Dott. Salvatore Pisconti

S.C. di Oncologia Medica
ASL TARANTO

POSTOPERATIVE THERAPY IN HEAD AND NECK CANCER:STATE OF THE ART, RISK SUBSET, PROGNOSIS AND UNSOLVED QUESTIONS

N Denaro, E G Russi V Adamo I Colantonio M C Merlano

Oncology 2011; 81:21-29

- In General, the 5 year survival rate for patients with stage III or IV disease in the range of 30-40%

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High-risk features

- Extracapsular extension,
- Close or positive margins,

- Node-positive status (N2–3),
- Bone, perineural or lymph vascular invasion

Local and distant control is unsatisfactory in the presence of high-risk features

ADJUVANT RADIOTHERAPY AND SURVIVAL FOR PATIENTS WITH NODE-POSITIVE HEAD AND NECK CANCER: AN ANALYSIS BY PRIMARY SITE AND NODAL STAGE

JOHNNY KAO, M.D.,* AMIR LAVAF, M.D.,* MARITA S. TENG,[y] DELPHINE HUANG,* AND ERIC M. GENDEN, M.D.[y]

Departments of *Radiation Oncology, and [y]Otolaryngology and Head and Neck Surgery, Mount Sinai School of Medicine, New York, NY

Purpose: Adjuvant radiotherapy (RT) is frequently recommended for node-positive head and neck squamous cell carcinoma (HNSCC) treated with primary surgery. The impact of RT on survival for various subgroups of node-positive HNSCC has not been clearly demonstrated.

Methods and Materials: Within the Surveillance, Epidemiology, and End Results (SEER) Database, we identified 5297 patients with node-positive (N1 to N3) HNSCC treated with definitive surgery with or without adjuvant RT between 1988 and 2001. The median follow-up was 4.4 years.

Table 1. Patient characteristics and prevalence of adjuvant radiation therapy (RT) use

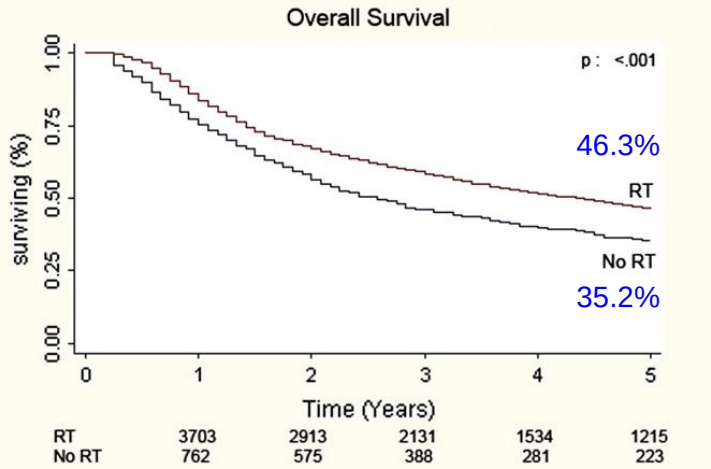
Characteristic	No. of patients (n = 5,297)	% Receiving observation (n = 990)	% Received adjuvant RT (n = 4,307)	p
Tumor size (cm)				0.4
≤2	1,232	19.7	80.3	
2.1–4	2,217	19.0	81.0	
≥4	811	17.0	83.0	
Unknown	1,037	18.0	82.0	
Tumor extent				0.004
Localized (SEER Stage 3)	2,716	20.2	79.8	
Invasive (SEER Stage 4)	2,581	17.1	82.9	
N stage (2002 AJCC)				<0.001
N1	2,451	22.5	77.5	
N2a	1,337	16.7	83.3	
N2b	898	14.6	85.4	
N2c	359	16.7	83.3	
N3	252	9.1	90.9	
Primary site				<0.001
Lip	38	28.9	71.1	
Other oral cavity	1,654	24.9	75.1	
Oropharynx	1,940	13.3	86.7	
Hypopharynx	647	15.9	84.1	
Larynx	797	21.3	78.7	
Sinonasal and ear	28	25.0	75.0	
Other	193	15.5	84.5	
Grade				<0.001
1 (Well differentiated)	376	23.9	76.1	
2 (Moderately differentiated)	2,505	20.4	79.6	
3 (Poorly differentiated)	2,032	15.7	84.3	
4 (Undifferentiated)	64	20.3	79.7	
Unknown	320	17.2	82.8	
Marital status				0.004
Single	765	16.3	83.7	
Widowed, divorced, or separated	1,403	21.6	78.4	
Married	2,945	17.7	82.3	
Unknown	184	21.7	78.3	

Abbreviations: ACCC = American Joint Committee on Cancer; SEER = Surveillance, Epidemiology and End Results.

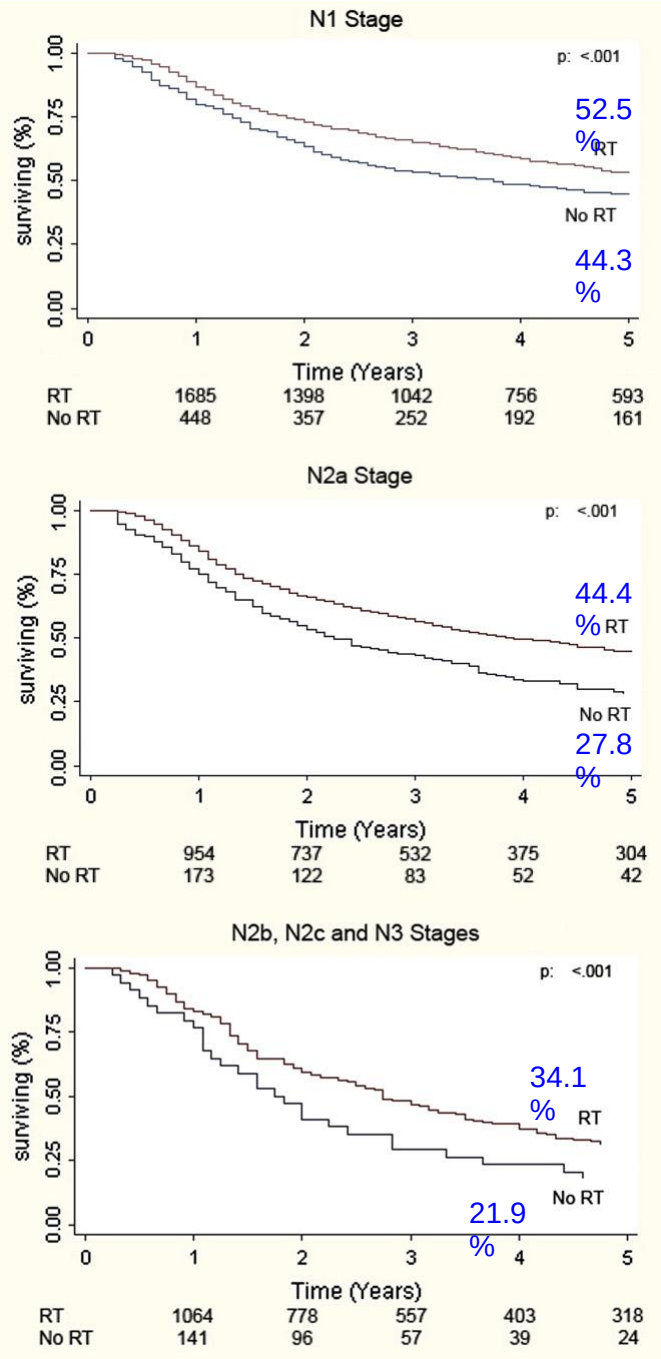
Kao J, et al.; Int J Radiat Oncol Biol Phys 2008; 71: 362–370.

Predictors of adjuvant RT use and survival

Impact on survival by nodal stage



Plot of overall survival for all node-positive patients stratified by adjuvant radiotherapy (RT) use



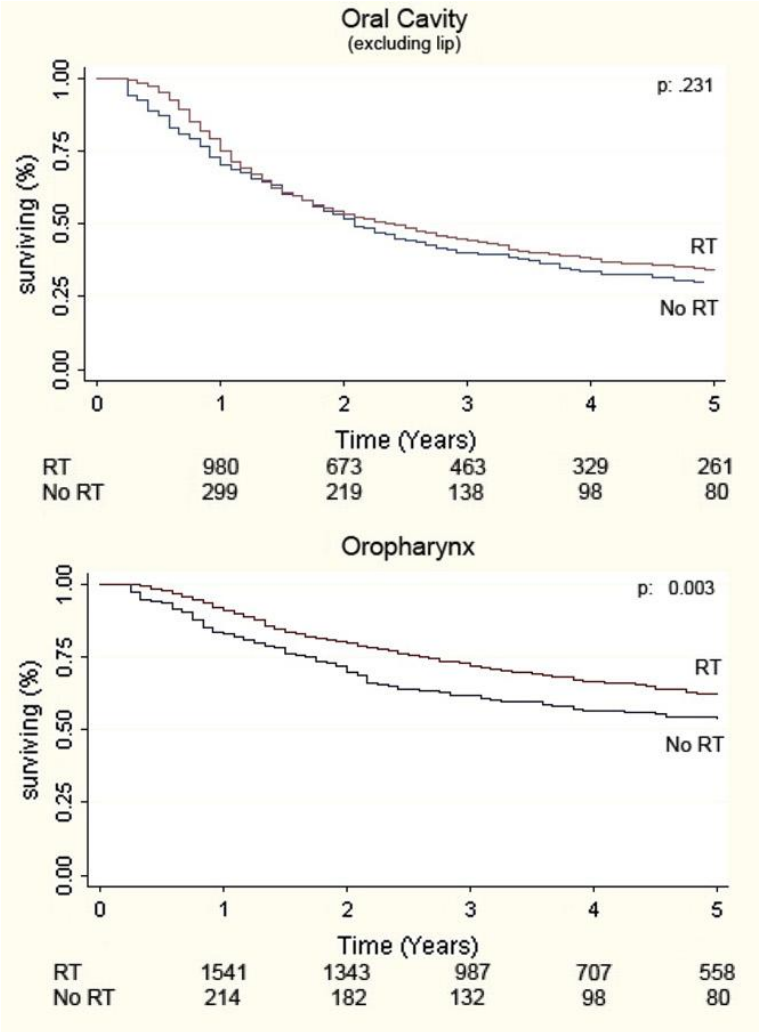
Risk of death with adjuvant radiation by N stage on multivariable analysis

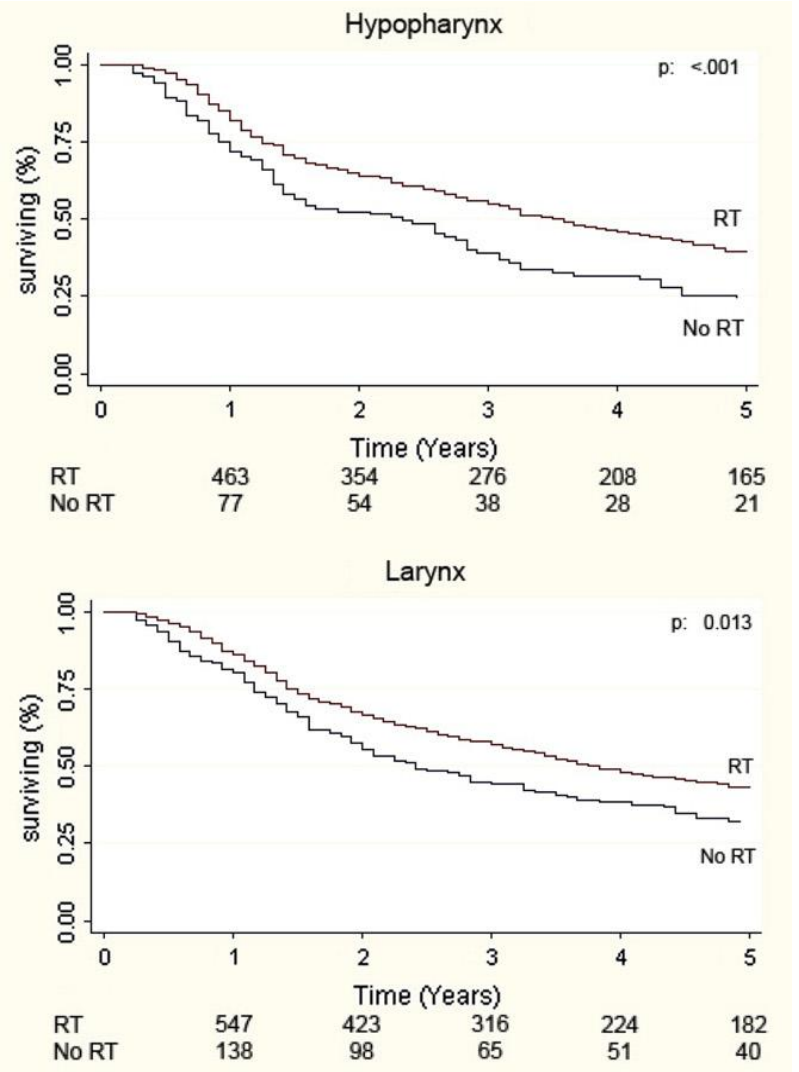
N stage	HR	SE	95% CI	*p*
N1	0.779	0.059	0.673–0.903	0.001
N2a	0.818	0.083	0.670–0.999	0.048
N2b–N3	0.621	0.061	0.512–0.753	<0.001

Kao J, et al.; Int J Radiat Oncol Biol Phys 2008; 71: 362–370.

Predictors of adjuvant RT use and survival
Impact on survival by primary site

Overall survival for patients with node-positive disease and primary tumors of the oral cavity, oropharynx, hypopharynx, and larynx, stratified by adjuvant radiotherapy (RT) use





Kao J, et al.; Int J Radiat Oncol Biol Phys 2008; 71: 362–370.

Predictors of adjuvant RT use and survival

Impact on survival by primary site

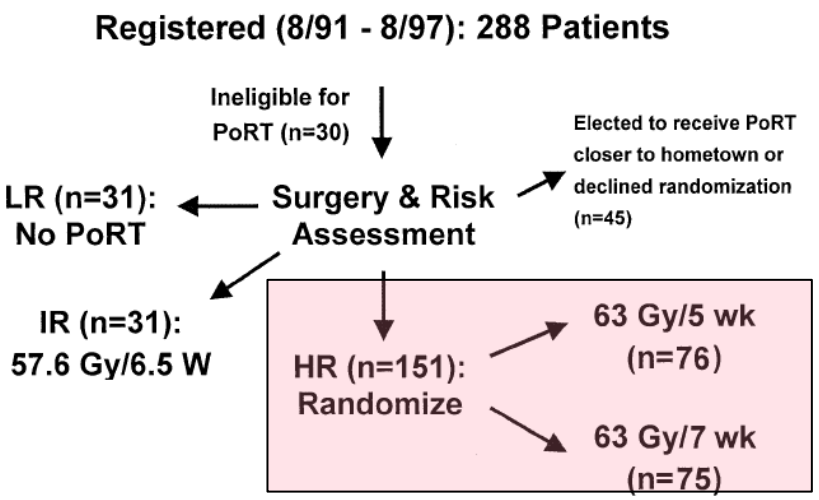
Table 3. Effect of adjuvant radiation on 3- and 5-year overall survival (OS) analyzed by subsite and N stage

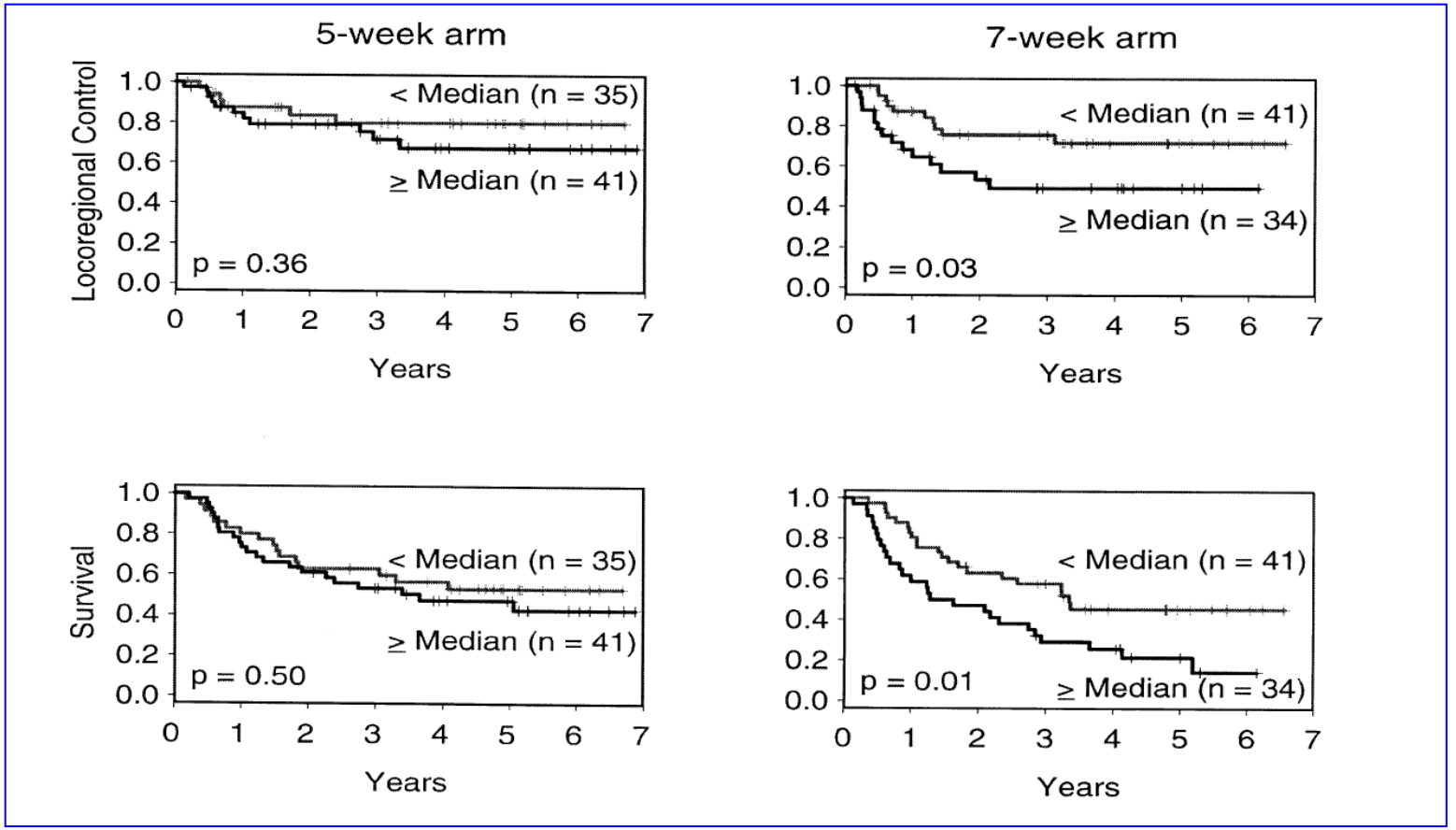
	No RT		RT		
N stage	3-year OS (%)	5-year OS (%)	3-year OS (%)	5-year OS (%)	*p*
Oral cavity (excluding lip)					0.231
N1	44.3	36.0	50.4	38.7	
N2a	44.3	28.0	42.5	34.7	
N2b, N2c, N3	20.9	13.3	36.7	26.5	
Oropharynx					0.003
N1	71.6	65.0	77.6	67.9	
N2a	51.1	44.6	67.9	55.3	
N2b, N2c, N3	45.8	30.7	66.0	56.9	
Hypopharynx					<0.001
N1	43.6	31.5	59.8	40.0	
N2a	52.4	17.9	60.1	46.3	
N2b, N2c, N3	26.2	20.8	45.3	32.1	
Larynx					0.013
N1	54.0	41.9	66.2	53.3	
N2a	32.9	16.4	55.2	39.7	
N2b, N2c, N3	29.4	17.7	46.5	31.0	

Kao J, et al.; Int J Radiat Oncol Biol Phys 2008; 71: 362–370.

Timing of PORT

MDACC trial

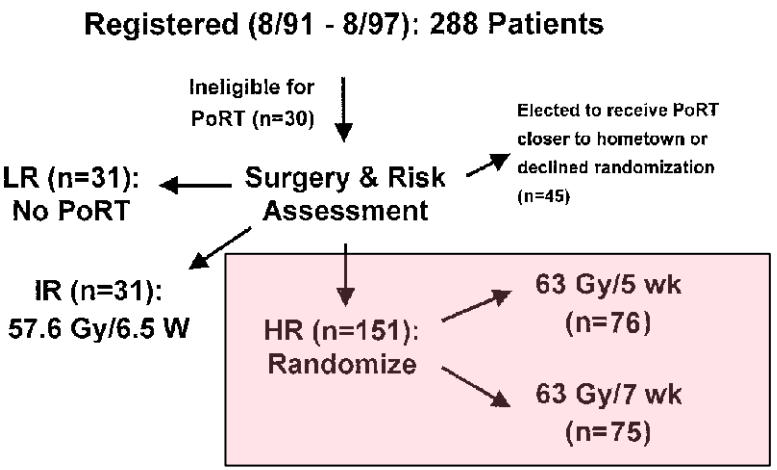


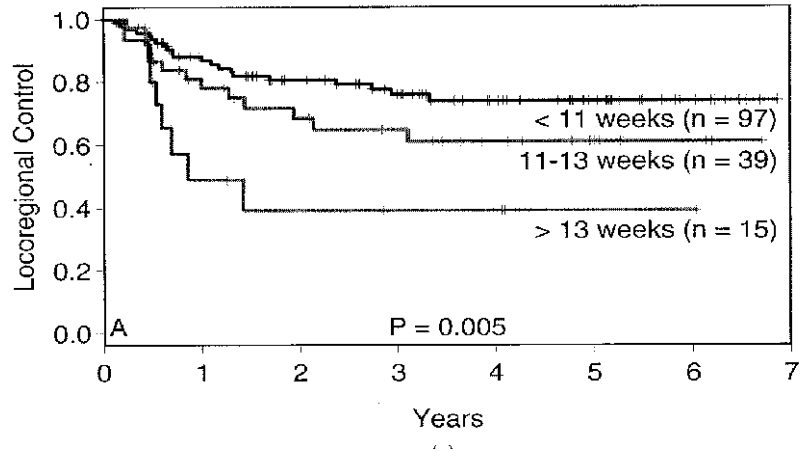


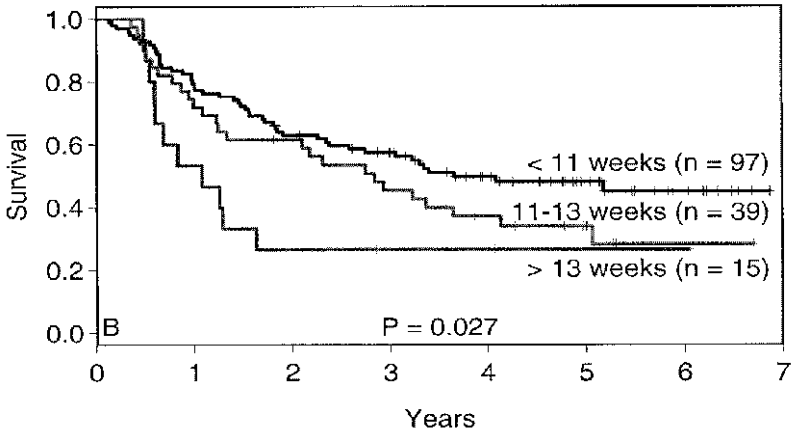
Ang KK et al.; Int J Radiat Oncol Biol Phys 2001;51:571–578

Timing of PORT

MDACC trial







"These findings emphasize that the combination of surgery and PORT should be considered a " treatment package" that needs to be delivered in a timely and coordinated fashion"

Ang KK et al.; Int J Radiat Oncol Biol Phys 2001;51:571–578

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- No clinical trials have been performed to assess the actity of postoperative RT in patients with small tumors (pT1, pT2) and neck ispilateral metastasis

Contents lists available at ScienceDirect

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journal homepage: www.thegreenjournal.com

Meta analysis

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 Collaborative Group [1]

[a] *Department of Biostatistics and Epidemiology, Institut Gustave-Roussy, Villejuif, France*
[b] *Department of Radiotherapy, Institut Gustave-Roussy, Villejuif, France*

Meta-analysis of randomised trials comparing loco-regional treatment to loco-regional treatment + chemotherapy in HNSCC patients

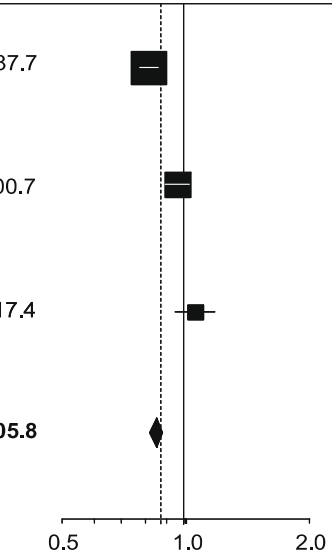
- ✓ 87 randomised trials
- ✓ 16,485 patients

Pignon J et al; Radiother Oncol 2009; 92: 4–14.

MACH-NC

(a) Hazard ratio of death.

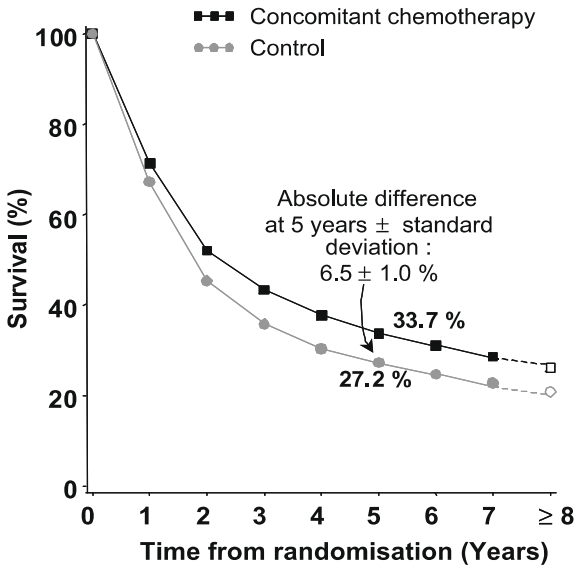
Timing	No. Deaths / No. Entered LRT+CT	LRT	O-E	Variance	Hazard Ratio	HR [95% CI]
Concomitant	3171/4824	3389/4791	-326.4	1587.7		0.81 [0.78;0.86]
Induction	1877/2740	1813/2571	-40.0	900.7		0.96 [0.90;1.02]
Adjuvant	631/1244	661/1323	17.9	317.4		1.06 [0.95;1.18]
Total	**5679/8808**	**5863/8685**	**-348.5**	**2805.8**		**0.88 [0.85;0.92]**



Test for heterogeneity: χ^2_{107} = 179.8 p < 0.0001 I^2 = 41%

Test for interaction: χ^2_2 = 26.60 p < 0.0001

LRT+CT effect: p < 0.0001



Absolute benefit of 6.5% at 5 years

Pignon J et al; Radiother Oncol 2009; 92: 4–14.

Meta-analisi MACH-NC:
CT/RT concomitante - Livello di evidenza 1

Vantaggio assoluto in sopravvivenza a 5 anni rispetto la sola RT = 6.5%

Vantaggio statisticamente significativo sul controllo locale e metastasi a distanza

Non ci sono differenze fra poli-CT e mono-CT

Massimo beneficio con CDDP

Dose totale CDDP è importante

Vantaggio CT correla con età del paziente

Chemioradioterapia concomitante con CDDP: standard di cura

Vantaggio è indipendente dal tipo di RT utilizzata

- *Pignon, Radiother Oncol 2009*

The NEW ENGLAND JOURNAL of MEDICINE

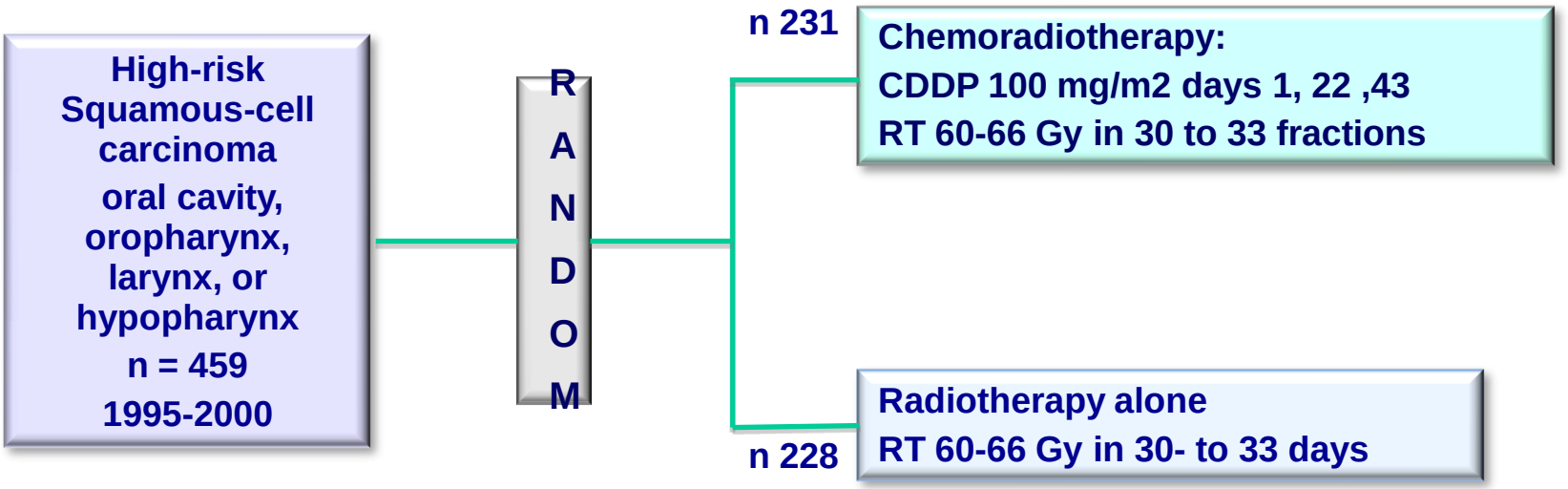
ESTABLISHED IN 1812 NOVEMBER 27, 2003 VOL. 349 NO. 22

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 Chao, M.D., Glen Peters, M.D., Ding-Jen Lee, M.D., Ph.D., Andrea Leaf, M.D., John Ensley, M.D., and Jay Cooper, M.D.

ABSTRACT

RTOG 95-01/Intergroup Trial



Primary end point:
Local and regional tumor control

Cooper JS et al.; N Engl J Med 350 (19): 1937

The NEW ENGLAND JOURNAL of MEDICINE

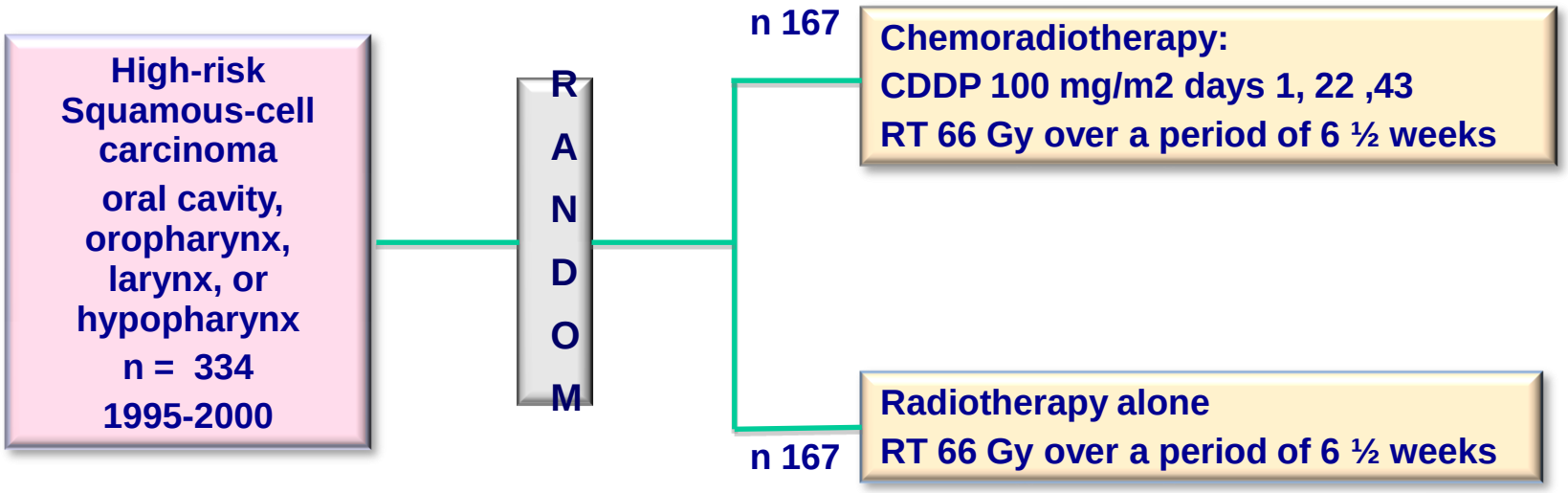
ORIGINAL ARTICLE

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

ABSTRACT

EORTC 22931 Trial



Primary end point:
Progression-free survival

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

Eligibility criteria: High risk SCCHN

EORTC 22931	• Stage of pT3 or pT4 and any nodal stage (N), except T3N0 of the larynx. • Stage T1 or T2 and N0 or N1 who had unfavorable pathological findings (extranodal spread, positive resection margins, perineural involvement, or vascular tumor embolism) • Oral-cavity or oropharyngeal tumors with involved lymph nodes at level IV or V
RTOG 95-01/Intergroup Trial	• Extracapsular extension of nodal disease • Histologic evidence of invasion of two or more regional lymph nodes, • Microscopically involved mucosal margins of resection

Cooper JS et al. N Engl J Med 2004;350:1937-1944.

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

RTOG 95-01

Table 1. Pretreatment Characteristics of the Patients.

Characteristic	Radiotherapy (N=210)	Combined Therapy (N=206)
Age		
18–69 yr — no. (%)	196 (93)	195 (95)
≥70 yr — no. (%)	14 (7)	11 (5)
Median — yr	55	56
Range — yr	28–79	24–80
High-risk characteristic — no. (%)		
Positive margins	39 (19)	34 (17)
≥2 Involved nodes or extracapsular spread	171 (81)	172 (83)
Sex — no. (%)		
Male	181 (86)	177 (86)
Female	29 (14)	29 (14)
Racial or ethnic group — no. (%)*		
White	154 (73)	156 (76)
Hispanic	12 (6)	5 (2)
Black	38 (18)	43 (21)
Asian	3 (1)	1 (<1)
Native American	2 (1)	0
Other	1 (<1)	1 (<1)
Karnofsky performance score — no. (%)		
60	6 (3)	1 (<1)
70	19 (9)	33 (16)
80	62 (30)	56 (27)
90	95 (45)	93 (45)
100	28 (13)	23 (11)
Differentiation of tumor — no. (%)		
Low	15 (7)	15 (7)
Intermediate	118 (56)	113 (55)
High	72 (34)	69 (33)
Not stated	5 (2)	9 (4)
Site of tumor — no. (%)		
Oral cavity	62 (30)	50 (24)
Oropharynx	78 (37)	99 (48)
Hypopharynx	26 (12)	15 (7)
Supraglottic	32 (15)	29 (14)
Glottic	11 (5)	11 (5)
Subglottic	1 (<1)	2 (1)

* Racial or ethnic group was self-reported.

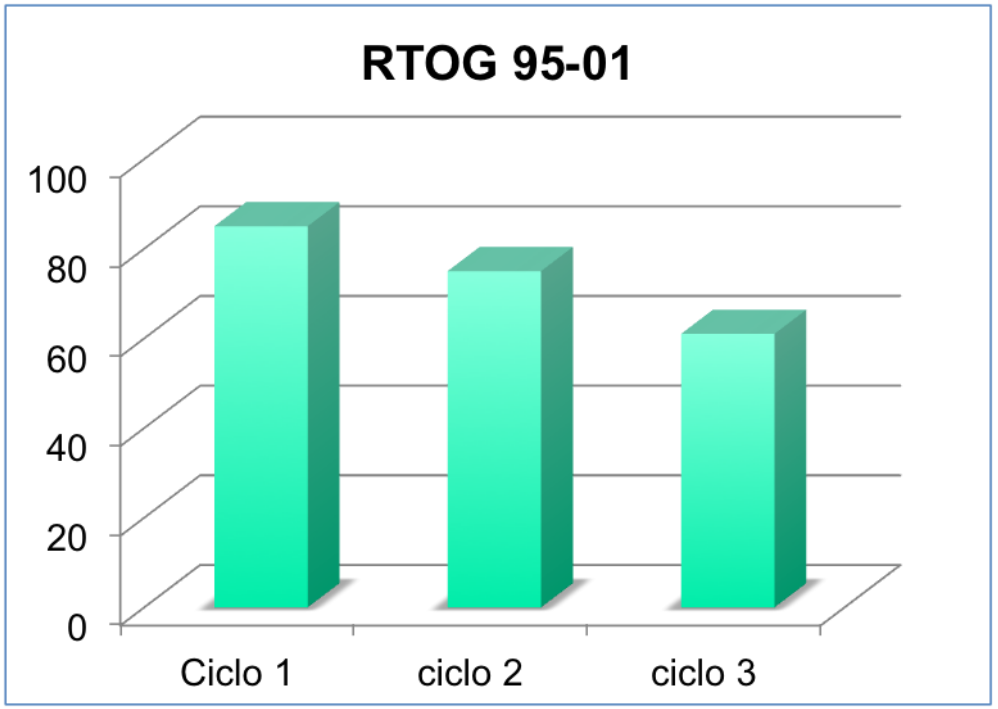
EORTC 22931

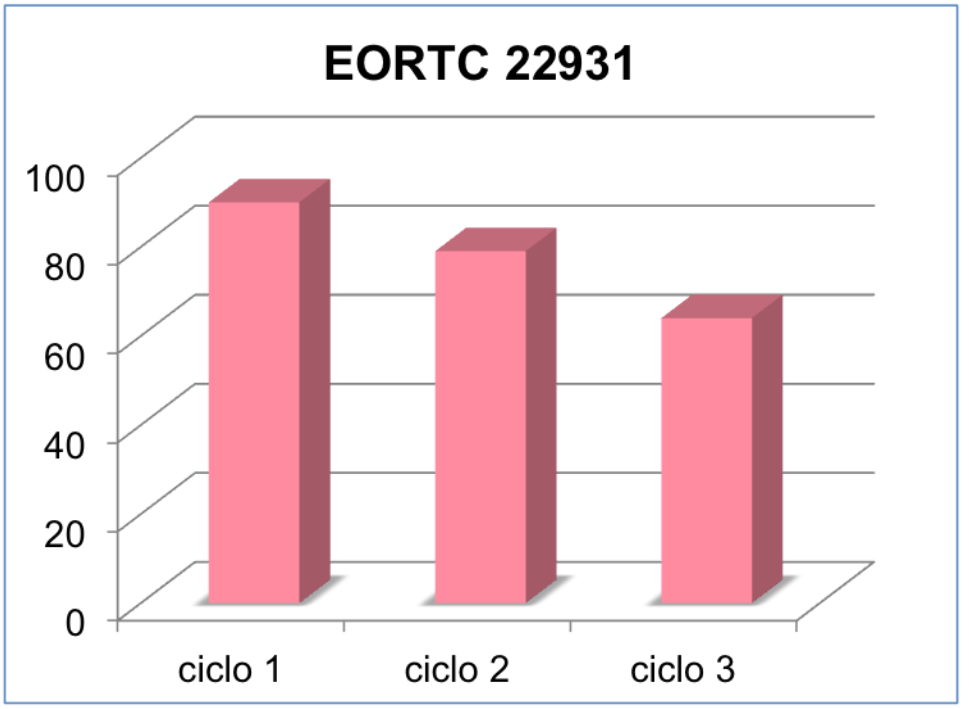
Table 1. Characteristics of Patients and Tumors.

Characteristic	Radiotherapy (N=167)	Combined Therapy (N=167)	Total (N=334)
Sex — no. (%)			
Male	155 (93)	153 (92)	308 (92)
Female	12 (7)	13 (8)	25 (7)
Unknown	0	1 (1)	1 (1)
Age			
18–50 yr — no. (%)	58 (35)	46 (28)	104 (31)
51–70 yr — no. (%)	109 (65)	121 (72)	230 (69)
Median — yr	53	55	54
Tumor stage — no. (%)*			
T1	16 (10)	11 (7)	27 (8)
T2	43 (26)	40 (24)	83 (25)
T3	49 (29)	44 (26)	93 (28)
T4	57 (34)	72 (43)	129 (39)
Unknown	2 (1)	0	2 (1)
Nodal stage — no. (%)*			
N0	42 (25)	37 (22)	79 (24)
N1	29 (17)	35 (21)	64 (19)
N2	84 (50)	83 (50)	167 (50)
N3	12 (7)	12 (7)	24 (7)
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)
Resection-margin status — no. (%)			
Positive	43 (26)	52 (31)	95 (28)
Negative	122 (73)	115 (69)	237 (71)
Unknown	2 (1)	0	2 (1)
Histologic differentiation — no. (%)			
Well differentiated	64 (38)	74 (44)	138 (41)
Moderately differentiated	70 (42)	60 (36)	130 (39)
Poorly differentiated	32 (19)	30 (18)	62 (19)
Unknown	1 (1)	3 (2)	4 (1)
Extracapsular spread — no. (%)			
Positive	89 (53)	102 (61)	191 (57)
Negative	78 (47)	65 (39)	143 (43)
Perineural involvement — no. (%)			
Yes	24 (14)	21 (13)	45 (13)
No	140 (84)	143 (86)	283 (85)
Unknown	3 (2)	3 (2)	6 (2)
Vascular embolisms — no. (%)			
Yes	31 (19)	35 (21)	66 (20)
No	135 (81)	131 (78)	266 (80)
Unknown	1 (1)	1 (1)	2 (1)
Lymph-node involvement — no. (%)			
0–1 Positive	73 (44)	72 (43)	145 (43)
≥2 Positive	93 (56)	89 (53)	182 (54)
Unknown	1 (1)	6 (4)	7 (2)

* The tumor (T) and nodal (N) staging system of the Union Internationale contre le Cancer was used.[14]

Compliance to the Treatment





Cooper JS et al. N Engl J Med 2004;350:1937-1944.

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

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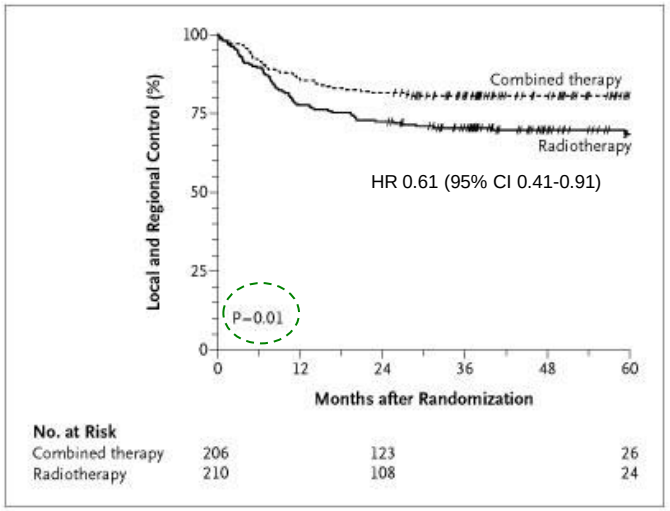
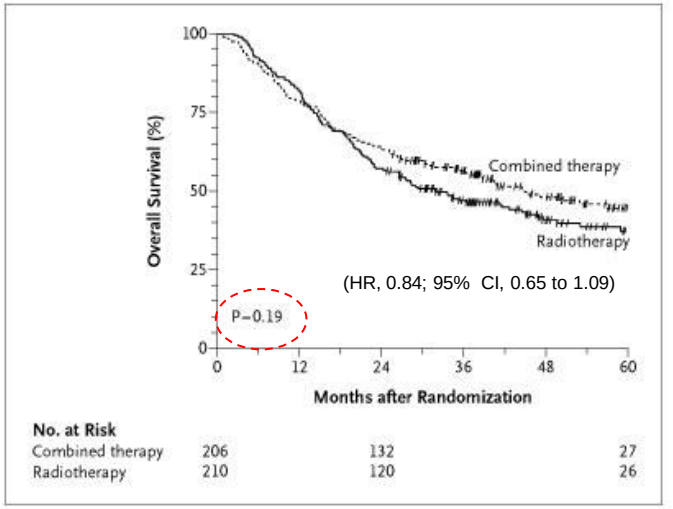
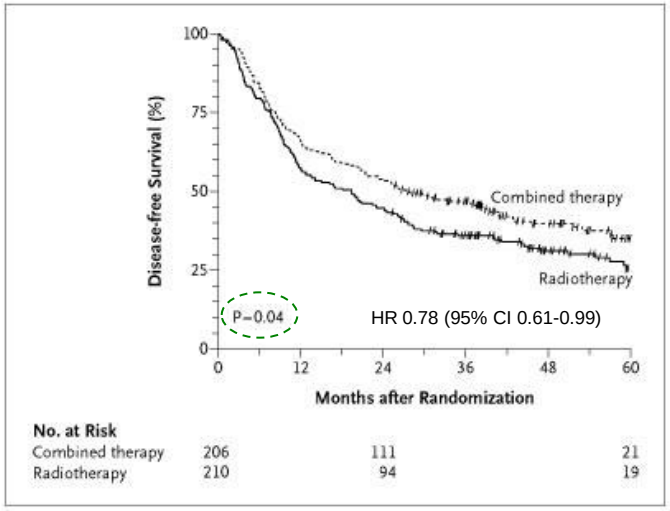






Overall survival did not differ significantly between groups

Cooper JS et al. N Engl J Med 2004;350:1937-1944.

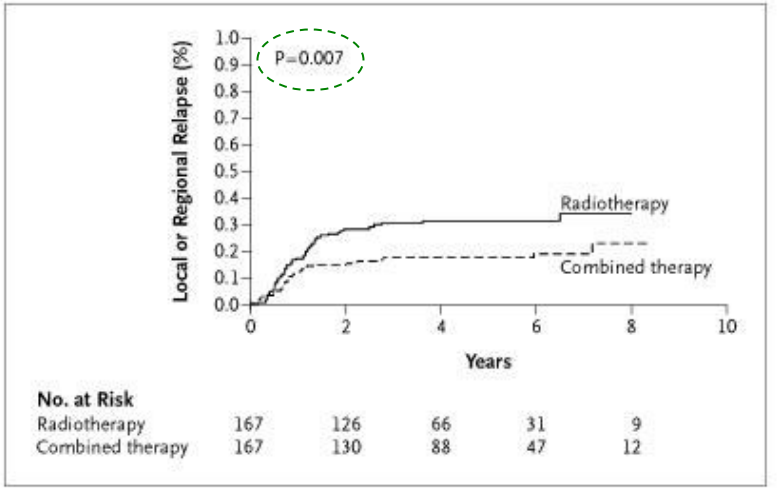
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

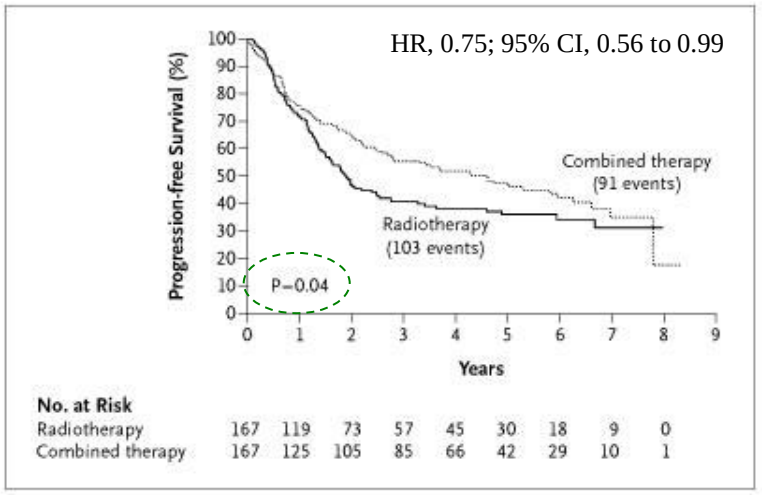
Postoperative Irradiation with or without Concomitant Chemotherapy for Locally Advanced Head and Neck Cancer

EORTC 22931

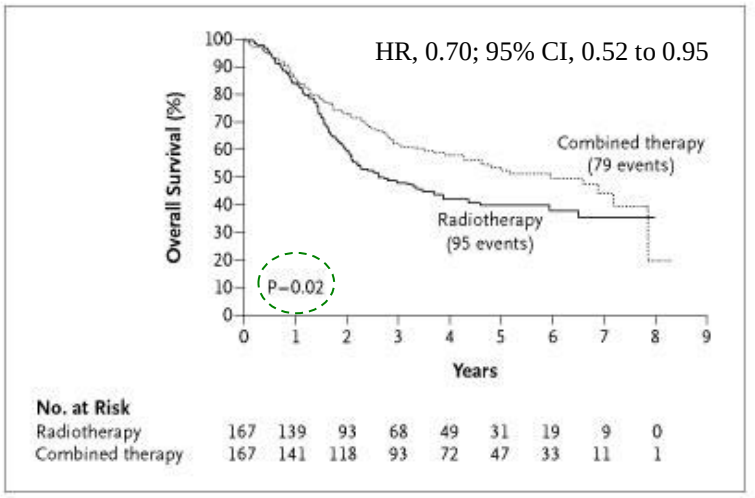
Cumulative Incidence of Local and Regional Relapses



Progression-free survival



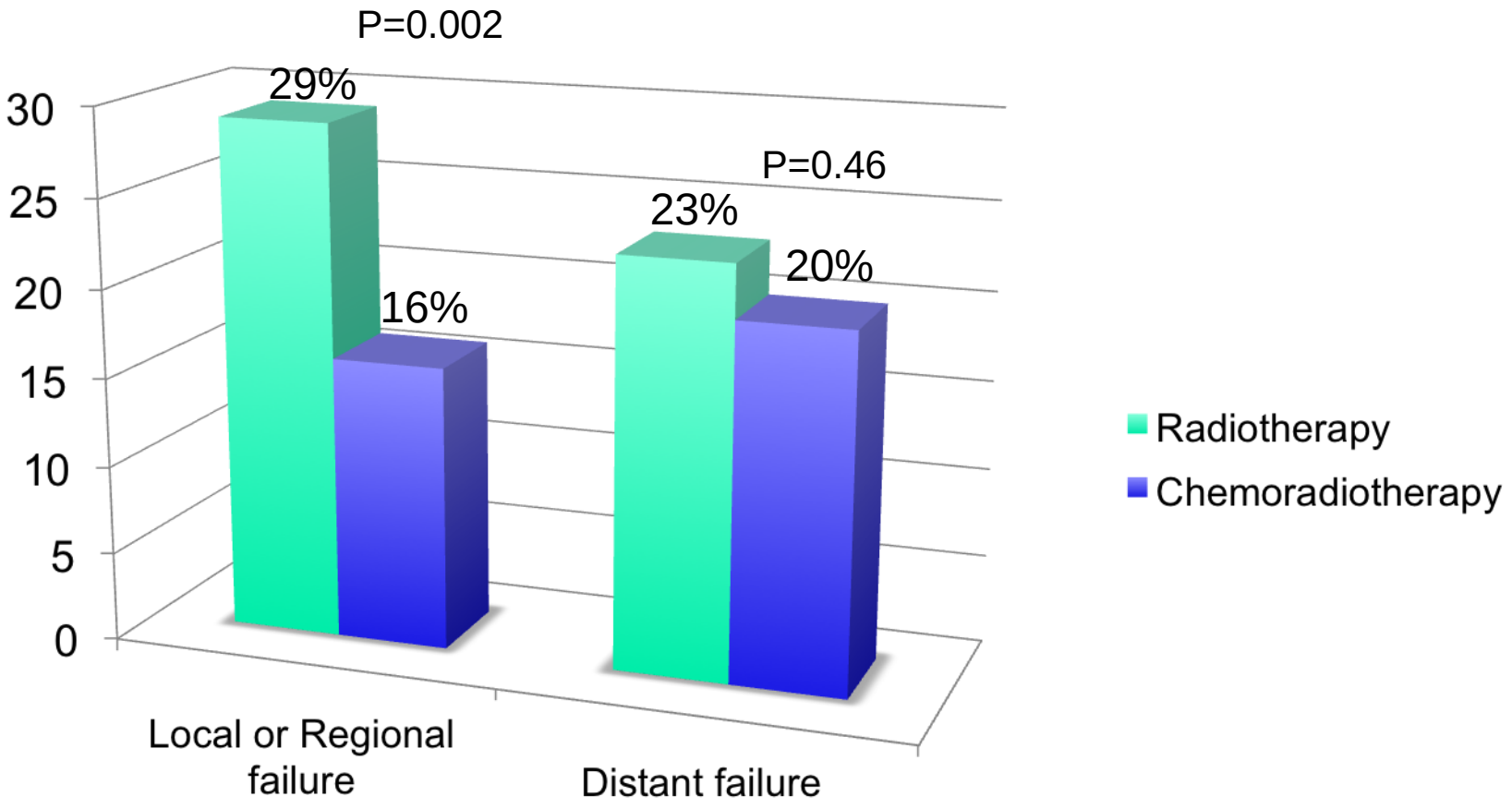
Overall Survival



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

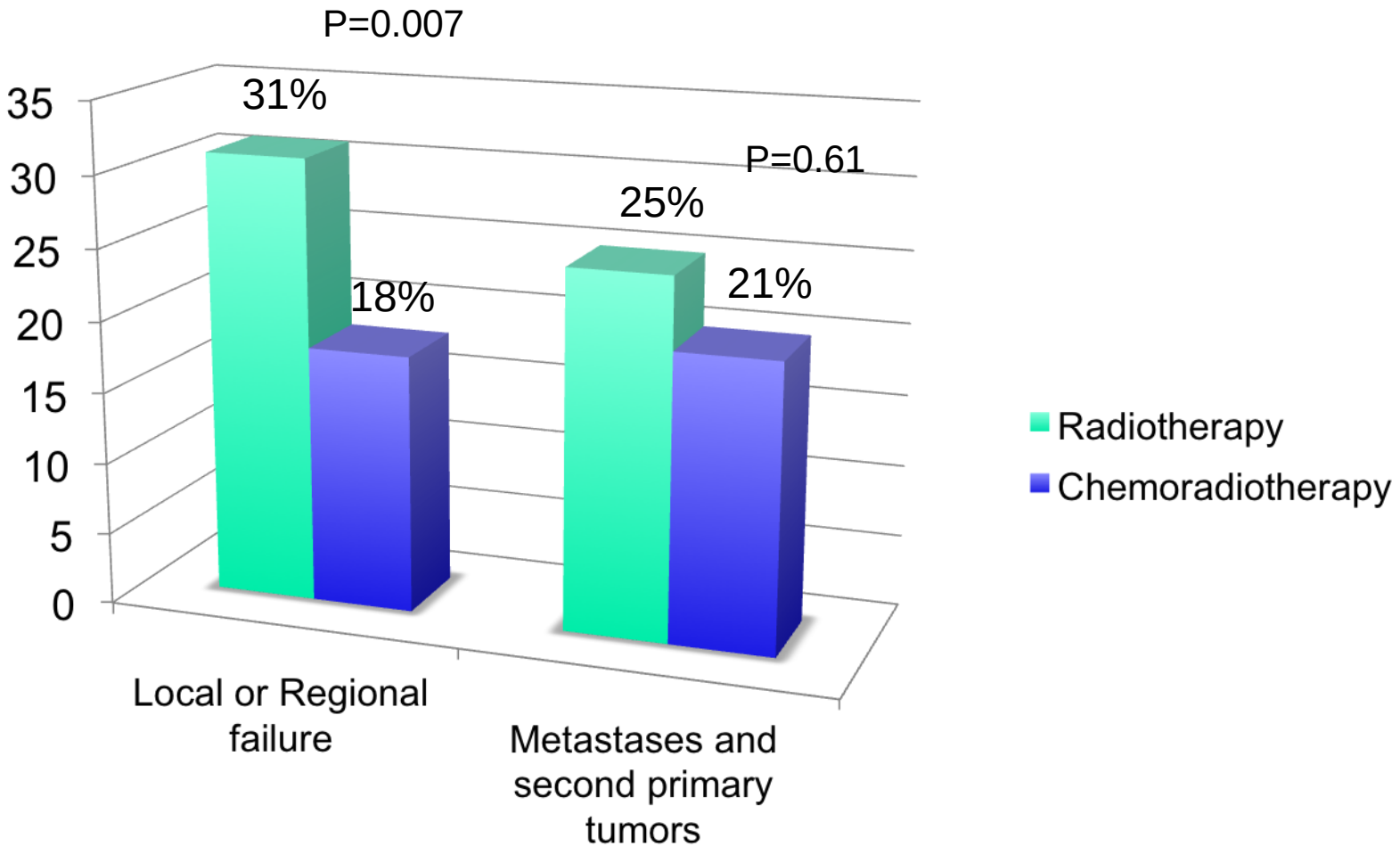
RTOG 95-01/Intergroup Trial

Patterns of failure



EORTC 22931 Trial

Estimate five-years incidence of regional failure, metastases and second tumors



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

Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501).

Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A, Ozsahin EM, Jacobs JR, Jassem J, Ang KK, Lefèbvre JL.

Department of Radiation Oncology, Oncology Institute of Southern Switzerland, CH-6504 Bellinzona, Switzerland. jacques.bernier@hcuge.ch

Pooled analysis: results

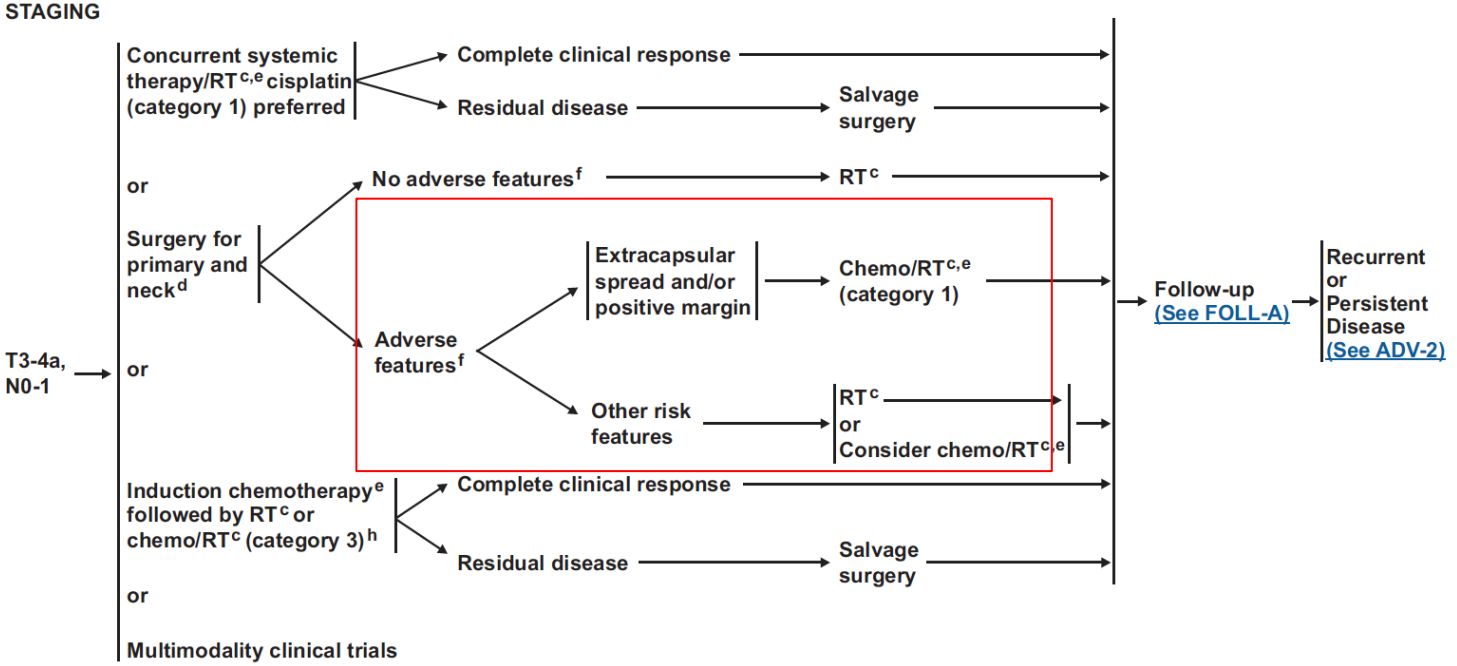
Patients with extracapsular extension (ECE) and/or microscopically involved surgical margins derived benefits in locoregional control (48% risk reduction), DFS (23% risk reduction), and OS (30% risk reduction) with the addition of cisplatin to adjuvant RT

There was a trend in favor of CERT in the group of patients who had stage III-IV disease, perineural infiltration, vascular embolisms, and/or clinically enlarged level IV-V lymph nodes secondary to tumors arising in the oral cavity or oropharynx

Patients who had two or more histopathologically involved lymph nodes without ECE as their only risk factor did not seem to benefit from the addition of chemotherapy in this analysis.

NCCN Guidelines™ Version 2.2011
Cancer of the Oropharynx

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



[f]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).

Table 3. Main prospective trials on CT/RT in a postoperative setting

CT/RT studies	Patients	LRC, %			OS, %			DFS, %		
		RT	CT/RT	p	RT	CT/RT	p	RT	CT/RT	p
EORTC 22931, Bernier et al. [6], 2004	334	69	83	0.007	40	53	0.02	36	47	0.04
RTOG 9501, Cooper et al. [7], 2004	459	72	82	0.01	57	64	0.19	45	54	
Bachaud et al. [29], 1996	83	55	70	0.0014	13	36	<0.01	23	45	<0.02
Smid et al. [32], 2003	114	69	86	0.037	64	74	0.036	60	76	0.099
Laramore et al. [33], 1992	442	71	74	NS	44	48	NS	38	46	NS
Haffty et al. [34], 1997	113	67	87	0.015	44	67	<0.03	16	13	NS
Bernier and Bentzen [35], 2003	334	64	83	0.0014	49	65	0.0057	41	59	0.096
ARO 96-3, Fietkau et al. [36], 2006	440	72.2	88.6	0.00259	50.1	62.4	0.024	48.6	58.1	

OS = Overall survival; DFS = disease-free survival; NS = not significant.

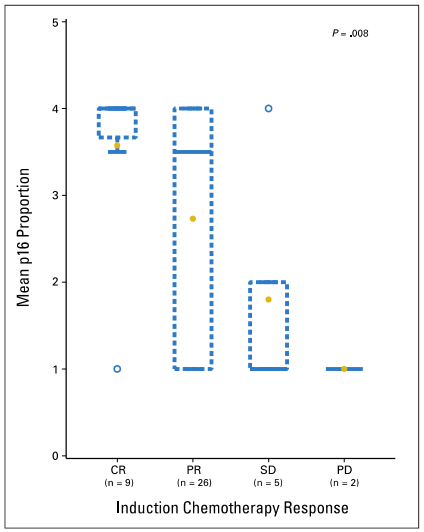
VOLUME 26 · NUMBER 19 · JULY 1 2008

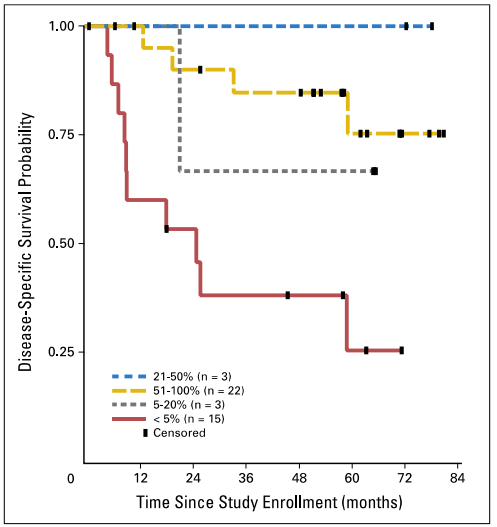
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

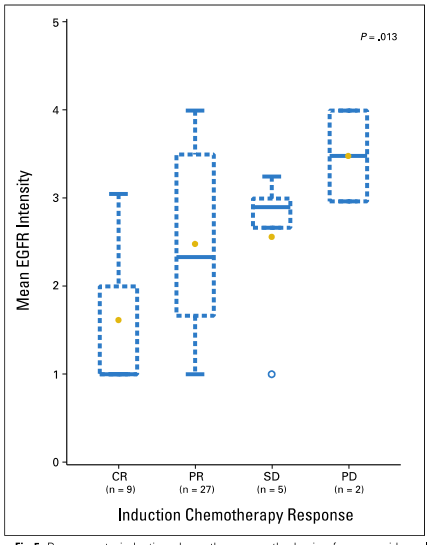
EGFR, p16, HPV Titer, Bcl-xL and p53, Sex, and Smoking As Indicators of Response to Therapy and Survival in Oropharyngeal Cancer

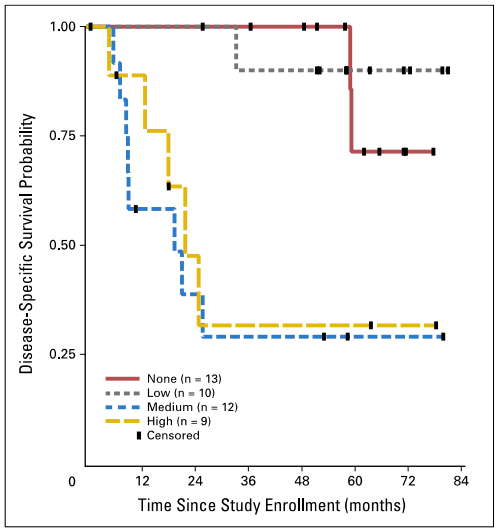
Bhavna Kumar, Kitrina G. Cordell, Julia S. Lee, Francis P. Worden, Mark E. Prince, Huong H. Tran, Gregory T. Wolf, Susan G. Urba, Douglas B. Chepeha, Theodoros N. Teknos, Avraham Eisbruch, Christina I. Tsien, Jeremy M.G. Taylor, Nisha J. D'Silva, Kun Yang, David M. Kurnit, Joshua A. Bauer, Carol R. Bradford, and Thomas E. Carey





HPV titer was significantly associated with p16 expression (P .0001.)p16 was significantly associated with response to induction chemotherapy (IC) (P .008), chemotherapy/radiotherapy (CRT, P .009), overall survival (OS, P .001), and disease-specific survival (DS P .003).





EGFR expression was inversely associated with response to (IC) (P .01), CRT (CRT; P .055), OS (P .001), and DSS (P .002) and was directly associated with current smoking (P .04), female sex (P .053), and lower HPV titer (P .03)

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Low EGFR and high p16 (or higher HPV titer) expression are markers of good response to organ-sparing therapy and outcome

High EGFR expression, combined low p53/high Bcl-xL expression, female sex, and smoking are associated with a poor outcome

Improved Survival of Patients With Human Papillomavirus–Positive Head and Neck Squamous Cell Carcinoma in a Prospective Clinical Trial

Carole Fakhry, William H. Westra, Sigui Li, Anthony Cmelak, John A. Ridge, Harlan Pinto, Arlene Forastiere, Maura L. Gillison

ECOG phase II trial

stage III or IV HNSCC of the oropharynx or larynx (n. 96 pts)

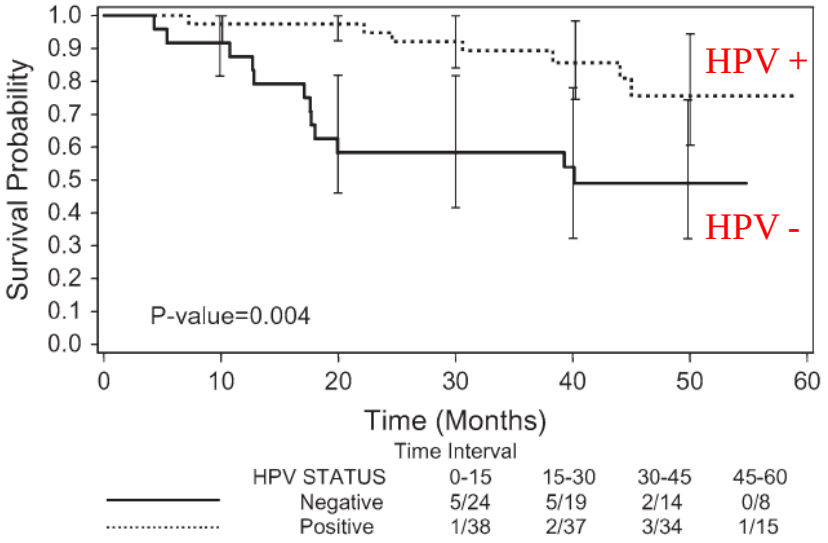
→

2 cycles of induction CT Paclitaxel-Carboplatin

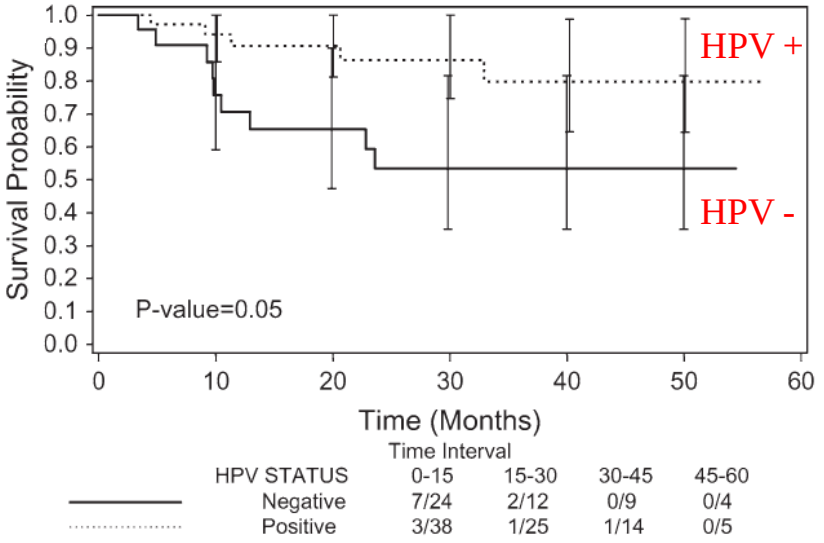
→

weekly intravenous paclitaxel and RT.

Overall survival



Progression Free-survival



Survival outcomes by tumor human papillomavirus (HPV) status in stage III-IV oropharyngeal cancer (OPC) in RTOG 0129.

2009 ASCO Annual Meeting

RTOG 0129

Randomized phase III trial:

standard fractionation (FX) radiotherapy (RT) and CDDP *vs* accelerated FX-RT and CDDP

60.6% (55.2-65.9) of pts HPV16-positive

After median follow-up of 4.4 years,

Cases with HPV-pos OPC had

better OS ($p < 0.0001$; 2-year 87.5% [82.8-92.2] vs 67.2% [58.9-75.4])

better PFS ($p < 0.0001$; 2-year 71.9% [65.5-78.2] vs 51.2% [42.4-59.9]).

POSTOPERATIVE THERAPY IN HEAD AND NECK CANCER:STATE OF THE ART, RISK SUBSET, PROGNOSIS AND UNSOLVED QUESTIONS
N Denaro, E G Russi V Adamo I Colantonio M C Merlano
Oncology 2011; 81:21-29

Proposed risk groups in an adjuvant setting

Risk	Characteristics
Low risk	young patients, HPV-positive tumors, no T3–4, no N2–3, no ENS, no heavy smokers, no positive or close margins, no vascular invasion
Intermediate risk	heavy smokers or HPV-positive tumors with high T (T3–4) or nodal stage (N2b to N3), or no smokers, T2–3 and HPV-negative tumors
High risk	HPV-negative tumor, smokers and T stage T3–4, N stage N2–3, bone perineural or lymphovascular invasion

Conclusions

- Combination of CH/RT as the standard treatment in patients at high risk of relapse
- Currently, the definition of high-risk pathologic features is given on the basis of clinicopathological parameters.
- New prognostic and predictive factors have been identified, including biomolecular aspects, HPV infection and lifestyle and are subject to dedicated clinical studies.
- The development of molecular targeted therapies opens up a promising field of investigation in less toxic postoperative treatment of LAHNC cancer