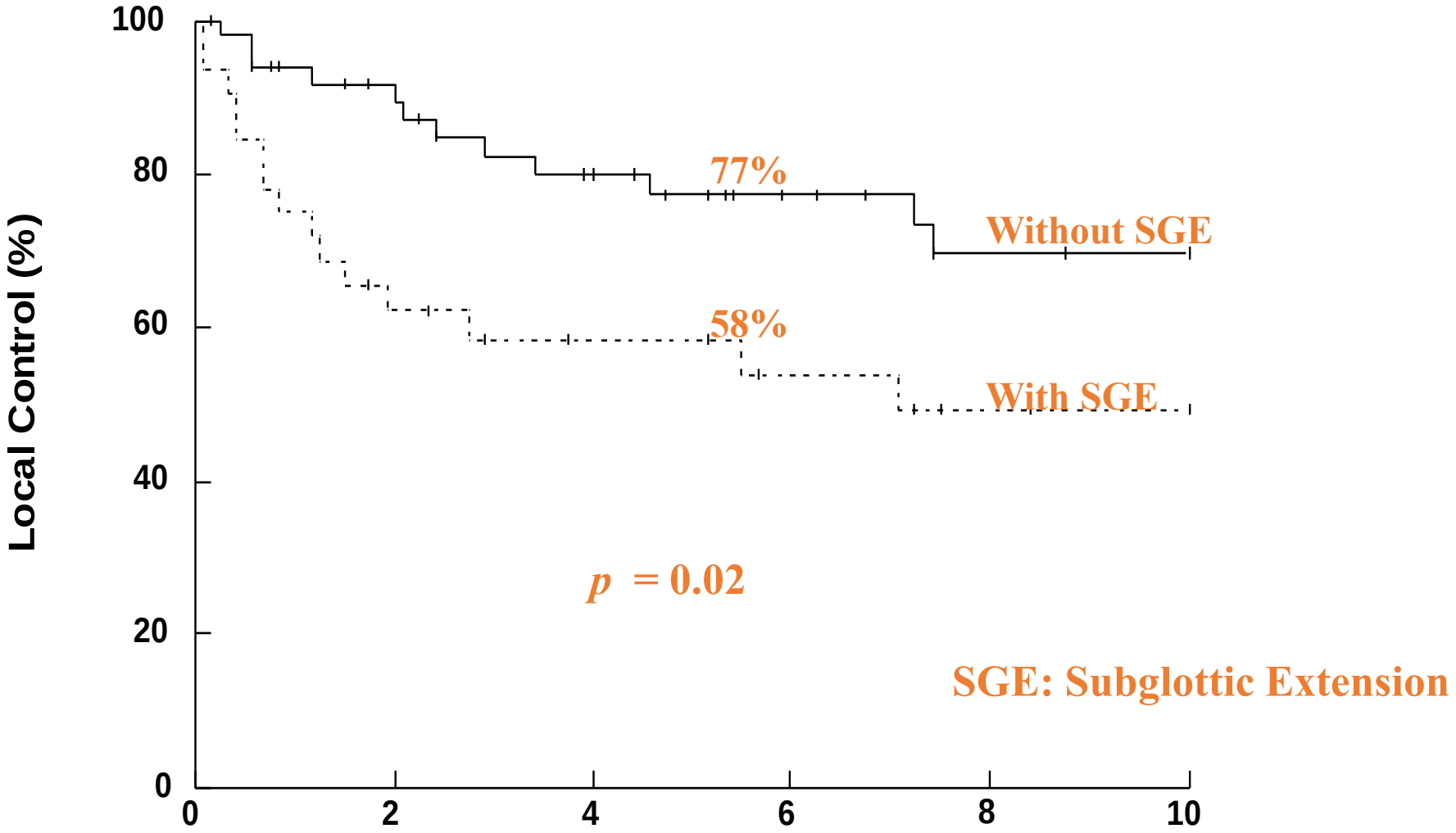
LOCAL CONTROL OF T2 LESIONS BY OVERALL TIME



LOCAL CONTROL FOR T2 GLOTTIC BY CORD MOBILITY



LOCAL CONTROL FOR T2 LESIONS BY SUBGLOTTIC EXTENSION



RADIOTHERAPY FOR EARLY GLOTTIC CARCINOMA (T1N0M0): RESULTS OF PROSPECTIVE RANDOMIZED STUDY OF RADIATION FRACTION SIZE AND OVERALL TREATMENT TIME

HIDEYA YAMAZAKI, M.D.,* KINJI NISHIYAMA, M.D.,* EIICHI TANAKA, M.D.,*

Table 1. Patient allocation to Arm A and B

Arm	Tumor length <2/3 of glottis	Tumor length ≥2/3 of glottis
Arm A (2 Gy/fr)		
A-1 (n = 31)	60 Gy/30 fr/6 wk	
A-2 (n = 57)		66 Gy/33 fr/6.6 wk
Arm B (2.25 Gy/fr)		
B-1 (n = 31)	56.25 Gy/25 fr/5 wk	
B-2 (n = 61)		63 Gy/28 fr/5.6 wk

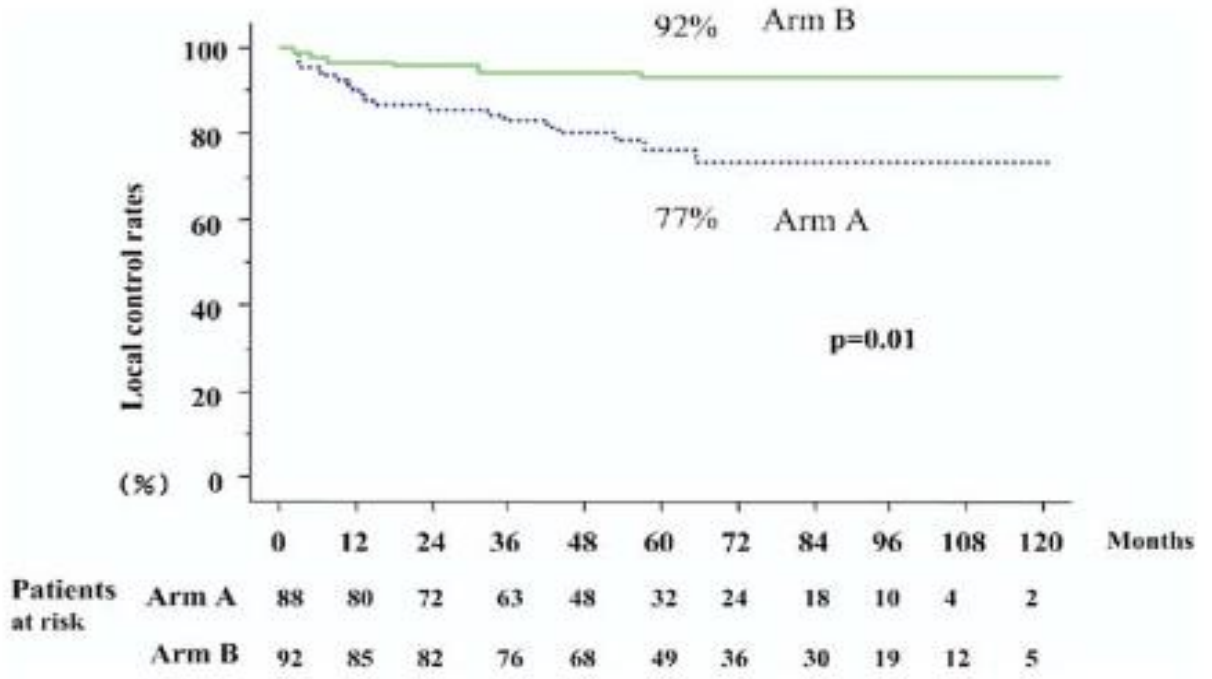


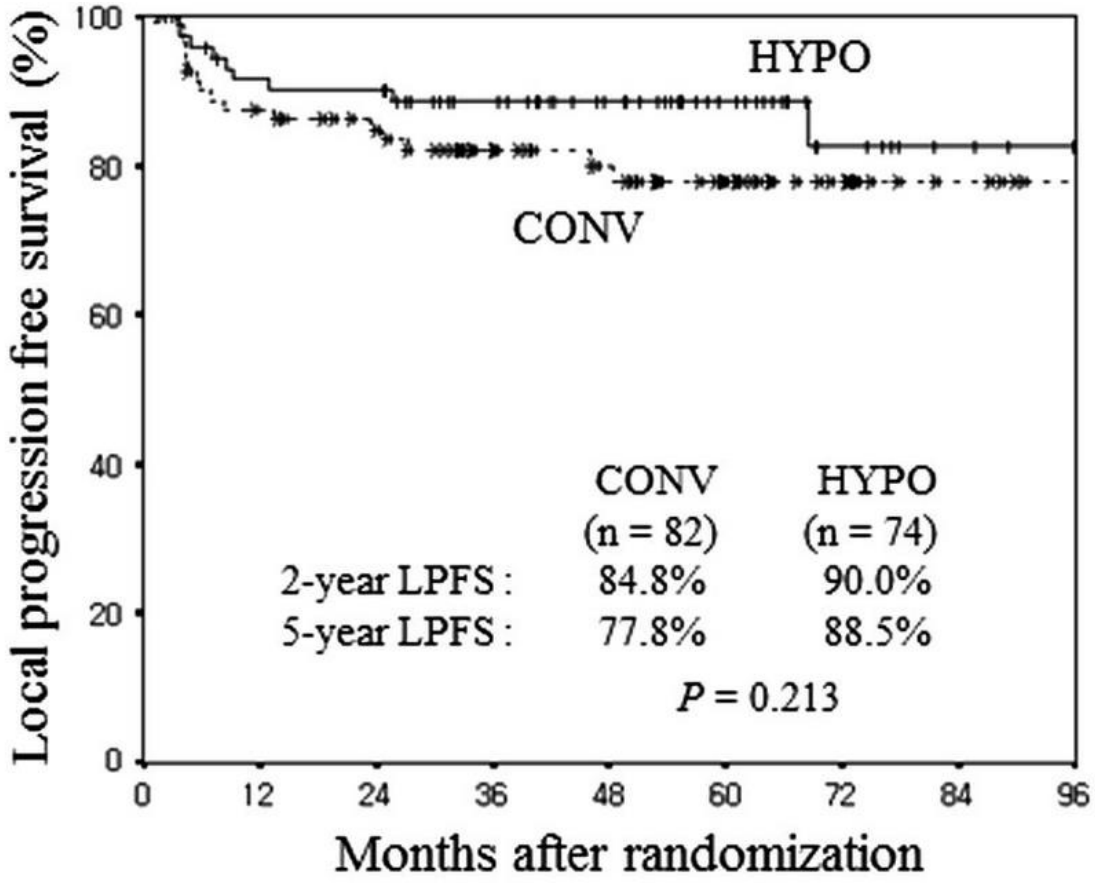
Fig. 1. Local control rates between Arms A and B.

Int. J. Radiation Oncology Biol. Phys., Vol. 64, No. 1, pp. 77–82, 2006

A prospective randomized trial comparing hypofractionation with conventional fractionation radiotherapy for T1–2 glottic squamous cell carcinomas: Results of a Korean Radiation Oncology Group (KROG-0201) study

Sung Ho Moon [a], Kwan Ho Cho [a,*], Eun Ji Chung [b], Chang Geol Lee [c], Kyu Chan Lee [d], Gyu-Young Chai [e],

Radiotherapy and Oncology 110 (2014) 98–103



Hypo: T1 63Gy/28; T2 67.5 Gy/30

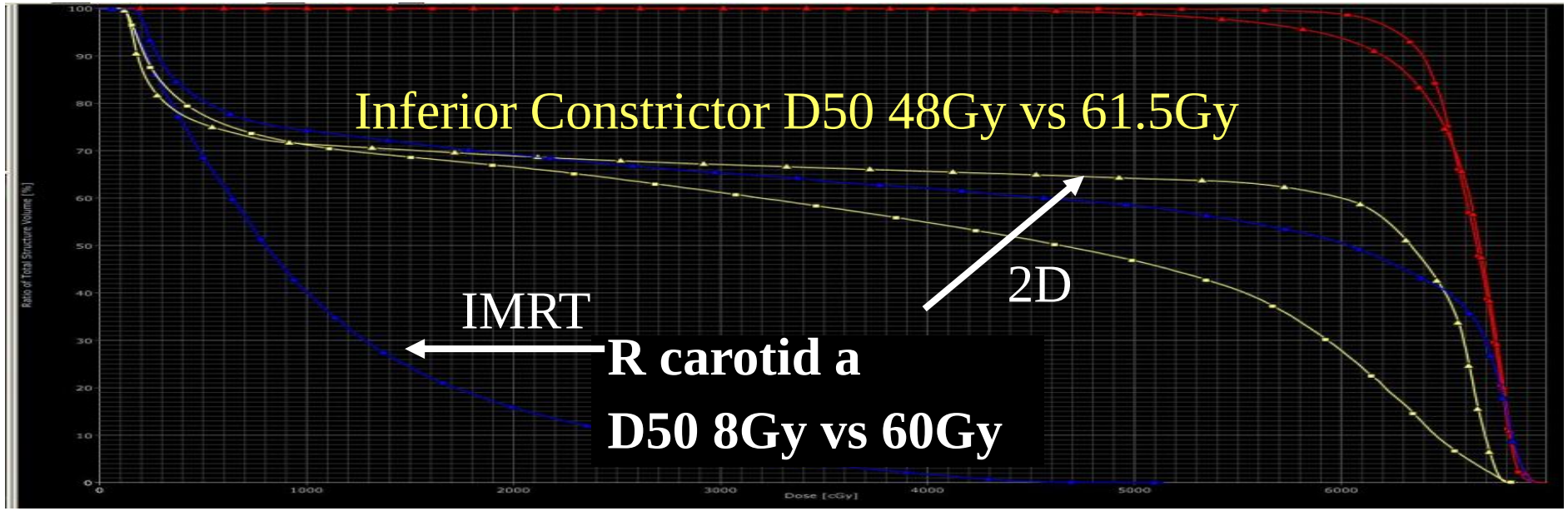
Conv: T1 66Gy/33; T2 70 Gy /35

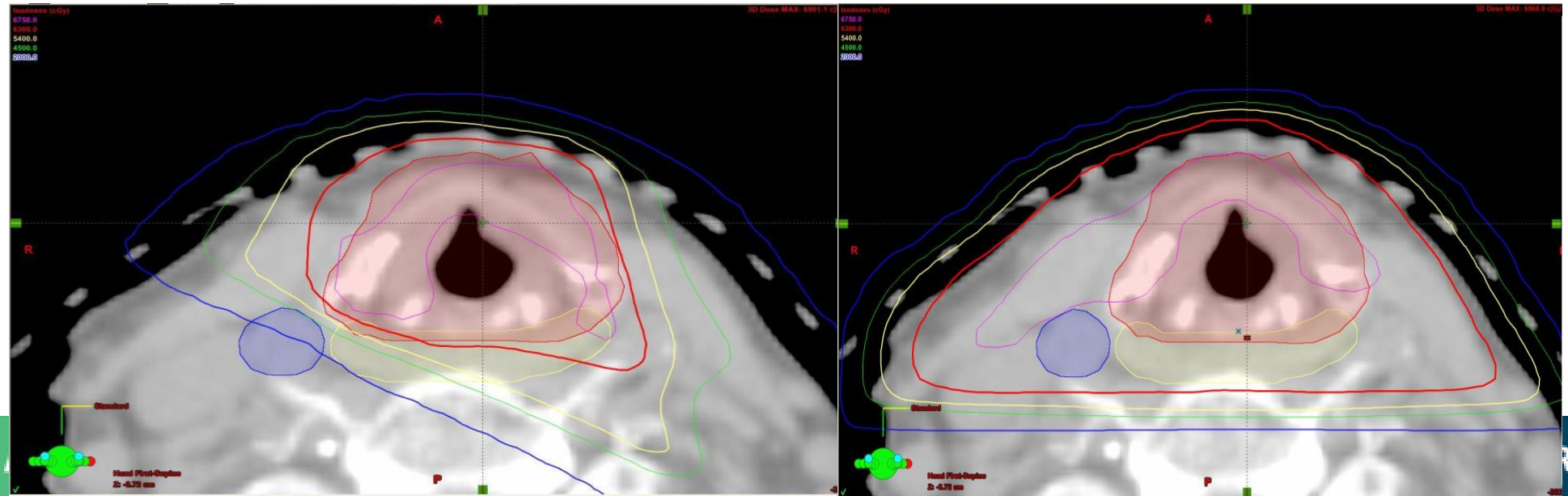
IMRT: Early Stage Glottic Larynx

- **Advantage:**
  - **Carotid sparing**
- **Disadvantage:**
  - **Geographical miss from contouring or intrafraction motion**
  - **Toxicity from dose inhomogeneity**

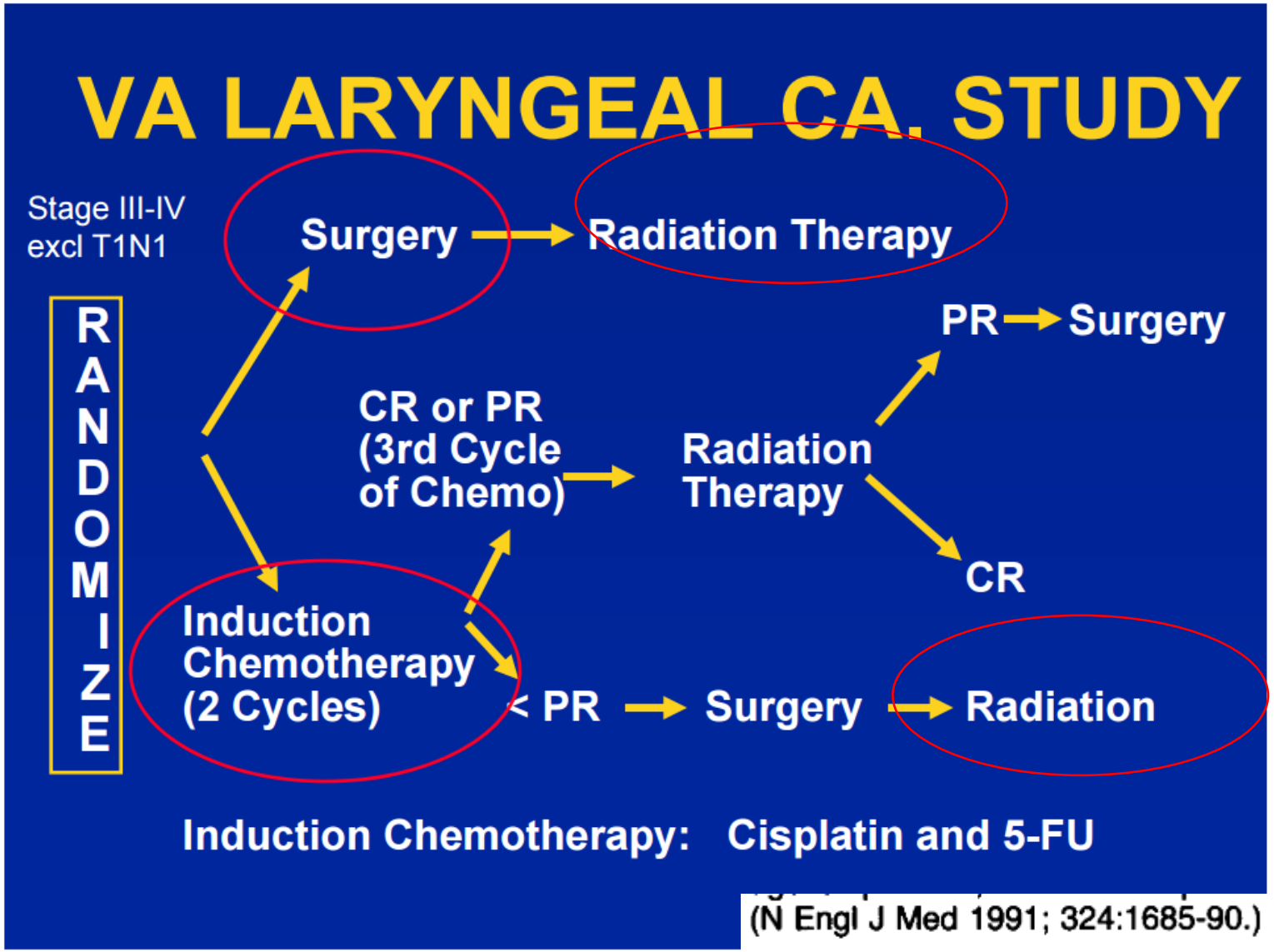
Gomez Radiat Oncol 2010
Chera IJROBP 2010
Rosenthal IJROBP 2010

IMRT: T1 Glottic Ca





Organ Preservation Treatment of Stage III/IV Larynx Cancer



Results of VA Protocol

- No Difference in 2 year survival – 68%
- Larynx Preservation in 64% in CT→RT group with:
  - Fewer Distant Metastases
  - Higher Local Recurrence
  - Salvage in 3/4
- Long-term (10yr) Quality of Life Follow-Up –
  - speech significantly better in CT→RT group
  - same incidence of swallowing difficulties in both groups
  - Less pain and depression with better global mental health in CT→ RT group

Arch Otol 124;964-971, 1998

Concurrent Chemotherapy and Radiotherapy for Organ Preservation in Advanced Laryngeal Cancer

Arlene A. Forastiere, M.D., Helmuth Goepfert, M.D., Moshe Maor, M.D., Thomas F. Pajak, Ph.D., Randal Weber, M.D., William Morrison, M.D., Bonnie Glisson, M.D., Andy Trotti, M.D., John A. Ridge, M.D., Ph.D., Clifford Ch
Glen Peters, M.D., Ding-Jen Lee, M.D., Ph.D., Andrea Leaf, M.D., John Ensley, M.D., and Jay Cooper,

N Engl J Med. 2003 Nov 27;349(22):2091-8.

RTOG 91-11
Phase III Trial to Preserve the Larynx

N = 547 stage III/IV

STRATIFY

Location:
- Glottic
- Supraglottic

T Stage:
- T2
- T3
- Early T4

N Stage:
- N0, N1
- N2, N3

RANDOMIZE

Arm 1 : Neoadjuvant CT + RT

CR, PR → Cis + 5-FU → RT x 1 Cycle

Cis + 5-FU X 2 Cycles

NR → Surgery → RT

Arm 2 : RT + cisplatin

Arm 3 : RT Alone

Neck dissections for all pts with node > 3cm or multiple nodes, 8 weeks after RT

RTOG 91-11

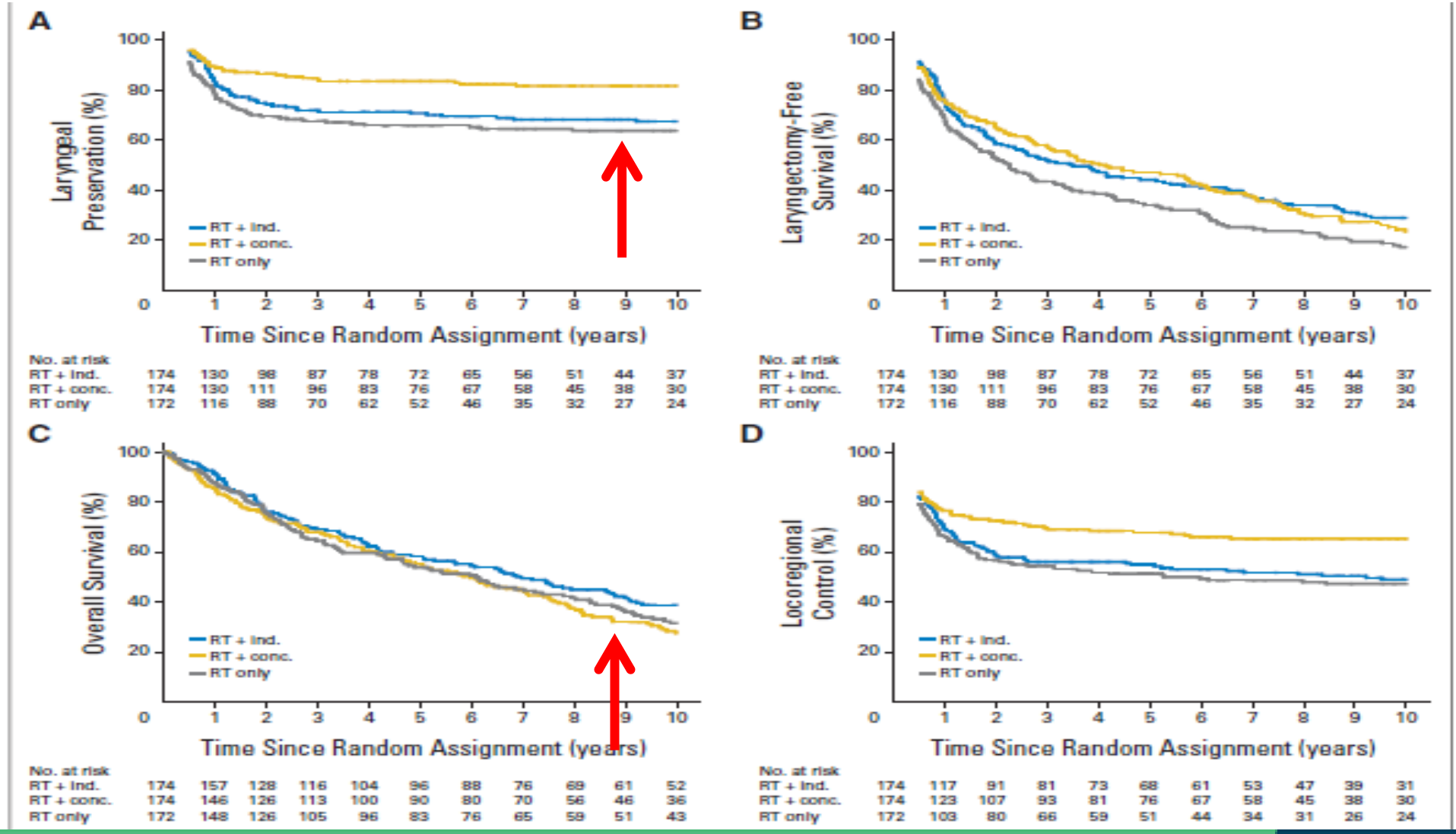
	VA	CCRT	RT
2 year Laryng-FS	75%	88%	70%
2 year LR control	61%	78%	56%
5 year DM	15%	12%	22%
5-yr. Survival	55%	54%	56%

Median F/U 3.8 years

N Engl J Med. 2003 Nov 27;349(22):2091-8.

*** Estimated from survival curves**

Concurrent Chemoradiation offers Best Cancer Control but Lower 10yr OS



T4a N+ Glottic
Supraglottic

Surgery Preferred +
Post-OP

Early Stage Hypopharynx Cancer

ORGAN PRESERVATION WITH RADIOTHERAPY FOR T1-T2 CARCINOMA OF THE PYRIFORM SINUS

Robert J. Amdur, MD,[1] William M. Mendenhall, MD,[1] Scott P. Stringer, MD,[2]

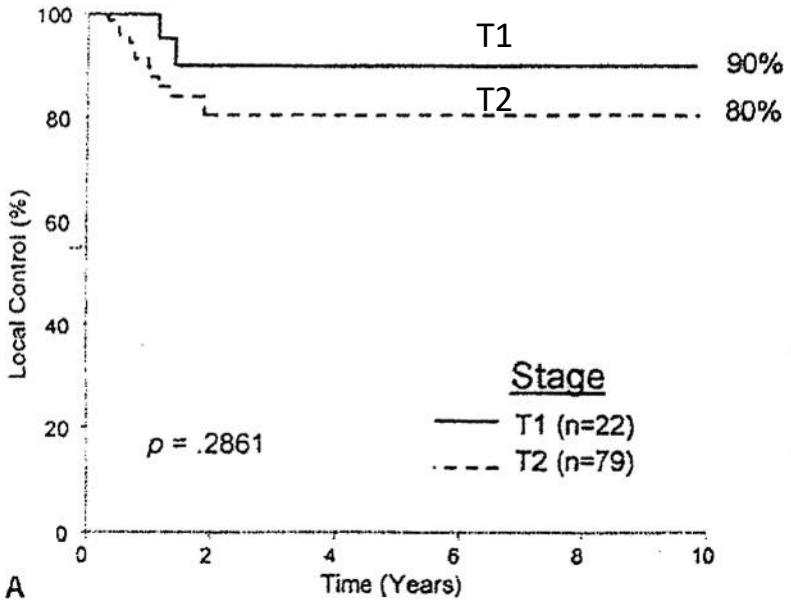


FIGURE 1. Actuarial rates of initial (A) ($p > .1$), and ultimate (B) ($p >$ initial control—stage T1, 90%; stage T2, 80%; ultimate control—stag

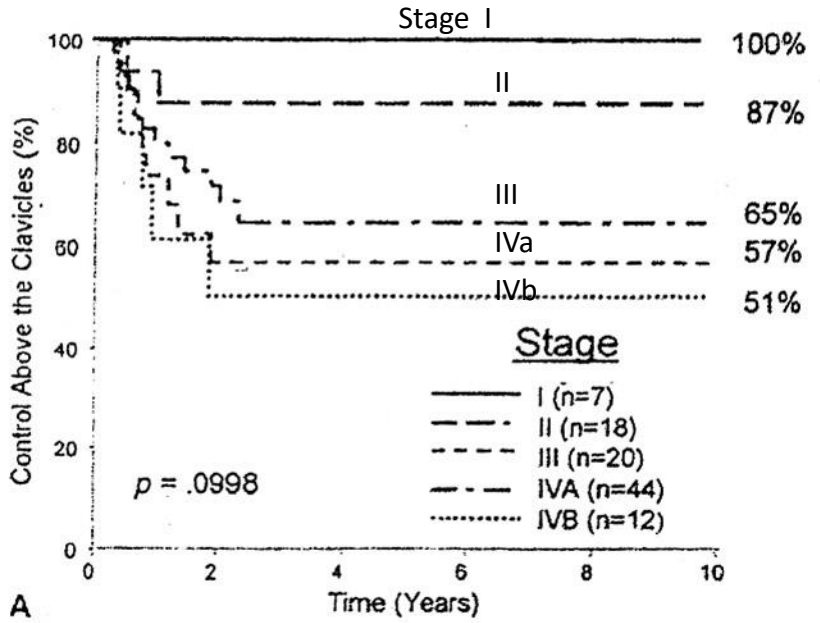


FIGURE 3. Actuarial rates of initial (A) ($p > .1$), and ultimate (B) (p as follows: Initial control—stage I, 100%; stage II, 87%; stage III, 57% stage III, 77%; stage IVA, 74%; and stage IVB, 61%.

Advanced Stage Hypopharynx Cancer

Larynx Preservation in Pyriform Sinus Cancer: Preliminary Results of a European Organization for Research and Treatment of Cancer Phase III Trial

Jean-Louis Lefebvre, Dominique Chevalier, Bernard Luboinski,

- 202 pts (Stage III: 57%, IV:37%)
  - Arm A: Surgery (TL+PP)→post-op RT
  - Arm B: CDDP/5FU x 2-3 cycles→ if CR → RT 70Gy/7wks alone
- 54% CR after induction chemotherapy
  - T2=82% (n=22); T3=48% (n=71), T4=0%(n=4)

Results

- Median F/U 51mo's
- Local failure arm A:B 12%:17% (p=ns)
- Regional failure arm A:B 19%:23% (p=ns)
- Distant Metastasis:A:B 36%:25% (p=0.04)
- Median OS arm A:B 25mo: 44mo's
- 5yr OS arm A:B 35%:30% (p=ns)
- Larynx Preservation 3yr/5yr: 42%/35%

GORTEC 2000-01 Phase III: Induction TPF vs PF for Organ Preservation in Hypopharynx/Larynx

- 213 LX or HPX requiring Total Laryngectomy
- Randomized to 3 cycles:
  - PF: CDDP (100mg/m2/d1) and 5 Fluorouracil (100mg/m2d1-5) q 3wks
  - TPF: Taxotere (75/mg/m2d1),CDDP (75mg/m2/d1) and 5 Fluorouracil (750mg/m2d1-5) q 3wks
- If CR or PR & recovery of normal vocal cord mobility →RT 70Gy/7wks

Calais, G. et al ASCO 2006

JNCI J Natl Cancer Inst, 2016, Vol. 108, No. 4

Long-Term Results of a Multicenter Randomized Phase III Trial of Induction Chemotherapy With Cisplatin, 5-fluorouracil, ± Docetaxel for Larynx Preservation

Guillaume Janoray, Yoann Pointreau, Pascal Garaud, Sophie Chapet,

- **Median F/U 105 mo's**
- **Compliance 82% (TPF) vs 67% (PF)**
- **Overall response: 83% (TPF) vs 61% (PF) (p=0.0013)**
- **Complete response: 61% (TPF) vs 47% (PF)**
- 10yr Larynx Preservation:70% (TPF) vs 47% (PF), p=0.01
- **5yr Larynx and esophageal dysfunction free survival measured by VHI and EORTC QOL 30**
  - **60% (TPF) vs 39% (PF) (all)**
  - **36% (TPF) vs 21% (PF) (alive)**
  - **8% PEG; 3% trach**

JNCI J Natl Cancer Inst, 2016, Vol. 108, No. 4

Larynx/Hypopharynx

Conclusions

- RT alone for early stage glottic larynx keep treatment time < 6 wks
- Early Stage Supraglottic larynx requires elective neck RT
- Concurrent chemoradiotherapy is the treatment for locally advanced larynx cancer
- Larynx preservation better in CCRT compared to induction, or RT alone but survival no different, due to increased non-cancer deaths
- Induction considered for advanced hypopharynx/larynx with poor organ function.
- Patients with T4a disease should consider upfront surgery then post-op RT+/-chemotherapy

Optimizing Organ Function Preservation

- Dysphagia
- Xerostomia
- Quality of Life

CT-based delineation of organs at risk in the head and neck region: DAHANCA, EORTC, GORTEC, HKNPCSG, NCIC CTG, NCRI, NRG Oncology and TROG consensus guidelines

Radiotherapy and Oncology, 2015-10-01, Volume 117, Issue 1, Pages 83-90,

Charlotte L. Brouwer, Roel J.H.M. Steenbakkers, Jean Bourhis, Wilfried Budach, Cai Grau, Vincent Grégoire, Marcel van

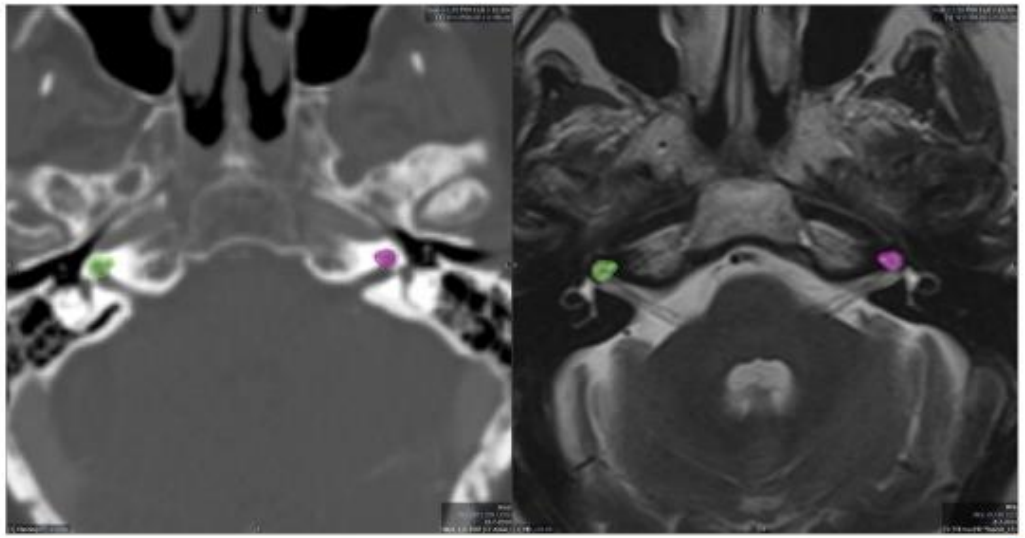


Fig. 2

Delineation of the cochlea in CT bone settings (left), matched to MRI-T2 (right).

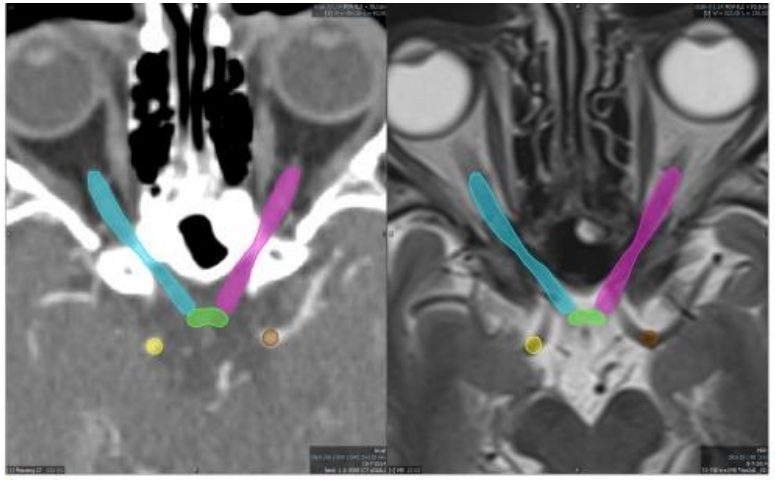
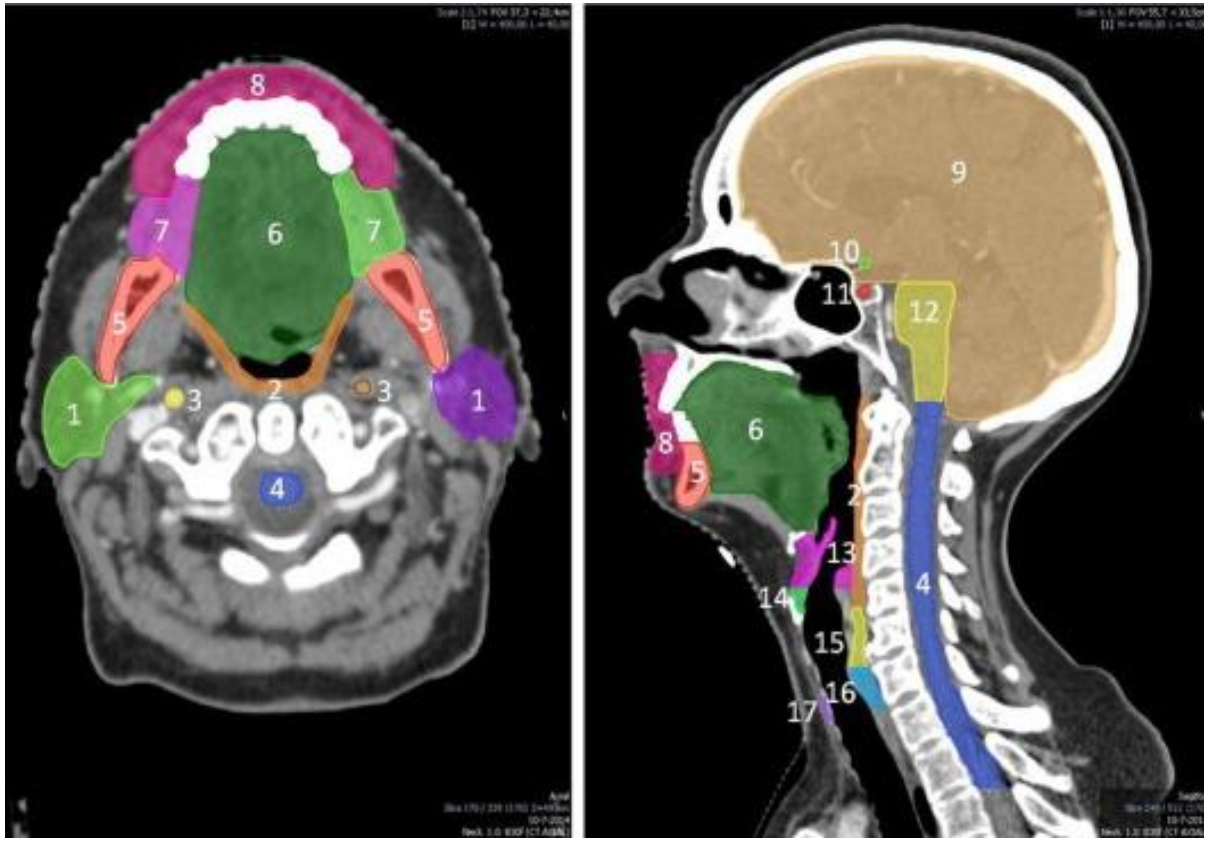
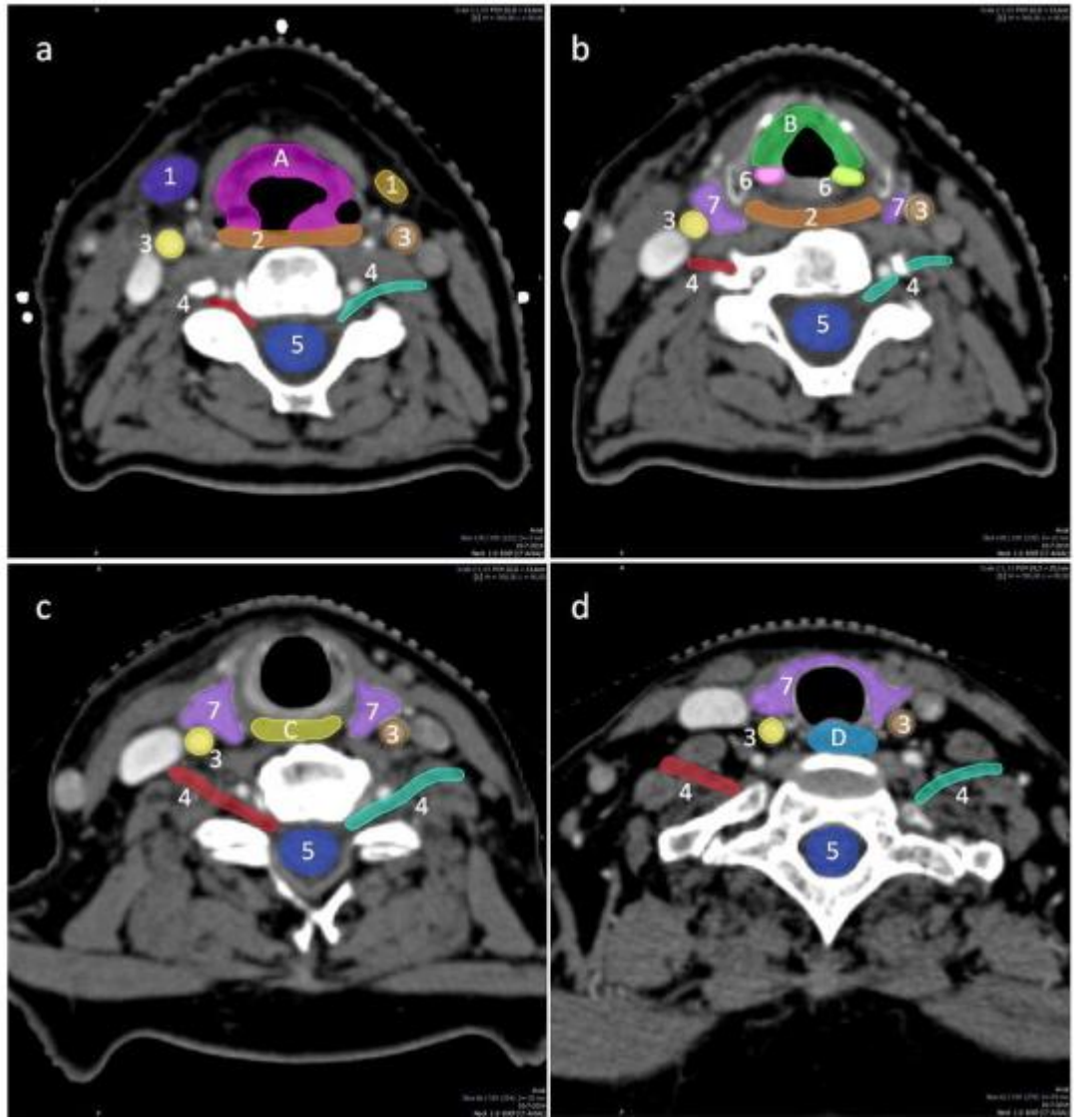


Fig. 5

Delineation of the optic nerves (blue and purple), optic chiasm (green) and carotid arteries (yellow and brown) on CT (left) and MRI-T2 (right).



Axial (left) and sagittal (right) view of the consensus delineations of the parotid glands (1), pharyngeal constrictor muscles (2), carotid arteries (3), spinal cord (4), mandible (5), extended oral cavity (6), buccal mucosa (7), lips (8), brain (9), chiasm (10), pituitary gland (11), brainstem (12), supraglottic larynx (13), glottic area (14), crico-pharyngeal inlet (15), cervical esophagus (16) and thyroid (17). (For the full atlas, the reader is referred to the Supplemental material .)



Axial CT slices showing the delineation of the supraglottic larynx (A) (a), glottic area (B) (b), crico-pharyngeal inlet muscle (C) (c), and cervical esophagus (D) (d). Other organs at risks visible are the submandibular glands (1), pharyngeal constrictor muscles (2), carotid arteries (3), brachial plexus (4), spinal cord (5), arytenoids (6) and thyroid

Dysphagia

RTOG-0129 Cisplatin + RT (3D/2D Technique)

PEG dependence 1yr 30%

IMRT: PEG:1-2%

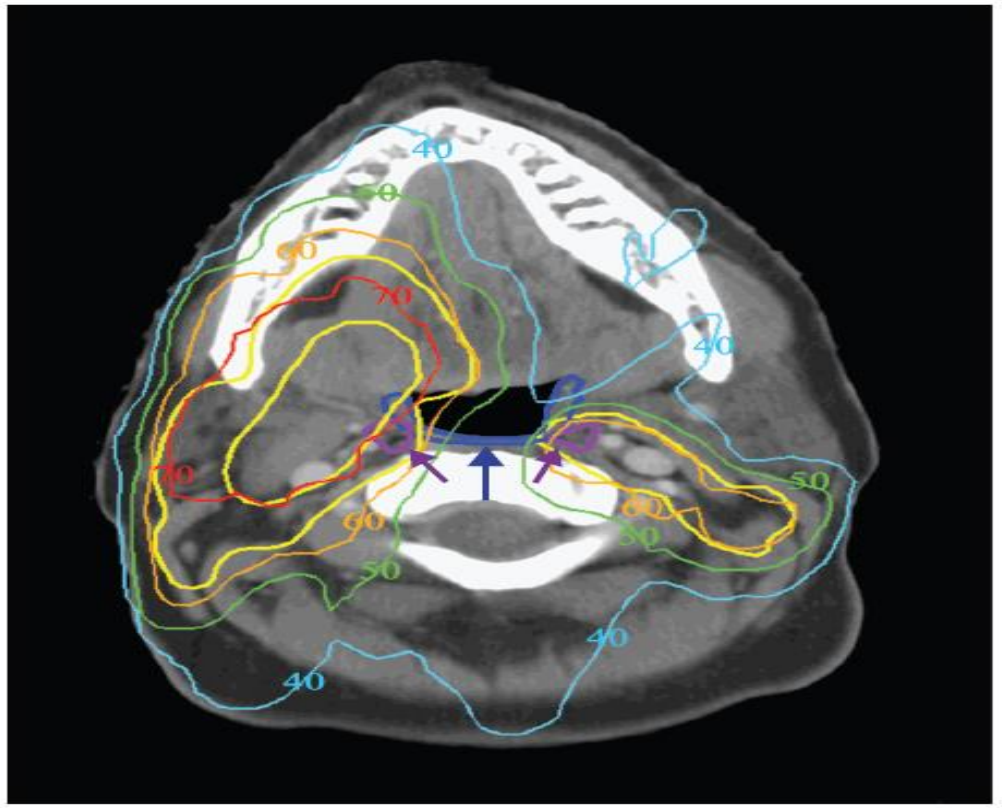
Measures of dysphagia:

Feeding tube dependence videofluoroscopy/silent aspiration dysphagia qol surveys

Intensity-Modulated Chemoradiotherapy Aiming to Reduce Dysphagia in Patients With Oropharyngeal Cancer: Clinical and Functional Results

73 III/IV Opx 70Gy/7wks + taxol/carbo/wk

Med F/U 36mo 3yr LRC 96% DFS 88%



Feng JCO 2010

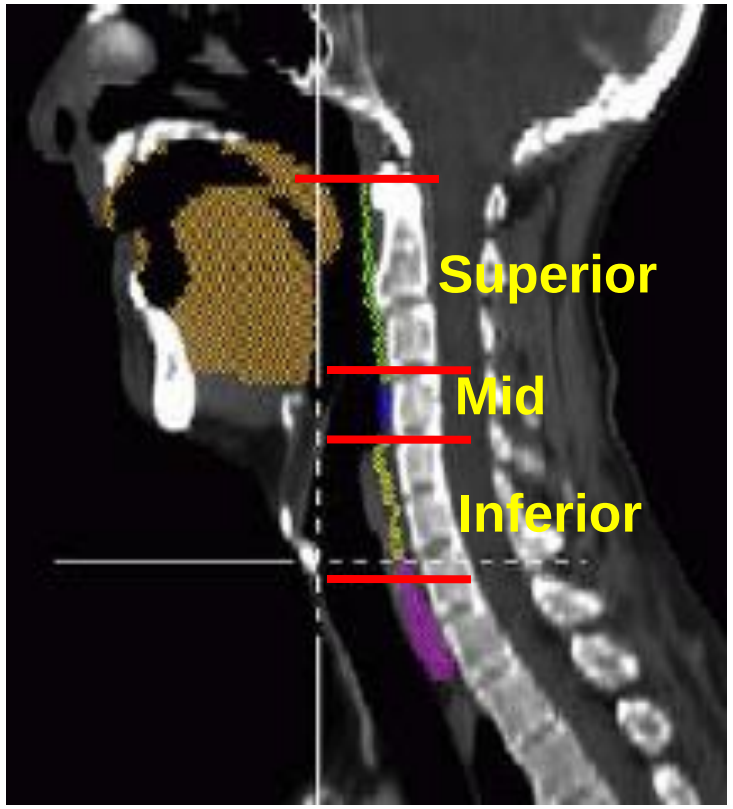
PEG dependence **1.4%** at 1yr
Dysphagia related to dose to PC,Lx, Esoph
Neck dissection/smoking/t-stage

Table 4. Videofluoroscopic-Measured Aspiration Rates and Summary Swallow Scores

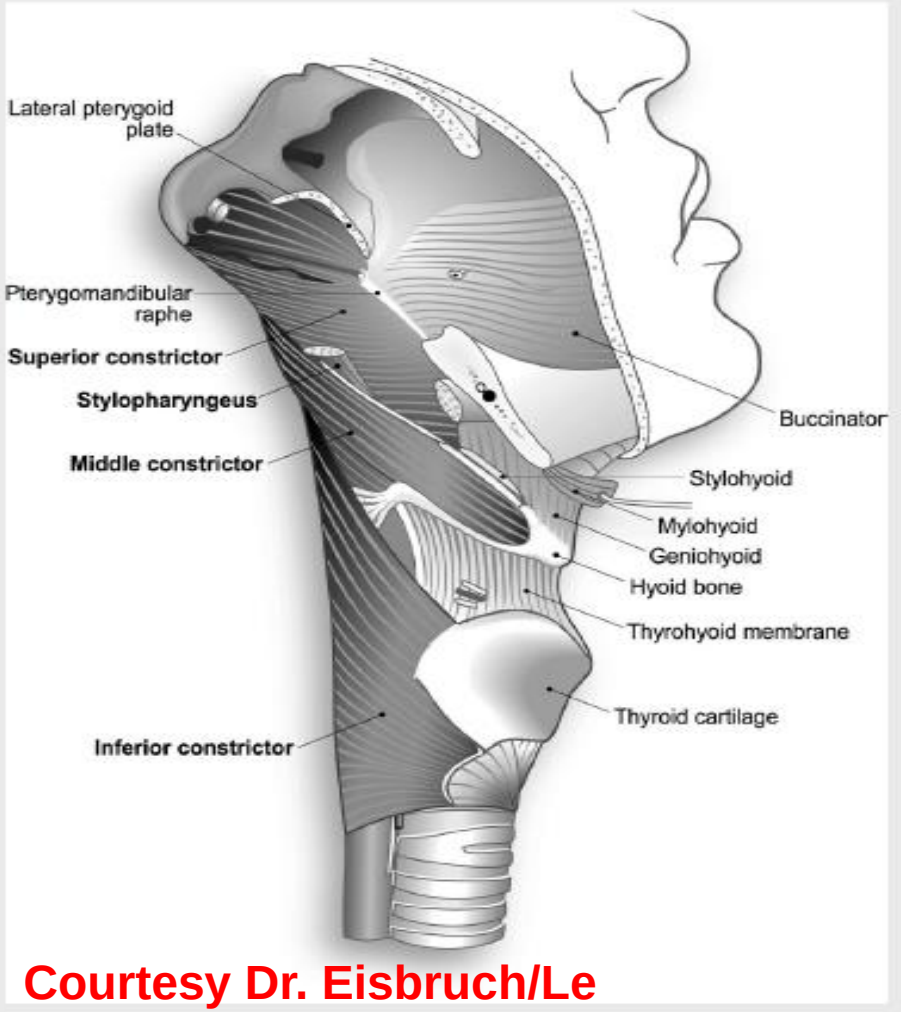
Time, months	No. of Patients With VF Studies	Patients With VF-Based Aspiration (%)		Patients Who Aspirated After Therapy but Did Not Aspirate Before Therapy	
		No.	%	No.	%
Pretherapy	72	8	11		
3	68	22	32	18	26
12	66	16	24	13	20
24	44	10	22	7	16

- **5 pts with strictures**
- **8 pts with pneumonia—all silent aspirators**

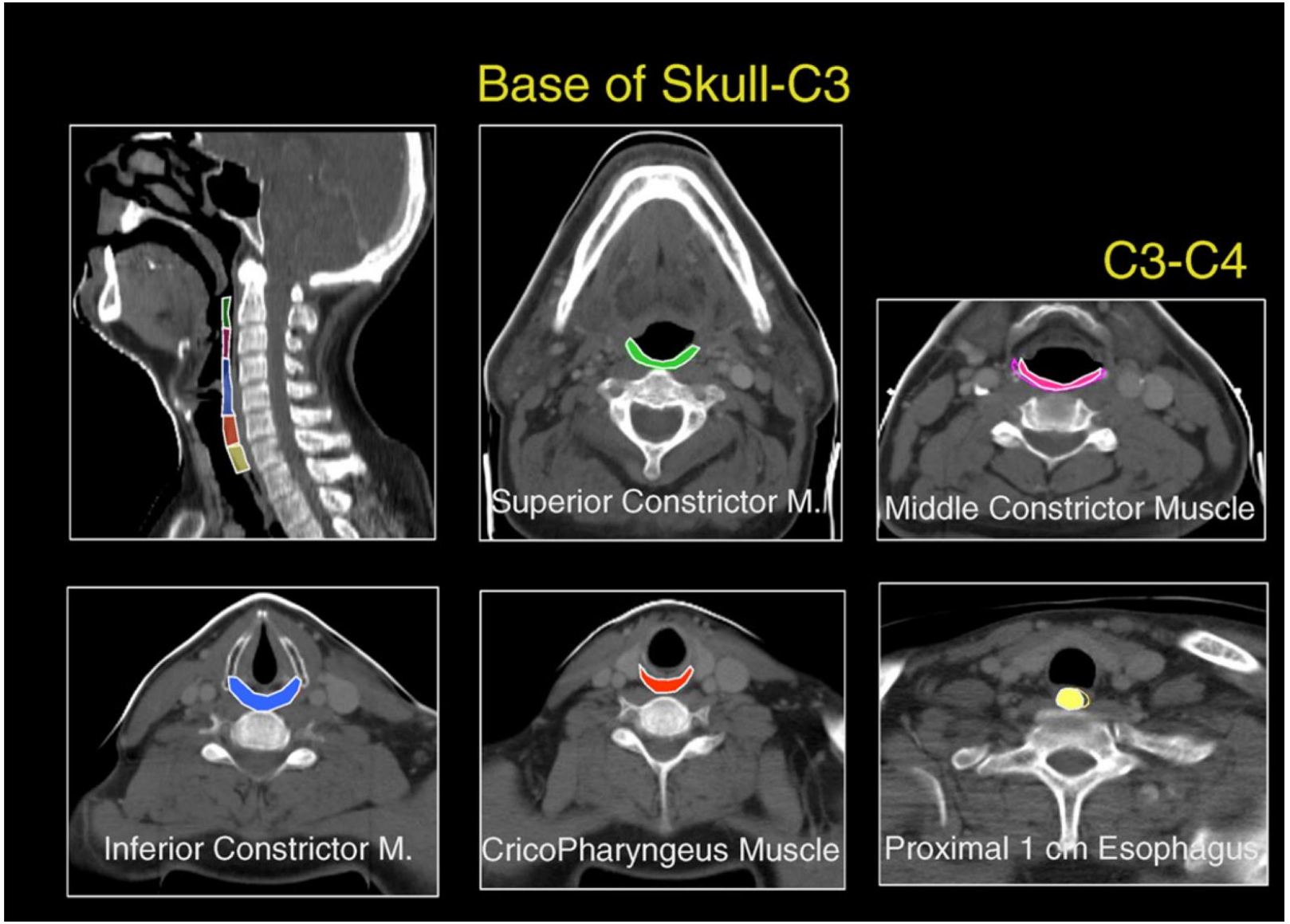
Pharyngeal Constrictors



Werbrouch J et al, IJROBP 2009, 73:1187

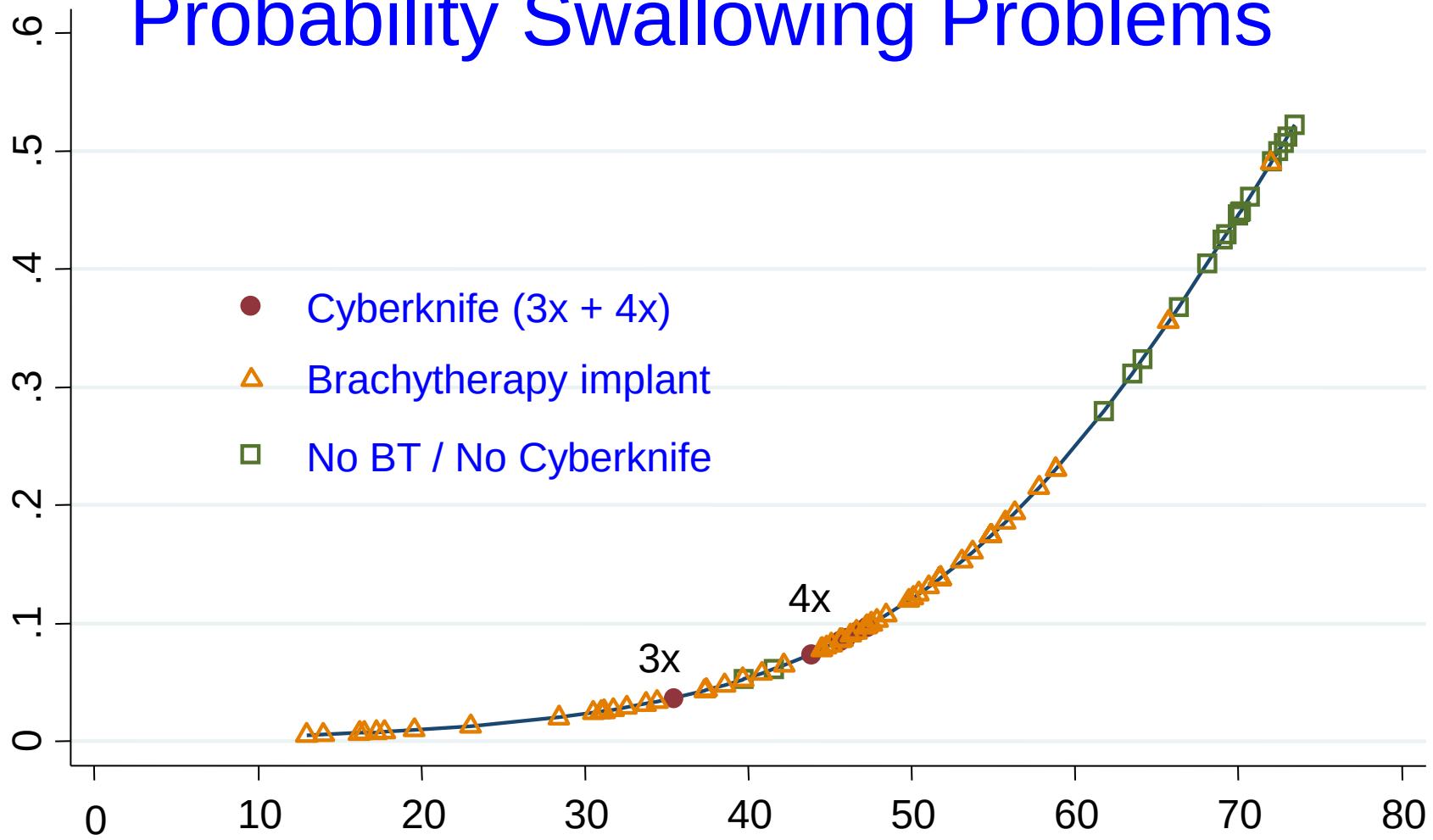


Courtesy Dr. Eisbruch/Le



Levendag PC, et al. *Radiother Oncol*. 2007

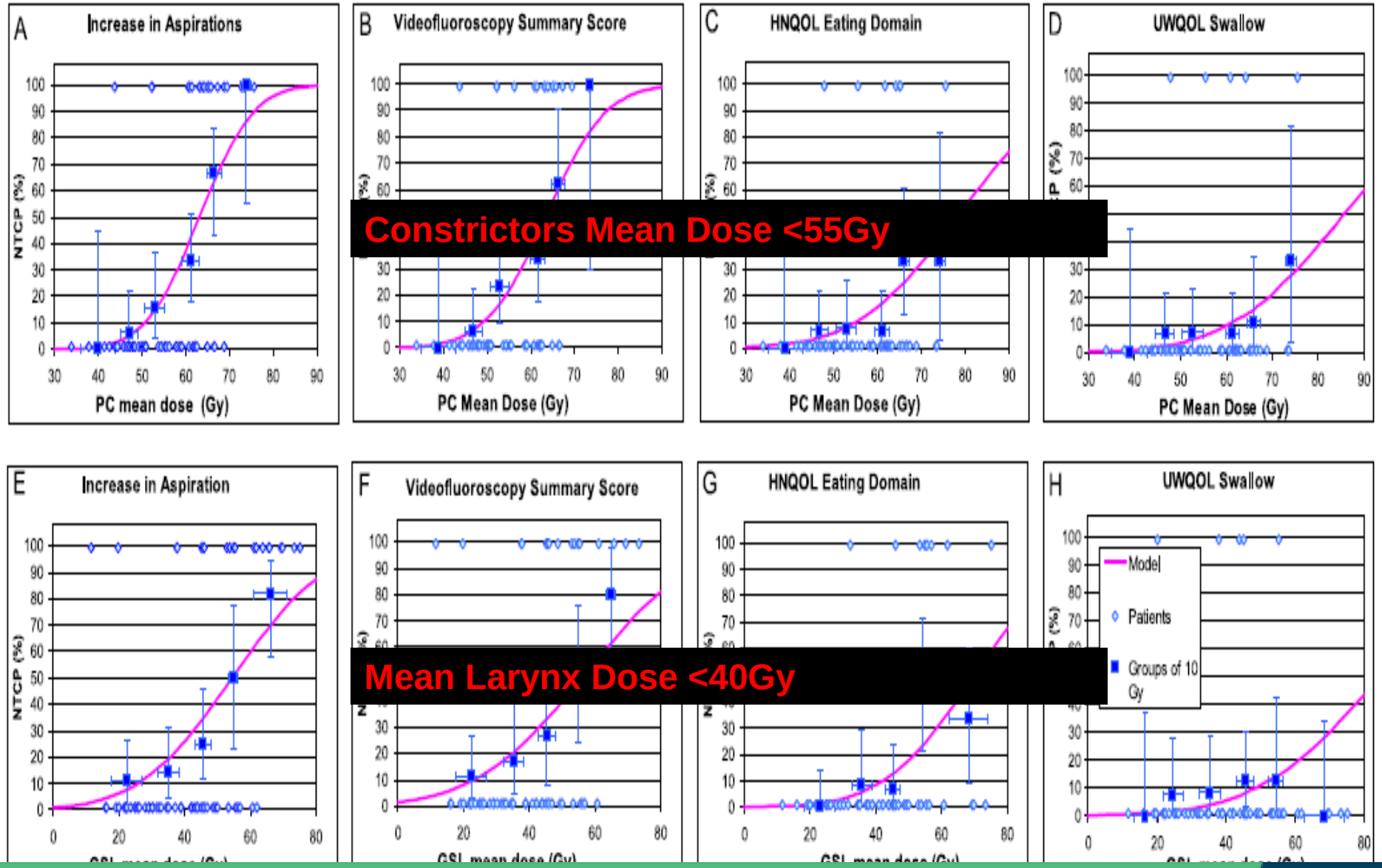
Probability Swallowing Problems



Dose superior constrictor muscle (Gy)

Mean Tolerance Doses and Swallowing Complications

	PEG-depend	Aspiration	Stricture	
Eisbruch (IJROBP,2011)		Lx<40Gy PC<56Gy	Esoph<48Gy	
Caudell (IJROBP,2010)	LX<50Gy IPC<50Gy	Lx<41Gy	SPC V65<1/3 MPC V65<3/4	
Caglar (IJROBP,2008)		Lx<48Gy IPC<54Gy	Esoph<40Gy	
Li	IPC<54Gy			


A
Increase in Aspirations
NTCP (%)
PC mean dose (Gy)
B
Videofluoroscopy Summary Score
PC Mean Dose (Gy)
C
HNQOL Eating Domain
PC Mean Dose (Gy)
D
UWQOL Swallow
PC Mean Dose (Gy)
Constrictors Mean Dose <55Gy
E
Increase in Aspiration
NTCP (%)
F
Videofluoroscopy Summary Score
G
HNQOL Eating Domain
H
UWQOL Swallow
Model
Patients
Groups of 10 Gy
Mean Larynx Dose <40Gy

Eliminating Radiotherapy to the Contralateral Retropharyngeal and High Level II Lymph Nodes in Head and Neck Squamous Cell Carcinoma Is Safe and Improves Quality of Life

Christopher R. Spencer, MD, MS[1]; Hiram A. Gay, MD[1]; Bruce H. Haughey, MBChB, MS, FACS[2]; Brian Nussenbaum, MD[2];

Cancer 2014;120:3994-4002.

- Washington University
- 748 pts opx/hpx/lx/unk primary
- IMRT—3 generations of elective coverage (1997-2010)in contralateral node neg neck
- A) Bilateral RS/RP, 260pts B)Sparing CL RS 205 pts C) Spared CL RS/RP 283 pts
- Median Followup 37mo's
- MDADI Dysphagia QOL and POF

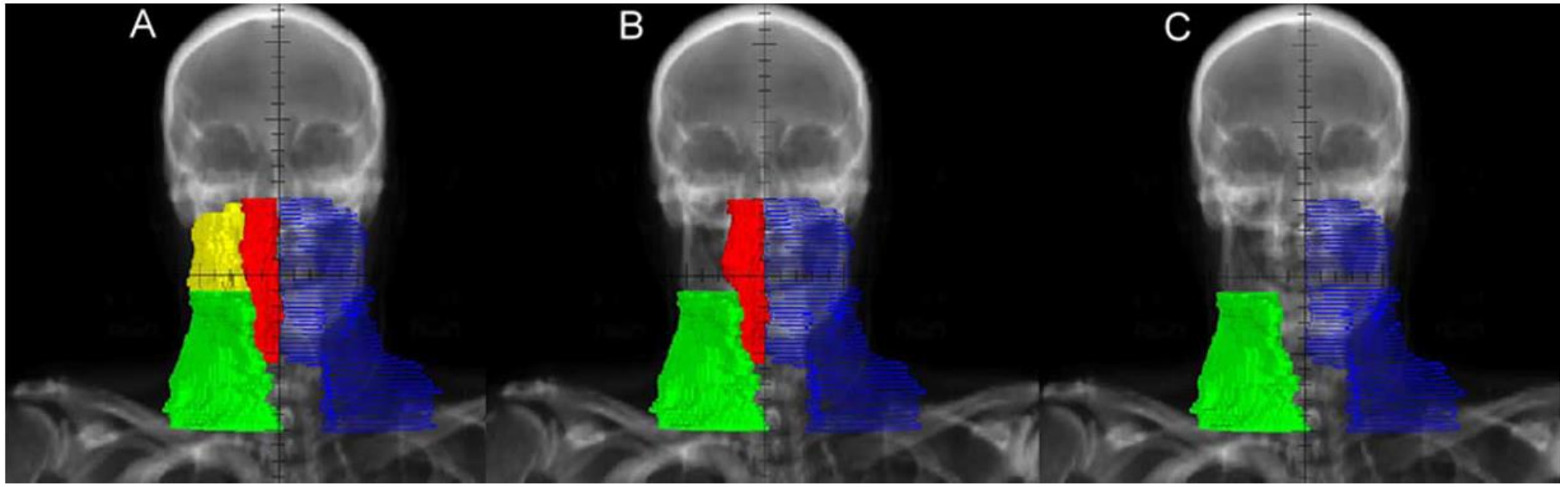
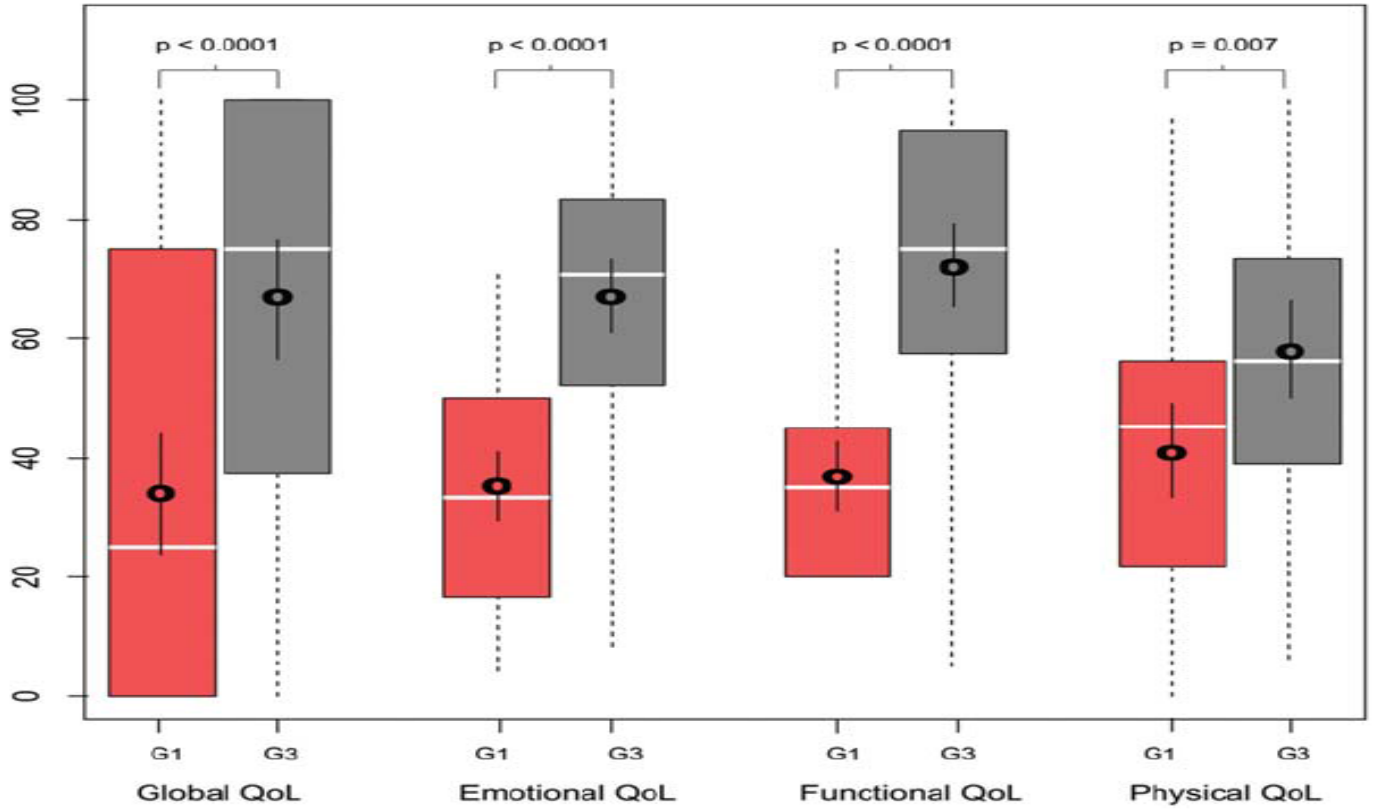


TABLE 1. Patient and Tumor Characteristics

Characteristic	No. of Patients (%)		
	Patients, n=406	Generation 2, n=172	Generation 3, n=234
Sex			
Men	319	137 (80)	182 (78)
Women	87	35 (20)	52 (22)
Age: Median [range], y	57 [23-90]	57 [23-90]	57 [25-87]
Tumor site[a]			
Oral cavity	64	25 (15)	39 (17)
Oropharynx	211	94 (55)	117 (50)
Larynx	86	35 (20)	51 (22)
Hypopharynx	27	10 (6)	17 (7)
Unknown primary	25	10 (6)	15 (6)
AJCC stage[b]			
I	7	3 (2)	4 (2)
II	26	12 (7)	14 (6)
III	82	31 (18)	51 (22)
IVA	234	97 (56)	137 (59)
IVB	28	18 (10)	10 (4)
Chemotherapy	248	95 (55)	153 (65)
Radiotherapy			
Definitive	148	61 (35)	87 (37)
Postoperative	258	111 (65)	147 (63)

Swallowing Better in Group C vs A



MDADI at >30mo in group A vs group C
Differences >18points are significant
NO FAILURES IN SPARED RS/RP LN'S

ICR The Institute of Cancer Research

CANCER RESEARCH UK

The ROYAL MARSDEN NHS Foundation Trust

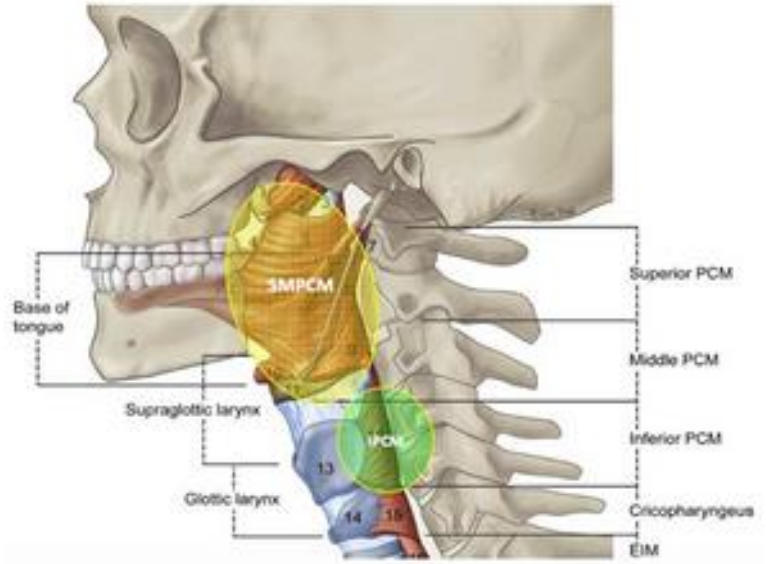
First results of DARS: A Randomised Phase III Study of Dysphagia-Optimised Intensity Modulated Radiotherapy (DO-IMRT) versus Standard IMRT (S-IMRT) in Head and Neck Cancer (CRUK/14/014)

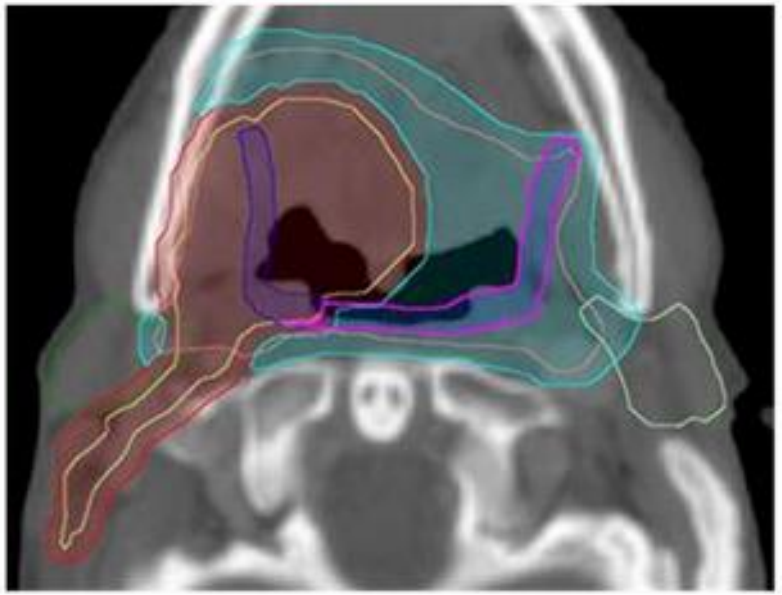
Professor Christopher Nutting

C. Nutting, K. Rooney, B. Foran, L.Pettit, M.Beasley, L.Finneran, J.Roe, J.Tyler, T.Roques, A.Cook, I.Petkar, S.Bhide, D.Srinivasan, C.Boon, E.De Winton, R.Frogley, K.Mertens, M.Emson, E.Hall on behalf of the DARS Investigators

ASCO 2020

Dysphagia-Optimised IMRT





- The volume of the superior & middle pharyngeal constrictor muscle (PCM) or inferior PCM **lying outside the high-dose clinical target volume (CTV65)** was set a mandatory mean dose constraint (<50 Gy) in DO-IMRT

Endpoints

Primary endpoint

- Difference in mean MD Anderson Dysphagia Inventory (MDADI) composite score at 12 months after treatment completion

Key secondary endpoints

- Longitudinal pattern of MDADI up to 2 years
- University of Washington-QOL
- PSS-HN domain scores
- The 100ml Water Swallow Test
- Video Fluoroscopy
- Acute and late radiation toxicity (CTCAE v4.0 and LENTSOMA)
- Locoregional tumour control and overall survival

Patient reported (blinded)

SLT reported (blinded)

Baseline characteristics (1)

	S-IMRT N=56		DO-IMRT N=56	
	N	%	N	%
Gender				
Male	49	88	41	73
Female	7	12	15	27
Site of tumour*				
Oropharynx	55	98	53	96
Hypopharynx	1	2	2	4
Chemotherapy*				
Concomitant chemotherapy	51	91	50	89
None	5	9	6	11
Age at randomisation				
<50	12	21	12	21
50-59	26	46	19	34
60-69	14	25	21	38
>70	4	7	4	7

* Balancing factor

Radiotherapy

- 111/112 had RT doses as prescribed

	Mean dose (Gy) S-IMRT Median (IQR)	Mean dose (Gy) DO-IMRT Median (IQR)	Mann-Whitney test P-value
Plan Inf-PCM*	49.8 (47.1-52.4)	28.4 (21.3-37.4)	<0.0001
Plan SM-PCM*	57.2 (56.3-58.3)	49.7 (49.4-49.9)	<0.0001

* Denotes the volume of the PCM outside CTV65

MDADI Composite score at 12 months

The MDADI composite score is a score out of 100 with high scores indicative of better swallowing function

Treatment Group	N	Mean	SD	95% CI	Difference between means	95% CI of difference	t-test P-value
S-IMRT	45	70.5	17.3	65.4, 75.8	7.2	0.4 – 13.9	0.037
DO-IMRT	52	77.7	16.1	73.3, 82.2			

UW-QOL swallowing at 12 months

Q5 Swallowing question of UW-QOL

	S-IMRT N (%)	DO-IMRT N (%)	
I can swallow as well as ever	7 (15.2)	21 (40.4)	+25%
I cannot swallow certain solid foods	37 (80.4)	30 (57.7)	-23%
I can only swallow liquid food	1 (2.17)	1 (1.92)	
I cannot swallow because it "goes down the wrong way" and chokes me	1 (2.17)	0	

Xerostomia

Most common quality of life complaint

Thick mucus and Dry Mouth

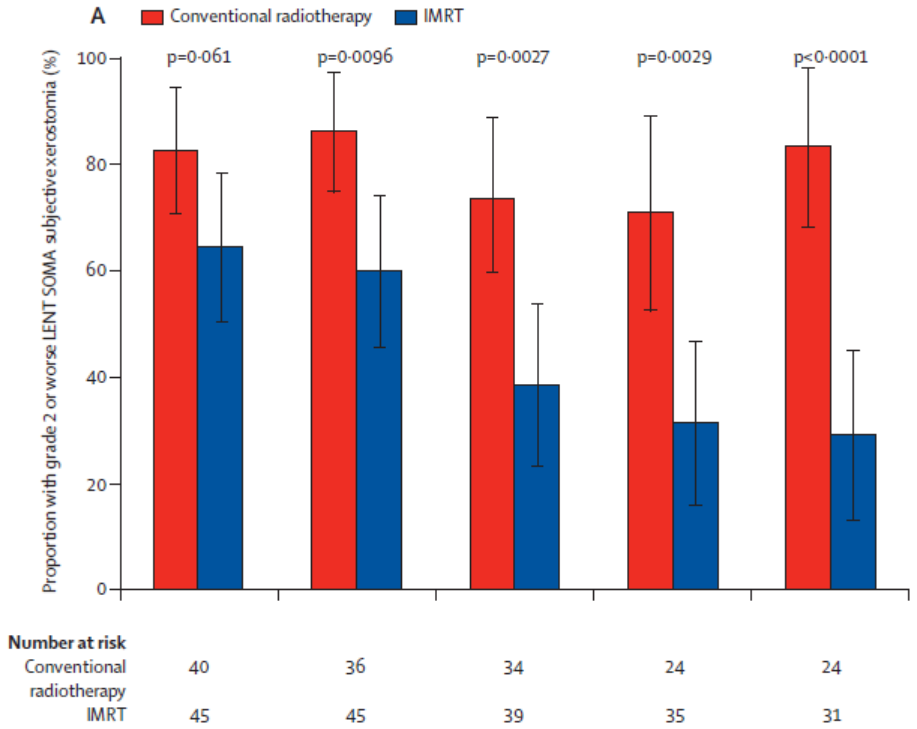
Affects ability to eat, speak, swallow

Major Impact on oral microbiome/dentition

Parotid Sparing with IMRT Decreases Xerostomia: PASSPORT Trial

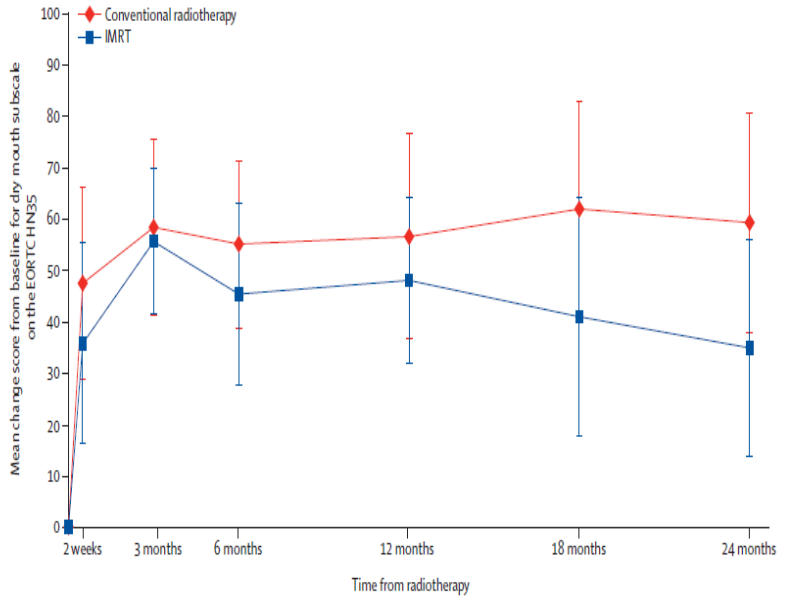
- 94 pts with OP/HP cancer randomized to IMRT vs 3DRT
- Whole contralateral parotid < 24Gy

Lent SOMA Score



Number at risk					
Conventional radiotherapy	40	36	34	24	24
IMRT	45	45	39	35	31

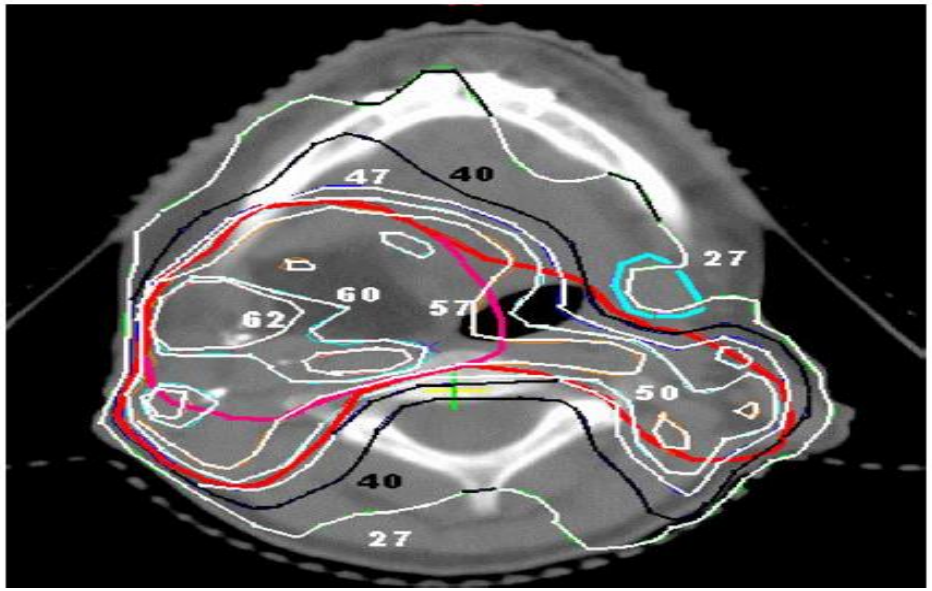
EORTC Dry Mouth Subscale



Conventional radiotherapy	26	24	23	23	21	18
IMRT	28	30	25	25	22	22
Difference in mean (99% CI)	11·7 (−14·4 to 37·8)	2·8 (−18·4 to 24·0)	9·7 (−13·5 to 32·9)	8·5 (−15·9 to 33·0)	21·0 (−8·9 to 50·9)	24·4 (−4·3 to 53·2)

Nutting CM et al, Lancet Oncol 2011, 12:127

Submandibular Gland Sparing



- 36 pts OPX (n=28) NPX treated with RT
- Case matched—18pts with SMG sparing and 18 without.
- SMG spared had lower N stage (no N2b-3) vs SMG non-spared group (59% N2b-3)

Saarilahti et al Radiotherapy and Oncology78 (2006) 270–75.

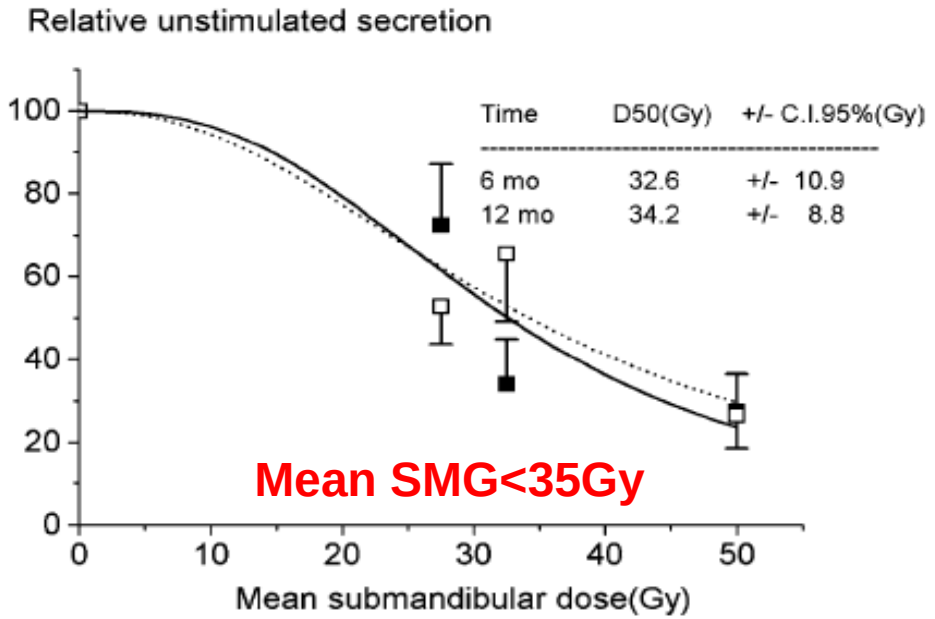


Table 3
Subjective and objective xerostomia assessed 12 months after IMRT

Xerostomia (LENT-SOMA score)	Submandibular gland sparing		*P*
	Yes, *N* (%)	No, *N* (%)	
Subjective xerostomia			
Gr. 0/1 (none/occasional dryness)	14 (78)	7 (39)	
Gr. 2/3 (partial/complete persistent dryness)	4 (22)	11 (61)	0.018
Objective xerostomia			
Gr. 0/1 (normal moisture)	14 (78)	9 (50)	
Gr. 2/3 (scan/sticky saliva)	4 (22)	9 (50)	0.083
Management of xerostomia			
Gr. 0/1 (none needed)	13 (72)	7 (39)	
Gr. 2/3 (occasional/frequent saliva substitute)	5 (28)	11 (61)	0.044

Reducing Xerostomia After Chemo-IMRT for Head-and-Neck Cancer: Beyond Sparing the Parotid Glands

- 78 pts III/IV Opx prospectively followed after IMRT designed to spare bilateral parotids, oral cavity, contralateral SMG
- Pt and observer reported xerostomia surveys and salivary collection up to 2yrs

Little, et al, Int J Radiat Oncol Biol Phys. 2012 Jul 1;83(3):1007-14.

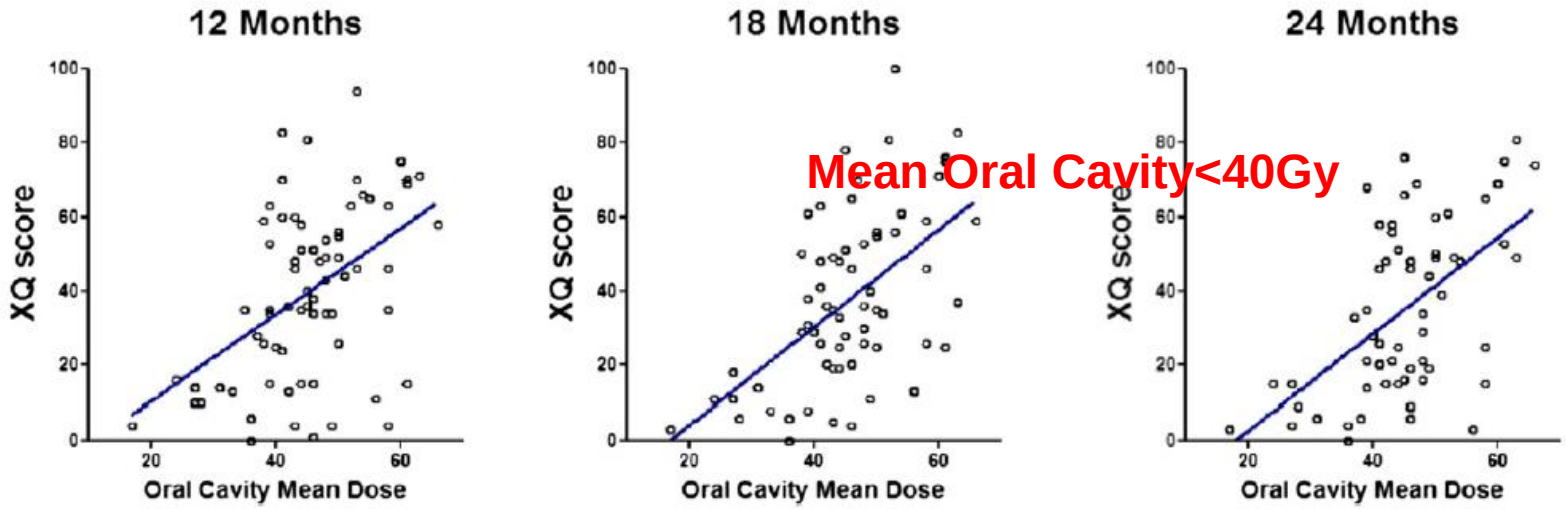


Fig. 1. Correlations between oral cavity mean doses and patient-reported xerostomia questionnaire (XQ) scores at various points after therapy. Individual data points and linear regression fits.

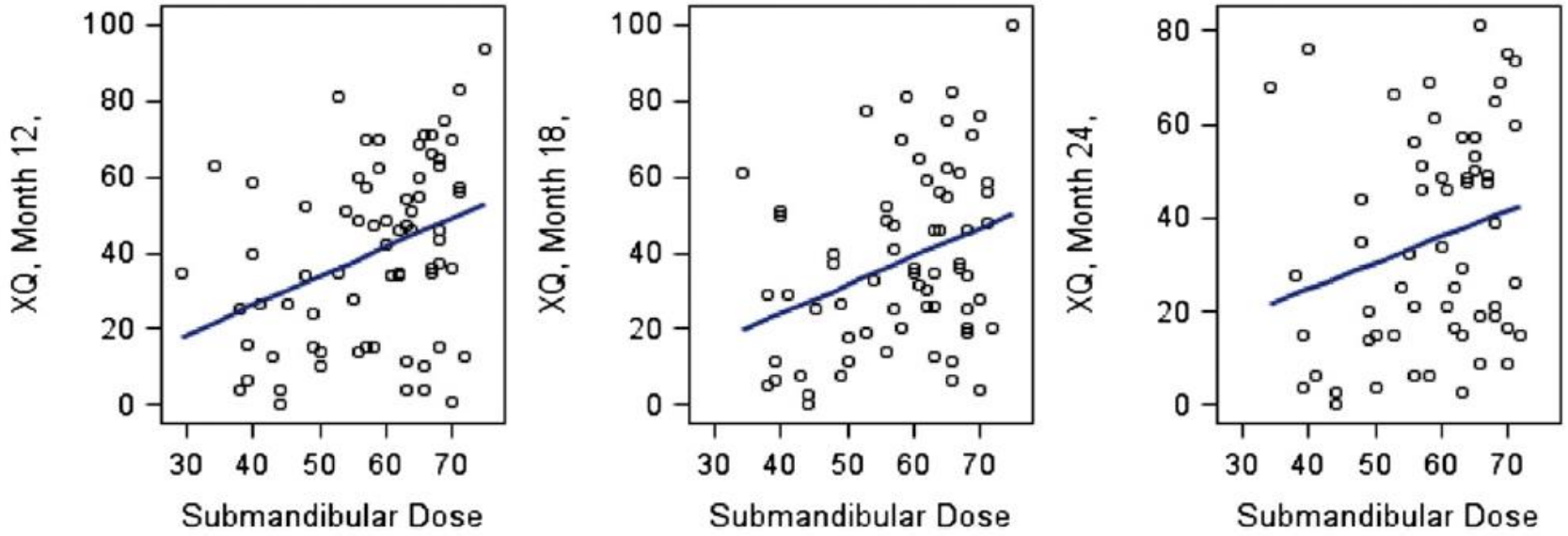
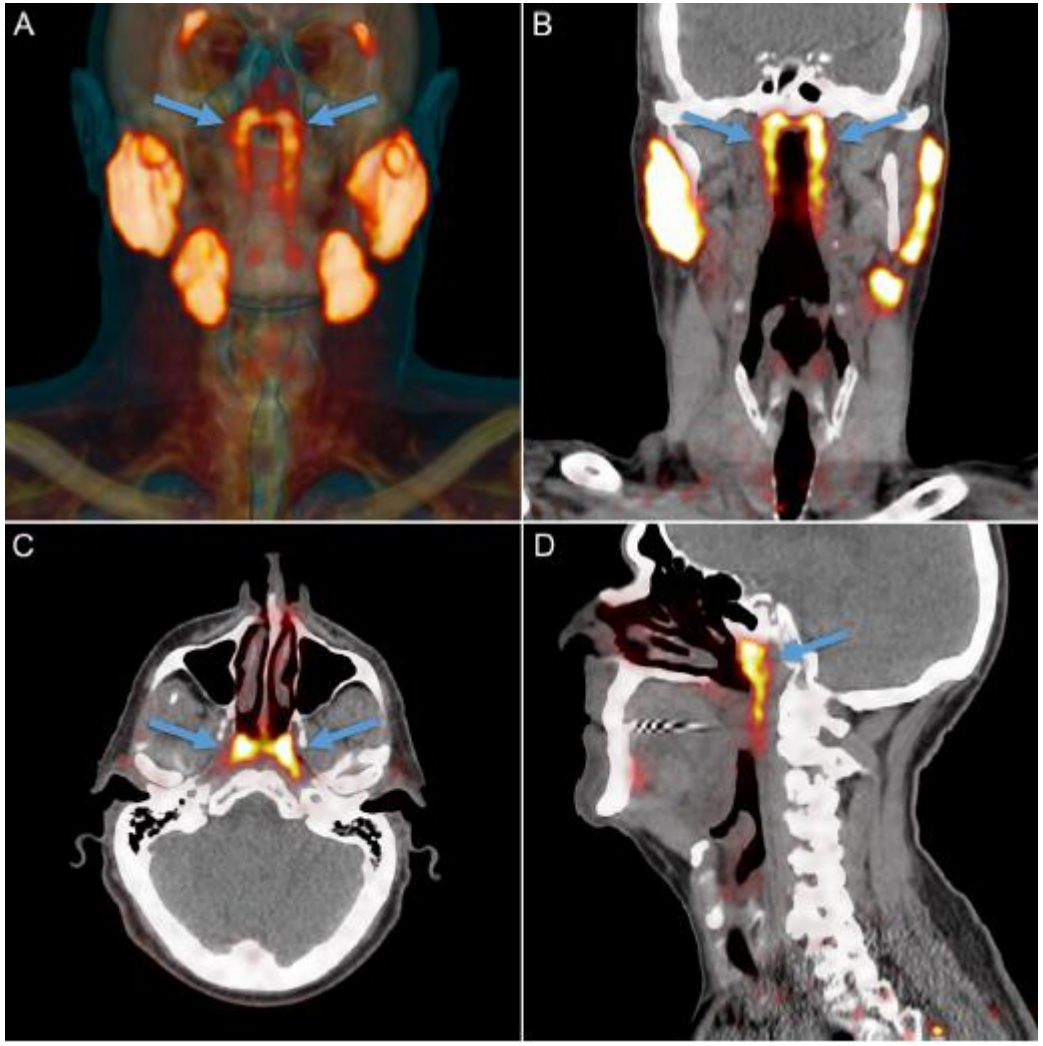


Fig. 2. Correlations between contralateral submandibular gland mean doses and patient-reported xerostomia questionnaire (XQ) scores at various points after therapy. Individual data points and linear regression fits.

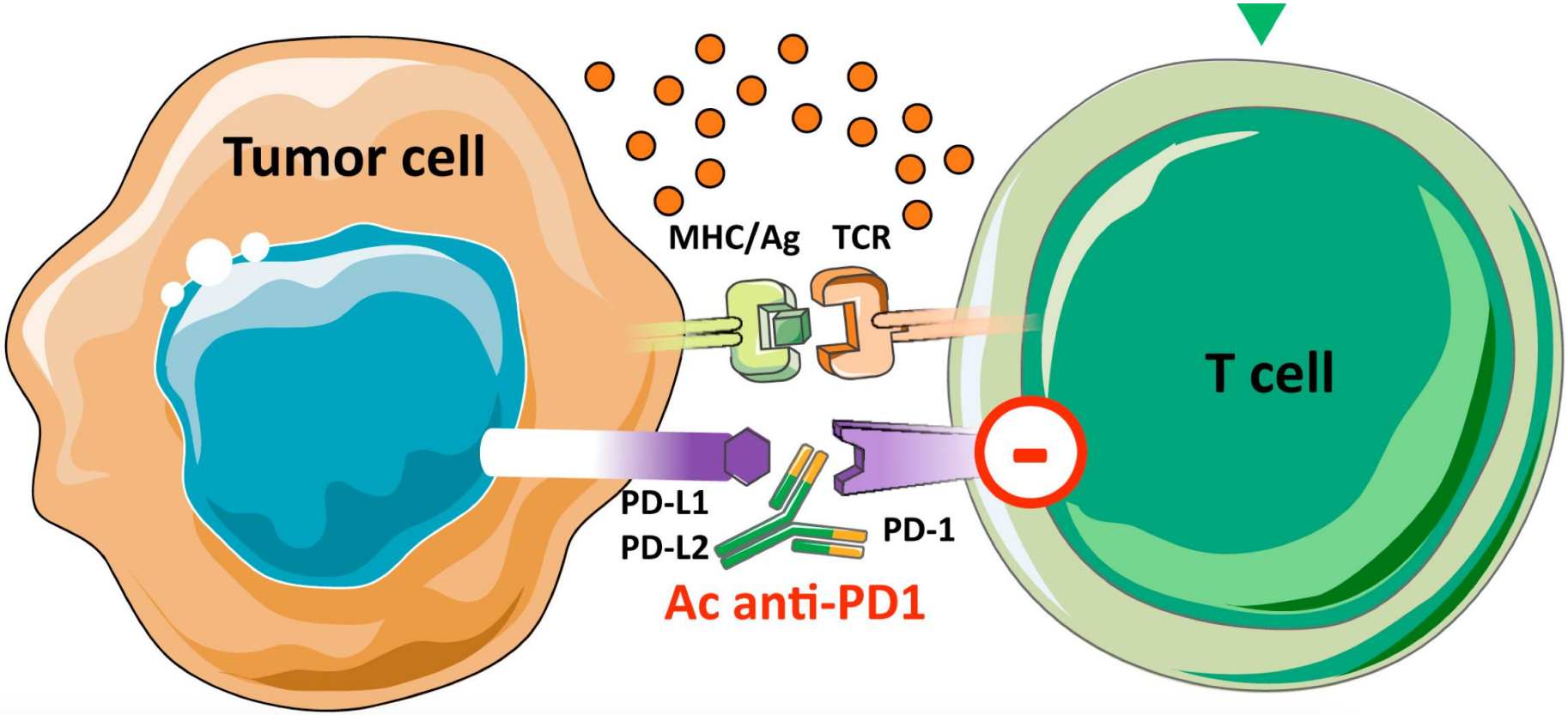
The tubarial salivary glands: A potential new organ at risk for radiotherapy

Matthijs H. Valstar [a,b,*], Bernadette S. de Bakker [c], Roel J.H.M. Steenbakkers [d], Kees H. de Jong [c],



Radiotherapy and Oncology xxx (2020)

Blockade of Checkpoint Inhibition Allows T-Cell Mediated Tumor Cytotoxicity



KEYNOTE-048 Study Design (NCT02358031)

Key Eligibility Criteria

- SCC of the oropharynx, oral cavity, hypopharynx, or larynx
- R/M disease incurable by local therapies
- ECOG PS 0 or 1
- Tissue sample for PD-L1 assessment[a]
- Known p16 status in the oropharynx[b]

Stratification Factors

- PD-L1 expression[a] (TPS ≥50% vs <50%)
- p16 status in oropharynx (positive vs negative)
- ECOG performance status (0 vs 1)

R 1:1:1

Pembrolizumab Monotherapy → Pembrolizumab 200 mg Q3W for up to 35 cycles

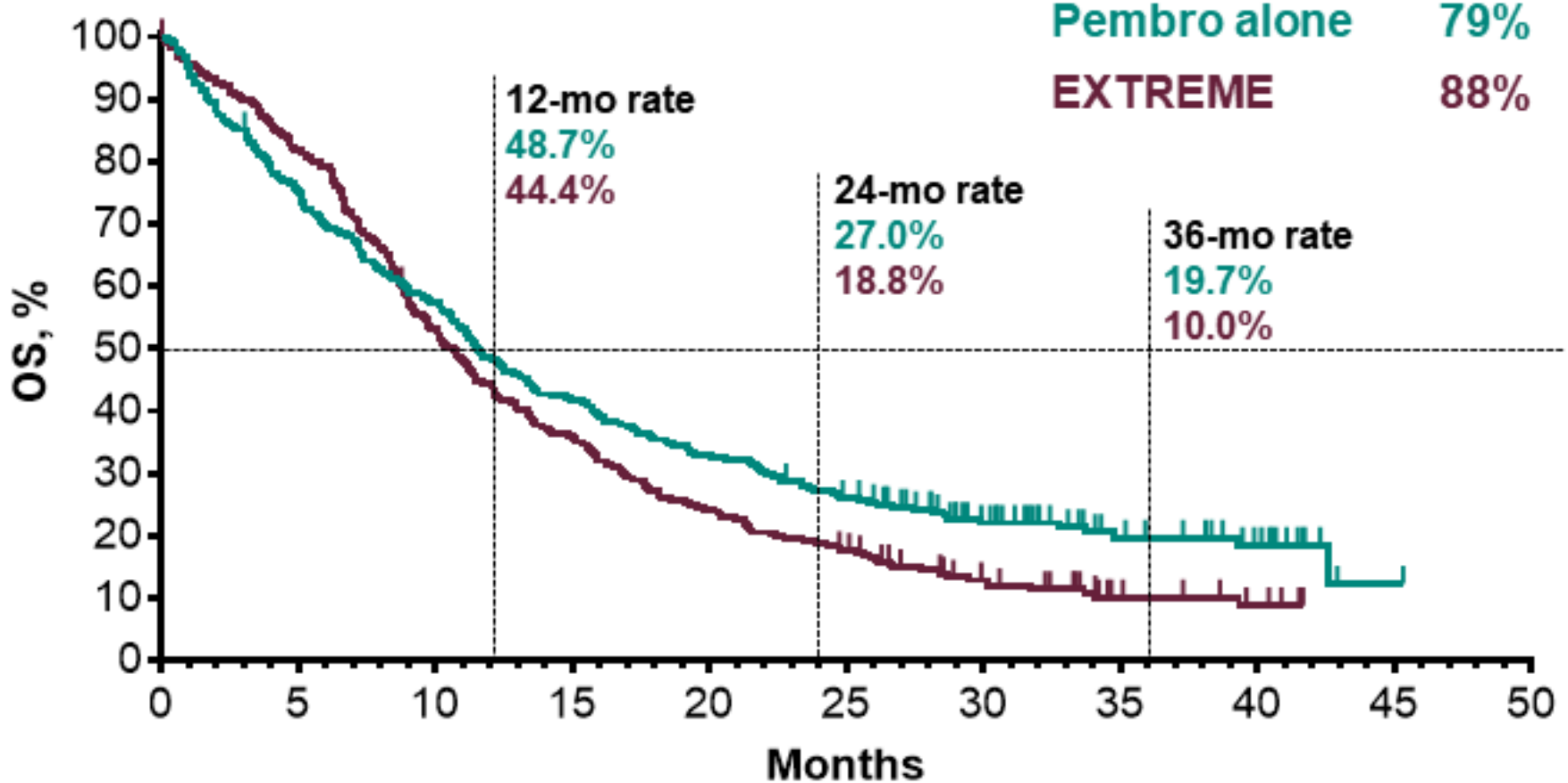
Pembrolizumab + Chemotherapy → Pembrolizumab 200 mg + Carboplatin AUC 5 OR Cisplatin 100 mg/m² + 5-FU 1000 mg/m²/d for 4 days for 6 cycles (each 3 wk) → Pembrolizumab 200 mg Q3W for up to 35 cycles total

EXTREME → Cetuximab 250 mg/m² Q1W[c] + Carboplatin AUC 5 OR Cisplatin 100 mg/m² + 5-FU 1000 mg/m²/d for 4 days for 6 cycles (each 3 wk) → Cetuximab 250 mg/m² Q1W

[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression.
[b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m².

OS, P vs E, Total Population

	Events	HR (95% CI)	*P*
Pembro alone	79%	0.83 (0.70-0.99)	0.0199[a]
EXTREME	88%		



Median (95% CI)
11.5 mo (10.3-13.4)
10.7 mo (9.3-11.7)

No. at risk

301	226	172	125	99	75	46	22	13	1	0
300	245	158	107	72	51	28	11	6	0	0

[a]Not statistically significant at the superiority threshold of $P = 0.0059$.
FA (data cutoff date: Feb 25, 2019).

Radiation and checkpoint blockade immunotherapy: radiosensitisation and potential mechanisms of synergy

Andrew B Sharabi, Michael Lim, Theodore L DeWeese, Charles G Drake

Lancet Oncology 2015;
16: e498–509

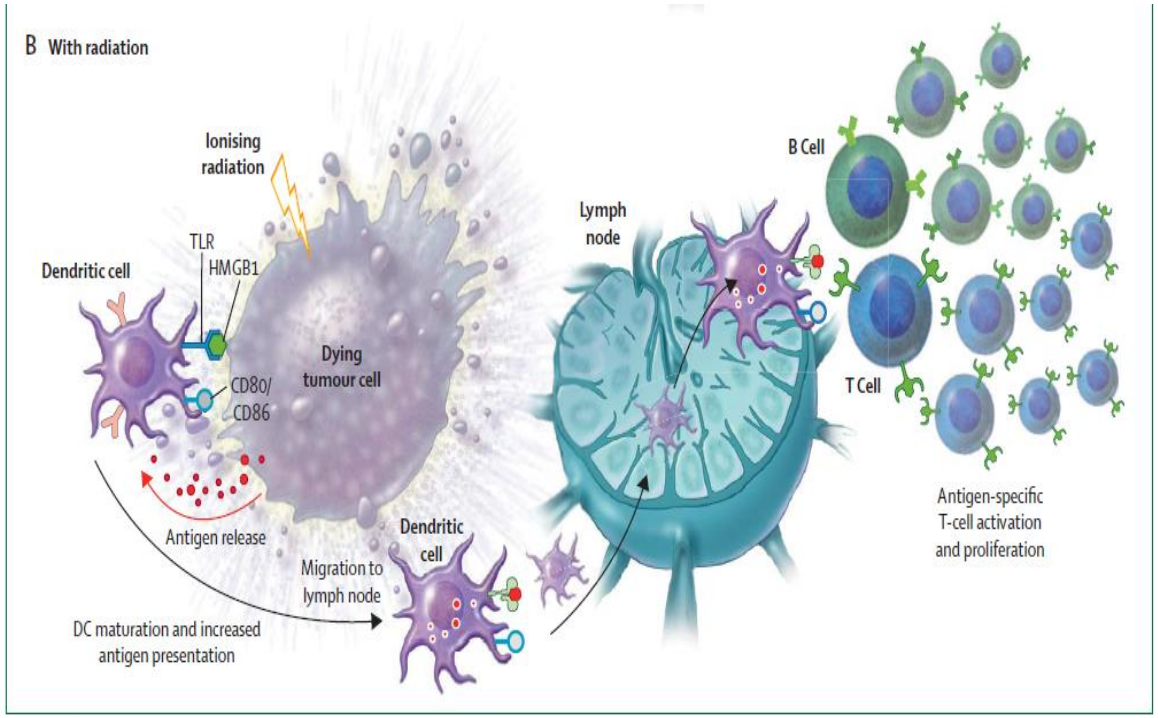


Figure 2: Radiation enhances cross-presentation of tumour antigens
(A) In the absence of danger signals, tumour antigen presentation is restricted or tolerogenic. (B) Radiation-induced danger signals enhance dendritic cell-mediated antigen presentation, resulting in activation and proliferation of tumour-specific CD8 T cells. TLR=Toll-like receptor.

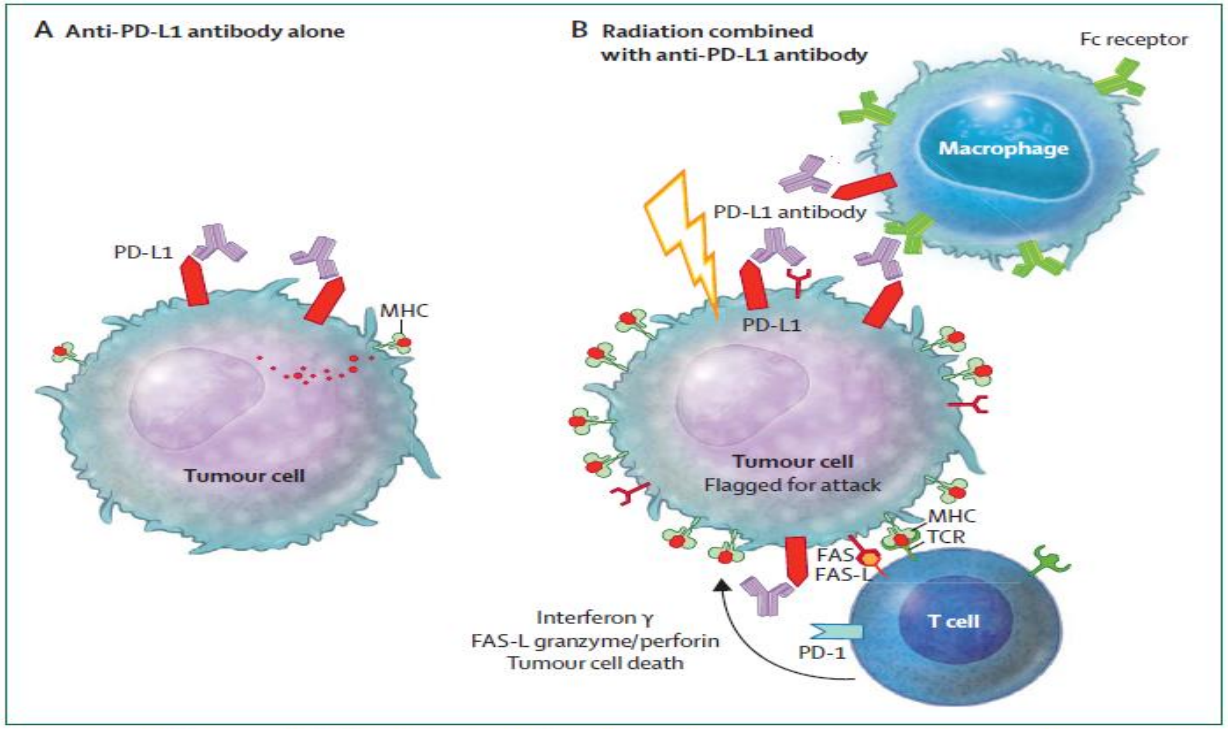


***Figure 3:* Radiation combined with checkpoint blockade immunotherapy increases tumour cell susceptibility to immune-mediated cell death**
(A) Anti-PD-L1 alone is not predominantly cytotoxic. (B) Radiation combined with anti-PD-L1 upregulates MHC and FAS on tumour cells, increasing susceptibility to T-cell-mediated cytotoxicity. TCR=T-cell receptor.

JAVELIN: Head and Neck 100

Phase 3, Randomized, Double-Blind, Placebo-Controlled Study

- HPV - stage III, IVa, and IVb; or nonoropharyngeal HPV + stage III, IVa, and IVb; or HPV + oropharyngeal disease T4 or N2c or N3 (AJCC 7)
- No prior therapy for advanced SCCHN
- Aged ≥18 y
- WHO PS score 0 or 1

R

Avelumab + CRT
(d 1 lead-in phase; d 8, 25, and 39 of the CRT phase; and every 2 wk for 12 mo)

Placebo + SOC CRT

Endpoints

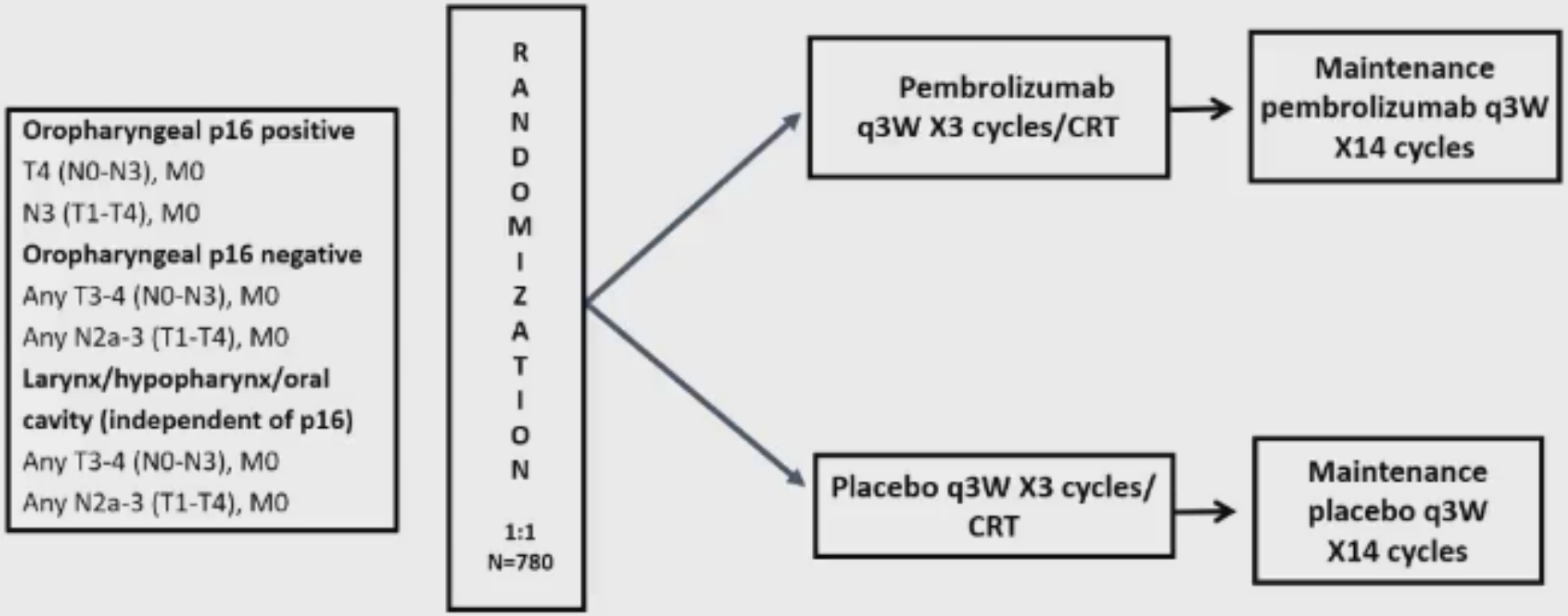
Primary
- PFS (RECIST v1.1)

Key secondary
- OS
- ORR
- LRC
- DMF
- DOR

697 patients enrolled; *fully accrued*

http://clinicaltrials.gov/ct2/show/NCT02952586

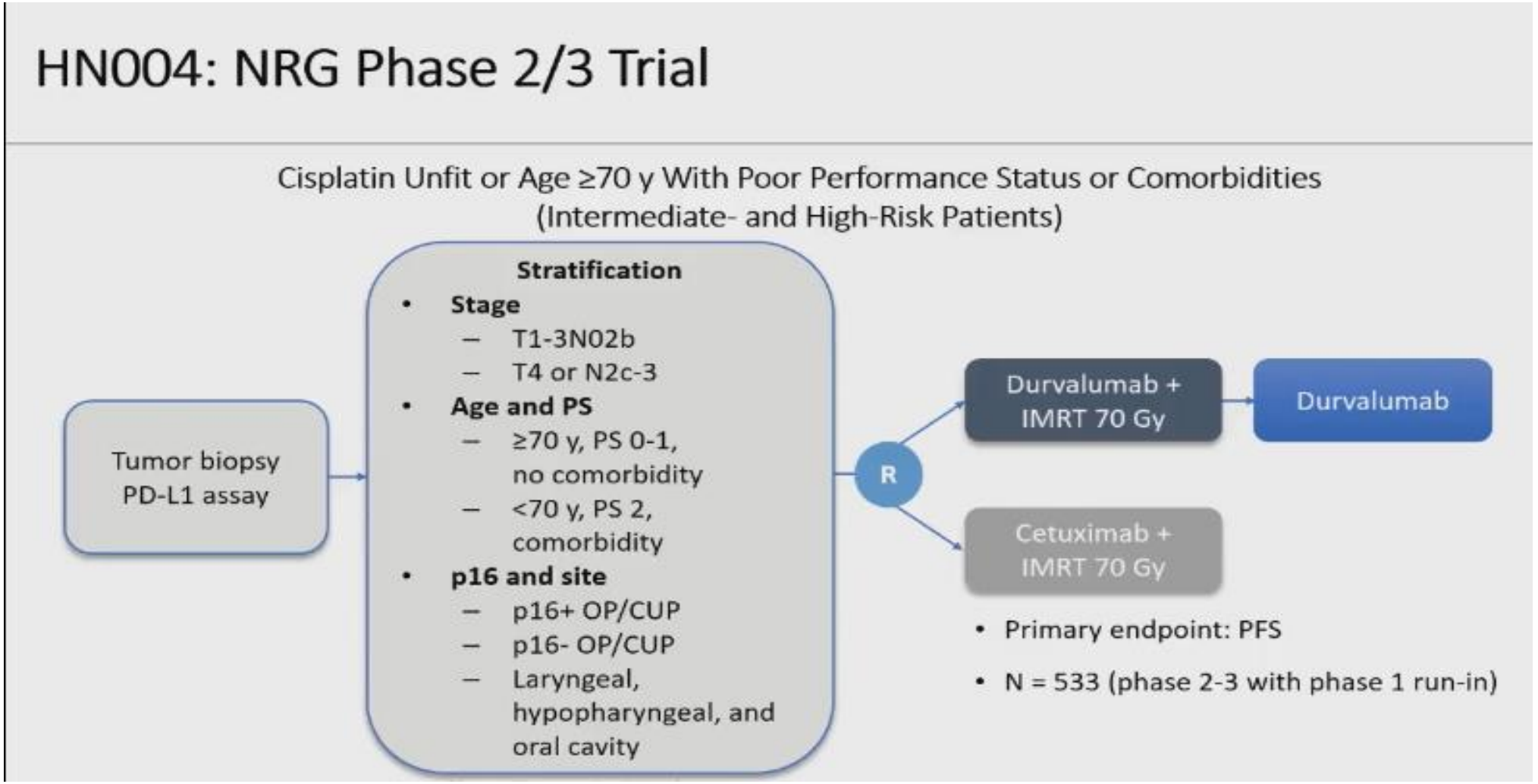
KEYNOTE-412 Trial Design (NCT03040999)



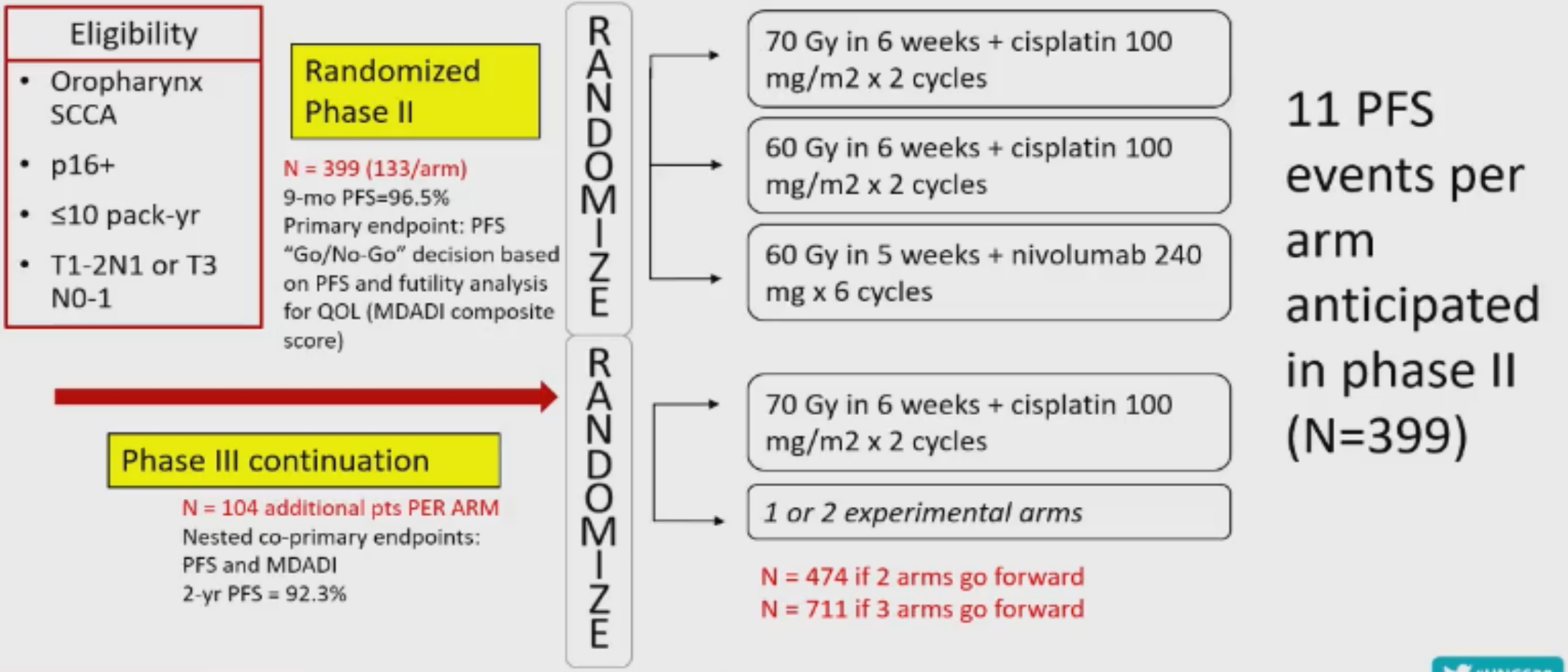
- Primary end point: Event Free Survival
- Secondary end points: Overall Survival, Safety and tolerability, QoL

CRT = Cisplatin 100 mg/m2 every 3 weeks x3 cycles for standard fractionation (SFX) or x2 cycles for accelerated fractionation (AFX); Radiotherapy schedules of 70 Gy in 35 fractions over 7 weeks for SFX and 70 Gy in 35 fractions over 6 weeks for AFX

NRG-HN004: Platinum Unfit



NRG-HN005: A Randomized Phase II/III Trial of De-intensified Radiation Therapy for Patients with Early Stage, p16-Positive, Non-Smoking-Associated Oropharyngeal Cancer



11 PFS events per arm anticipated in phase II (N=399)

#HNCS20

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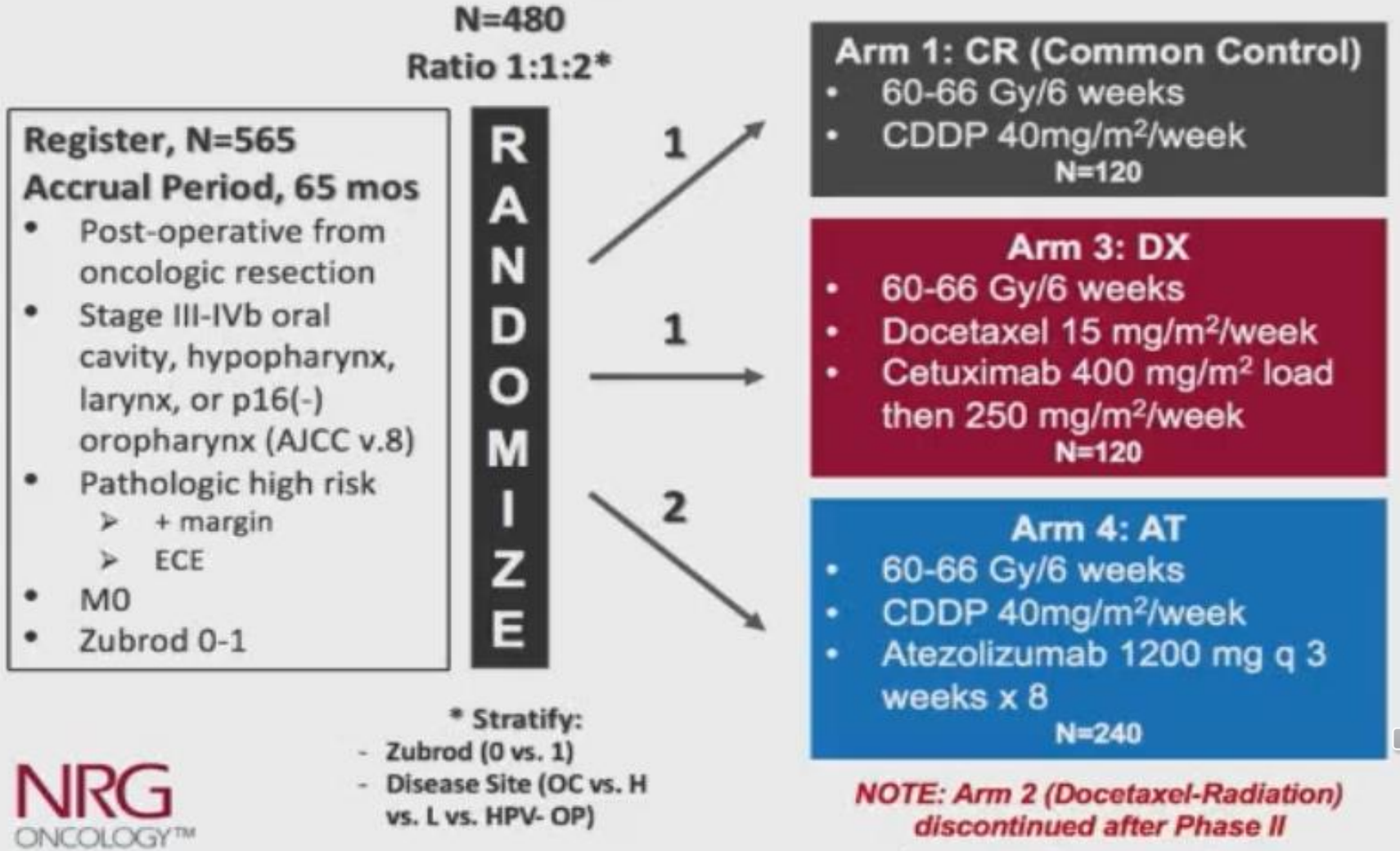
RTOG 1216 continued (PIs – Bauman, Harari, Rosenthal)

Schema



Conclusions

- Concurrent cisplatin-based chemoradiation remains the standard for advanced stage cancer
- Role of altered fractionation with chemotherapy/biologic treatment continues to evolve
- Significant advances in understanding the dosimetric parameters to preserve swallowing/salivary function
- Integration of checkpoint blockade immunotherapy with definitive and post-op radiation remains investigational