The International Federation of Head and Neck Oncologic Societies

Current Concepts in Head and Neck Surgery and Oncology 2018

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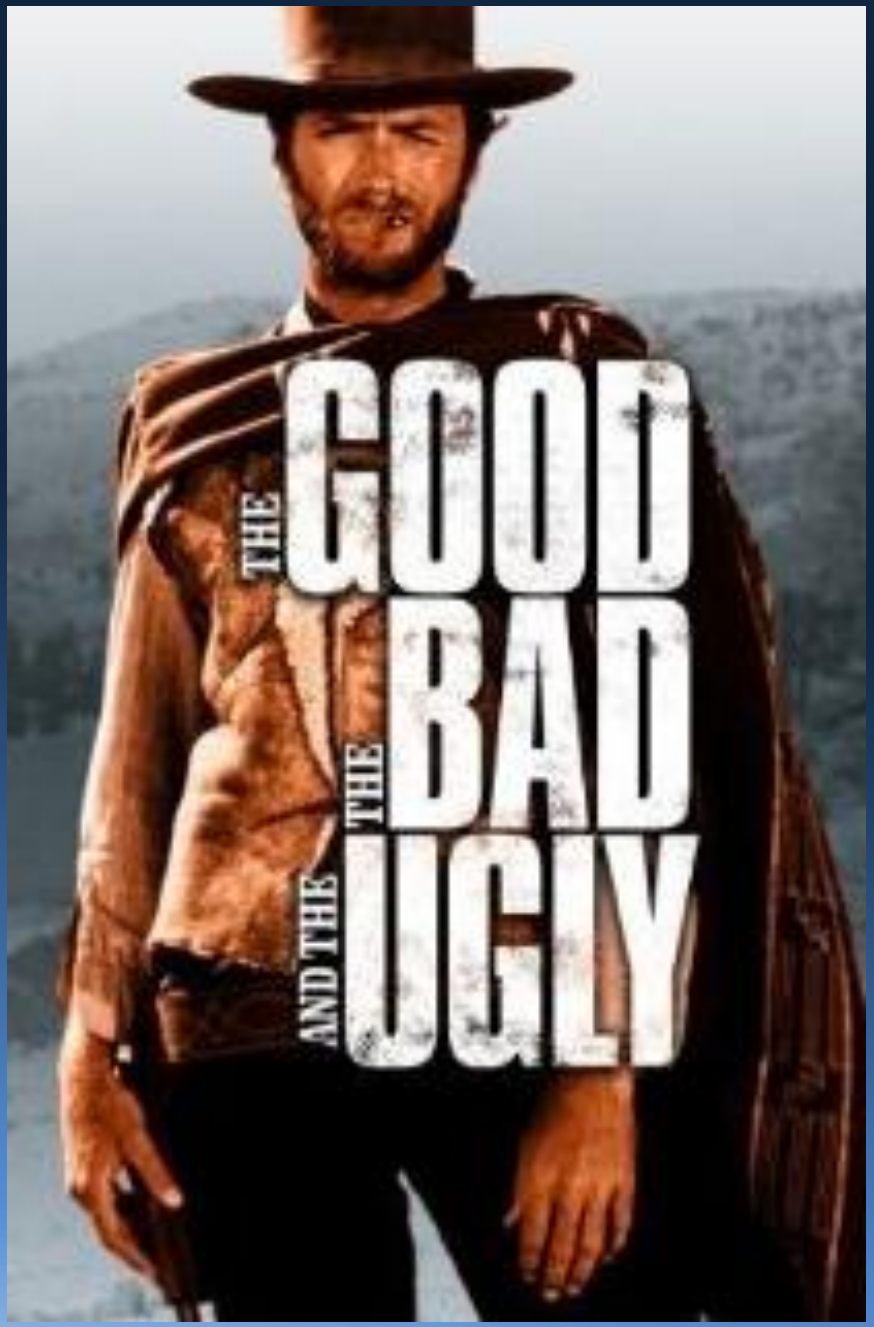
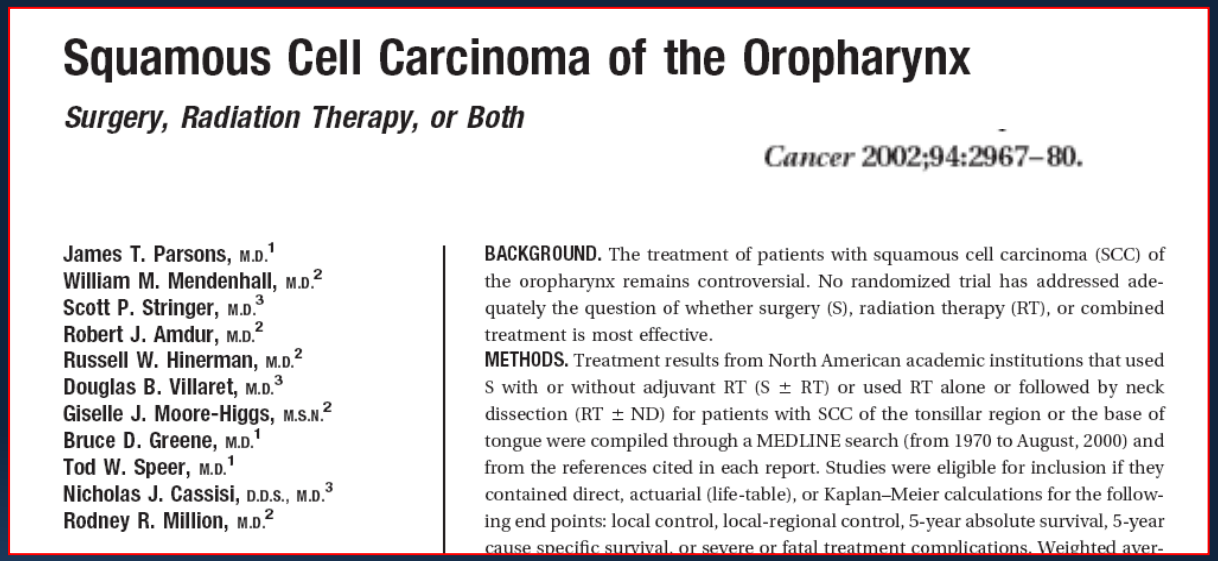
Current Concepts in Head and Neck Surgery and Oncology 2018

Oropharyngeal carcinoma: management paradigms in the era of HPV

Hisham Mehanna
Professor of Head and Neck Surgery
Director

Institute of Head and Neck Studies and Education
University of Birmingham


THE GOOD
THE BAD
AND THE UGLY



Squamous Cell Carcinoma of the Oropharynx

Surgery, Radiation Therapy, or Both

Cancer 2002;94:2967–80.

James T. Parsons, M.D.[1]
William M. Mendenhall, M.D.[2]
Scott P. Stringer, M.D.[3]
Robert J. Amdur, M.D.[2]
Russell W. Hinerman, M.D.[2]
Douglas B. Villaret, M.D.[3]
Giselle J. Moore-Higgs, M.S.N.[2]
Bruce D. Greene, M.D.[1]
Tod W. Speer, M.D.[1]
Nicholas J. Cassisi, D.D.S., M.D.[3]
Rodney R. Million, M.D.[2]

BACKGROUND. The treatment of patients with squamous cell carcinoma (SCC) of the oropharynx remains controversial. No randomized trial has addressed adequately the question of whether surgery (S), radiation therapy (RT), or combined treatment is most effective.

METHODS. Treatment results from North American academic institutions that used S with or without adjuvant RT (S ± RT) or used RT alone or followed by neck dissection (RT ± ND) for patients with SCC of the tonsillar region or the base of tongue were compiled through a MEDLINE search (from 1970 to August, 2000) and from the references cited in each report. Studies were eligible for inclusion if they contained direct, actuarial (life-table), or Kaplan–Meier calculations for the following end points: local control, local-regional control, 5-year absolute survival, 5-year cause specific survival, or severe or fatal treatment complications. Weighted aver-

Base of tongue ND:	S +/- RT vs	RT +/-
OS	49 %	52%
Severe complications	32%	3.8%
Fatal complications	3.5%	0.4%

VOLUME 22 · NUMBER 1 · JANUARY 1 2004

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Final Results of the 94-01 French Head and Neck Oncology and Radiotherapy Group Randomized Trial Comparing Radiotherapy Alone With Concomitant Radiochemotherapy in Advanced-Stage Oropharynx Carcinoma

Fabrice Denis, Pascal Garaud, Etienne Bardet, Marc Alfonsi, Christian Sire, Thierry Germain, Philippe Bergerot, Beatrix Rhein, Jacques Tortochaux, and Gilles Calais

N=226

5 yr OS: 22.4% vs 15.8% (p=.05)
5 yr LRC : 47.6% vs 24.7% (p=0.002)

NOT HPV+!!

CRT pronounced standard of care

Speech and voice outcomes in oropharyngeal cancer and evaluation of the University of Washington Quality of Life speech domain

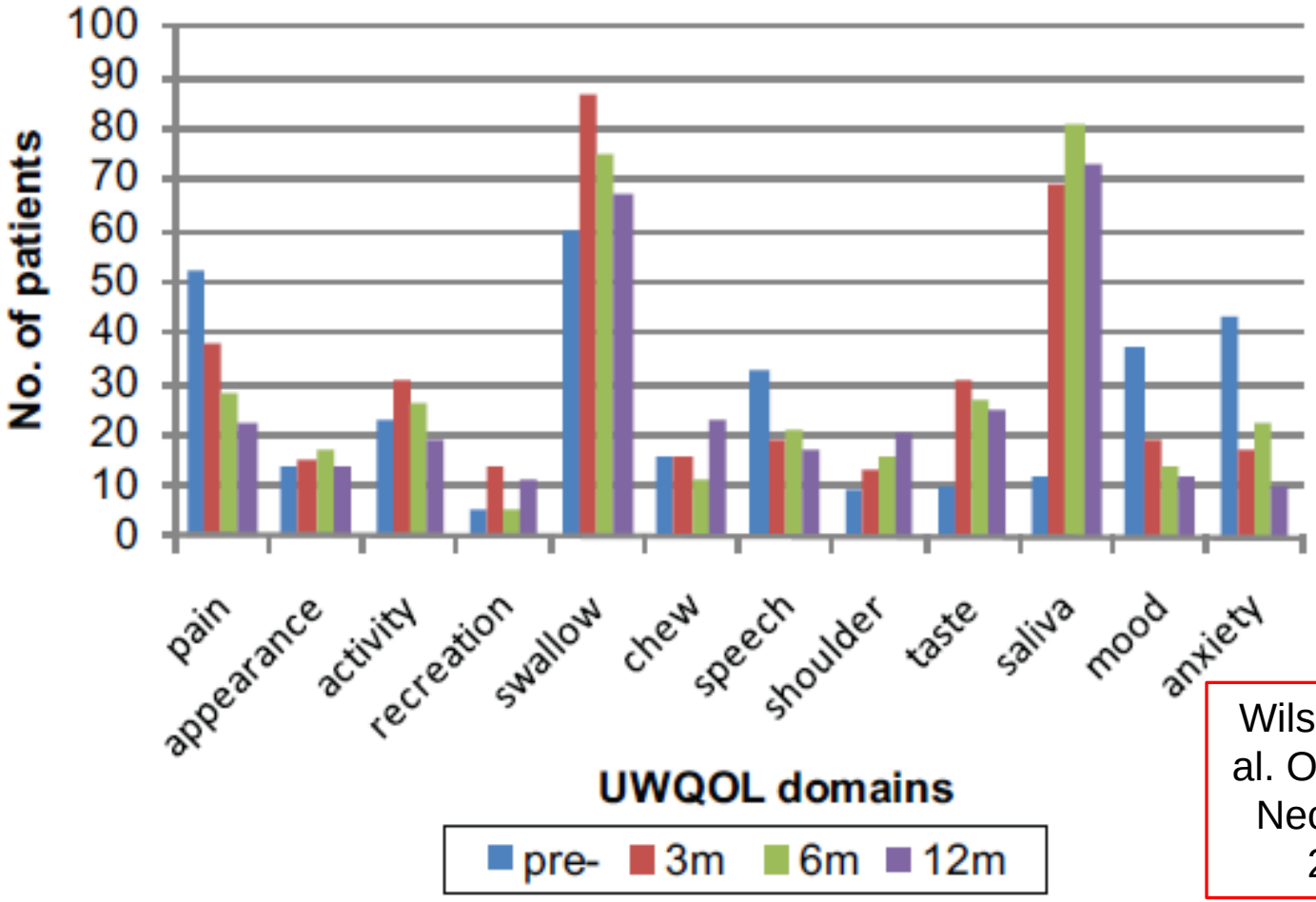
Thomas, L.,* Jones, T.M.,† Tandon, S.,‡ Carding, P.,§ Lowe, D.¶ & Rogers, S.**

**Alderhey Hospital, Liverpool, †School of Cancer Studies, University of Liverpool, Liverpool, UK, ‡Mersey Deanery, Liverpool, §Department of Speech, Voice and Swallowing, Otolaryngology, Freeman Hospital, Newcastle-upon-Tyne, ¶Regional Maxillofacial Unit, University Hospital Aintree, Liverpool, and **Regional Maxillofacial Unit, University Hospital Aintree, and Faculty of Health, Edge Hill University, Liverpool, UK*

Accepted for publication 17 September 2008
Clin. Otolaryngol. 2009, **34**, 34–42

The functional rationale

Patient priorities after CRT



Wilson JA et al. Otol Head Neck Surg 2011

Radiotherapy and Oncology 90 (2009) 189–195

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Swallowing dysfunction

A predictive model for swallowing dysfunction after curative radiotherapy in head and neck cancer

Johannes A. Langendijk [a,b,*], Patricia Doornaert [a], Derek H.F. Rietveld [a], Irma M. Verdonck-de Leeuw [c], C. René Leemans [c], Ben J. Slotman [a]

[a] *Department of Radiation Oncology, VU University Medical Center, Amsterdam, The Netherlands*
[b] *Department of Radiation Oncology, University Medical Center Groningen, The Netherlands*
[c] *Department of Otolaryngology/Head and Neck Surgery, VU University Medical Center, Amsterdam, The Netherlands*

N=594
Prospective dataset
Bilateral neck irradiation, accelerated radiotherapy and concomitant chemoradiation are independent prognostic factors of poor swallow

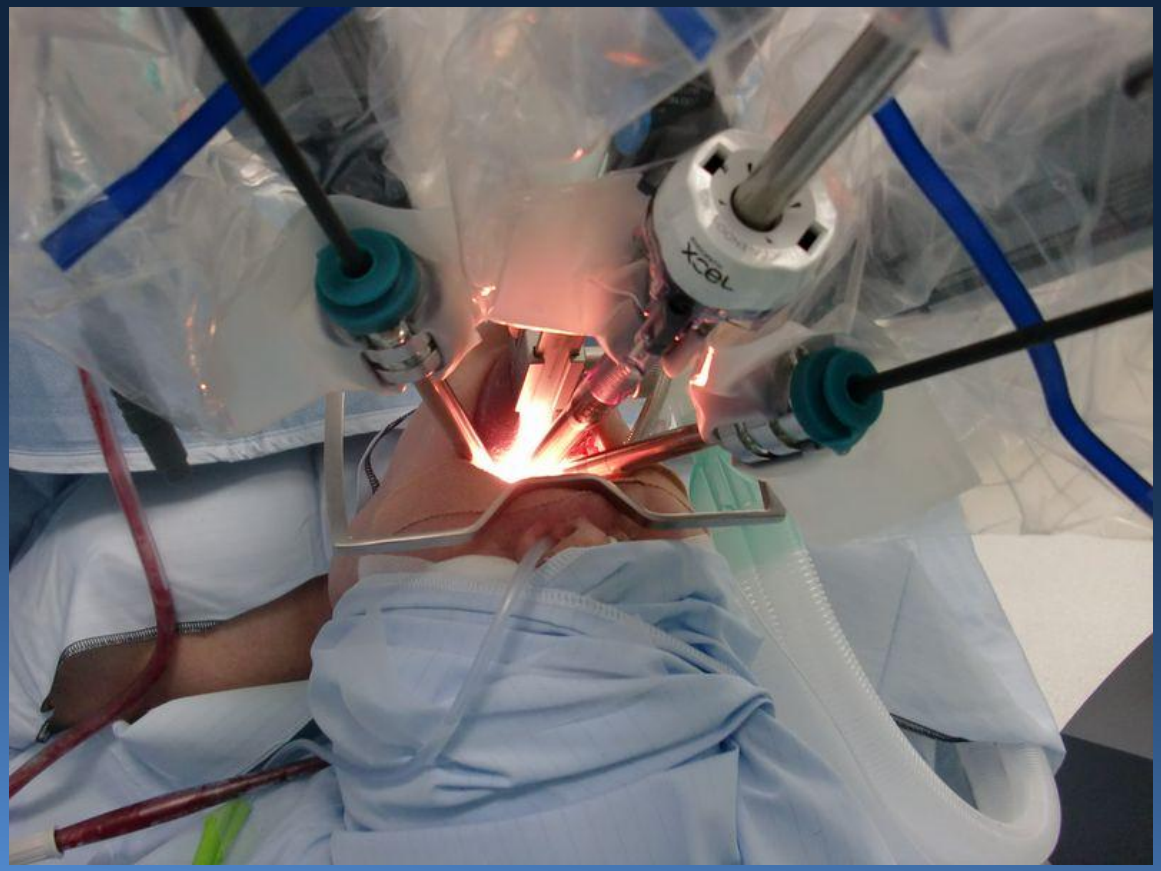
Changing world and changing treatment modalities

Surgery has moved on.....

- New function preserving surgical approaches
  - Transoral Laser Microsurgery
  - Transoral Robotic Surgery
- Greater expertise in free flap reconstruction
- Reduced postoperative morbidity & mortality

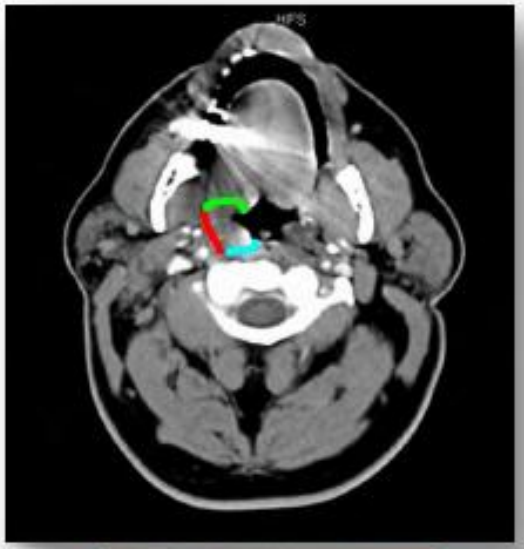
Da Vinci System

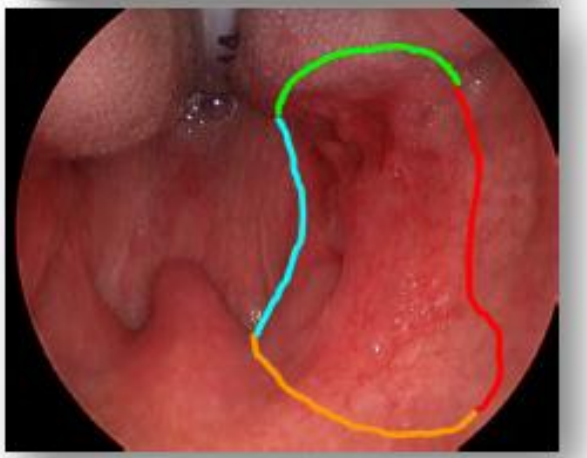
- Superior 3-D image
- Stereoscopic design with two 3 chip cameras
- 75% better resolution than any imaging system



Standardization of TORS Radical Tonsillectomy

- Superiorly – portion of soft palate
- Inferiorly – portion of the tongue base between tonsillar pillars
- Posteriorly
  - Superficial – posterior pharyngeal wall mucosa adjacent to posterior tonsillar pillar
  - Deep – Constrictor muscles over prevertebral fascia
- Laterally
  - Superficial – muscosa of the anterior tonsillar pillar and over pterygomandibluar raphe
  - Deep – Constrictor muscles over parapharyngeal fat pad

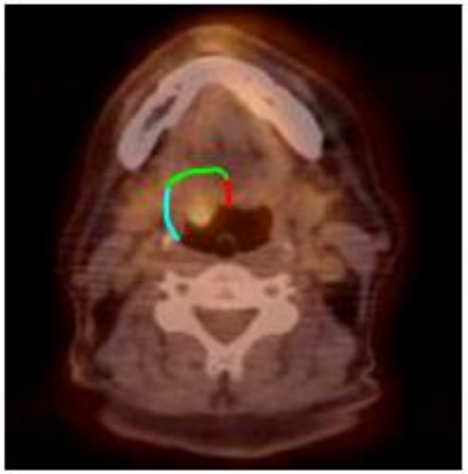


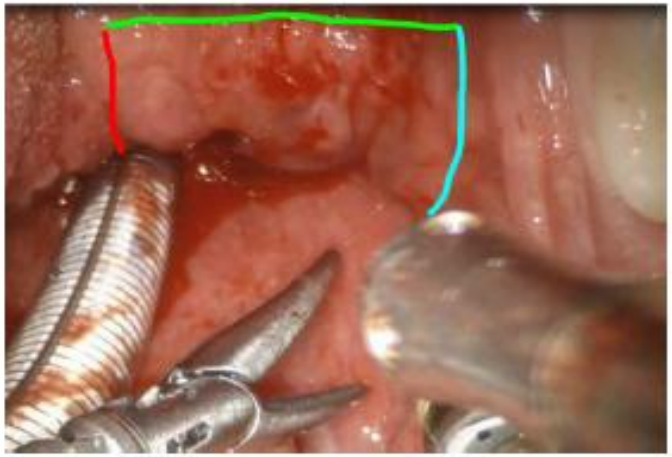


Slide courtesy Greg Weinstein

Standardization of TORS Tongue Base Hemiglossectomy

- **Midline**
  - **Superficial** – Midline tongue base mucosa
  - **Deep** - deep tongue musculature to level of hyoid region
- **Anteriorly**
  - **Superficial** – circumvallate papillae
  - **Deep** - deep tongue musculature to level of hyoid region
- **Inferiorly**
  - **Superficial** - vallecular mucosa
  - **Deep** - hyoepiglottic ligament
- **Laterally**
  - **Superficial** – mid tonsillar level mucosa /tonsil
  - **Deep** – constrictor muscles





Slide courtesy Greg Weinstein

TORS / TLM Outcomes

Received: 24 March 2017 | Revised: 18 August 2017 | Accepted: 16 November 2017
DOI: 10.1002/hed.25055

ORIGINAL ARTICLE

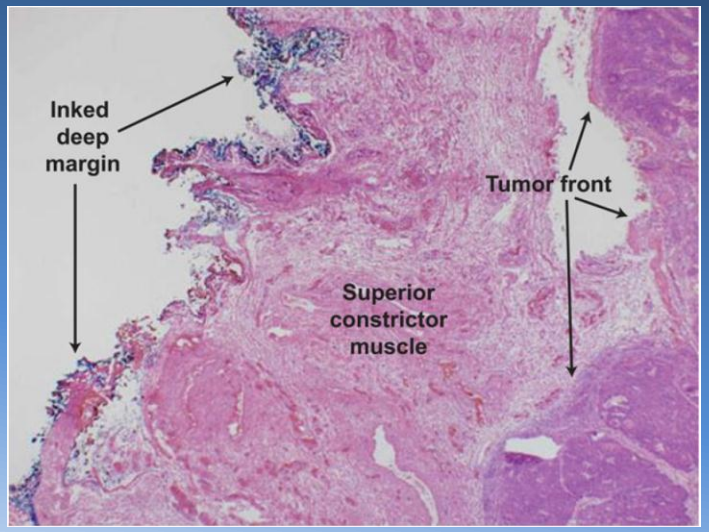
WILEY

Transoral robotic surgery for oropharyngeal carcinoma: Surgical margins and oncologic outcomes

Eric J. Moore MD[1] | Kathryn M. Van Abel MD[1] | Daniel L. Price MD[1] | Christine M. Lohse MS[2] | Kerry D. Olsen MD[1] | Ryan S. Jackson MD[3] | Eliot J. Martin PA-C[1]

N=314

No adjuvant RT for close, but negative margins
Adjuvant RT for N2b/N2c/N3, positive margins
Adjuvant CRT for ECS
3-year local control rate: 98%



The Laryngoscope

Margin Mapping in Transoral Surgery for Head and Neck Cancer

Michael L. Hinni, MD; Matthew A. Zarka, MD; Joseph M. Hoxworth, MD

N=128

Average margin distance: 1.98 mm
Zero-tolerance for disease positive bed
5 year local control rate: 99%

Oncologic outcomes

MAYO CLINIC

ORIGINAL ARTICLE

Long-term Functional and Oncologic Results of Transoral Robotic Surgery for Oropharyngeal Squamous Cell Carcinoma

Eric J. Moore, MD; Steven M. Olsen, MD; Rebecca R. Laborde, PhD; Joaquín J. García, MD; Francis J. Walsh, BA; Daniel L. Price, MD; Jeffrey R. Janus, MD; Jan L. Kasperbauer, MD; and Kerry D. Olsen, MD

ORIGINAL ARTICLE

Transoral Robotic Surgery for Advanced Oropharyngeal Carcinoma

Gregory S. Weinstein, MD; Bert W. O'Malley Jr, MD; Marc A. Cohen, MD; Harry Quon, MD

CME ASTRO

International Journal of Radiation Oncology biology • physics

www.redjournal.org

Critical Review

Critical Review: Transoral Laser Microsurgery and Robotic-Assisted Surgery for Oropharynx Cancer Including Human Papillomavirus–Related Cancer

Eric J. Moore, MD,* and Michael L. Hinni, MD†

**Otolaryngology/Head and Neck Surgery, Mayo Clinic, Rochester, Minnesota; and †Otolaryngology/Head and Neck Surgery, Mayo Clinic, Scottsdale, Arizona*

The Laryngoscope
Lippincott Williams & Wilkins, Inc.

Carcinoma of the Tongue Base Treated by Transoral Laser Microsurgery, Part Two: Persistent, Recurrent and Second Primary Tumors

The Laryngoscope

TRIOLOGICAL SOCIETY CANDIDATE THESIS

Prognostic Factors and Survival Unique to Surgically Treated p16+ Oropharyngeal Cancer

Bruce H. Haughey, MBChB, FRACS, FACS; Parul Sinha, MBBS, MS

ORIGINAL ARTICLE

TRANSORAL LASER MICROSURGERY AS PRIMARY TREATMENT FOR ADVANCED-STAGE OROPHARYNGEAL CANCER: A UNITED STATES MULTICENTER STUDY

Bruce H. Haughey, MBChB,[1] Michael L. Hinni, MD,[2] John R. Salassa, MD,[3] Richard E. Hayden, MD,[2] David G. Grant, MBChB,[3] Jason T. Rich, MD,[1] Simon Milov, MD,[1] James S. Lewis, Jr, MD,[4] Murli Krishna, MD[5]

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[2] Department of Otolaryngology–Head and Neck Surgery, Mayo Clinic, Scottsdale, Arizona
[3] Department of Otolaryngology, Mayo Clinic, Jacksonville, Florida
[4] Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, Missouri
[5] Department of Laboratory Medicine and Pathology, Mayo Clinic, Jacksonville, Florida

Accepted 4 October 2010
Published online 31 January 2011 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/hed.21669

ORIGINAL ARTICLE

Comparison of functional outcomes and quality of life between transoral surgery and definitive chemoradiotherapy for oropharyngeal cancer

Allen M. Chen, MD,[1*] Megan E. Daly, MD,[1] Quang Luu, MD,[2] Paul J. Donald, MD,[2] D. Gregory Farwell, MD[2]

[1]Department of Radiation Oncology, University of California Davis School of Medicine, Sacramento, California, [2]Department of Otolaryngology – Head and Neck Surgery, University of California Davis School of Medicine, Sacramento, California.

Accepted 9 January 2014
Published online 3 April 2014 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/hed.23610

UW-QoL domain	TORS +RT	CRT	P value
Swallowing	91.5	72.1	0.01
Chewing	88.7	82.3	NS
Speech	91.5	93.6	NS
Taste	64.5	62.4	NS
Saliva	58.1	53.8	NS

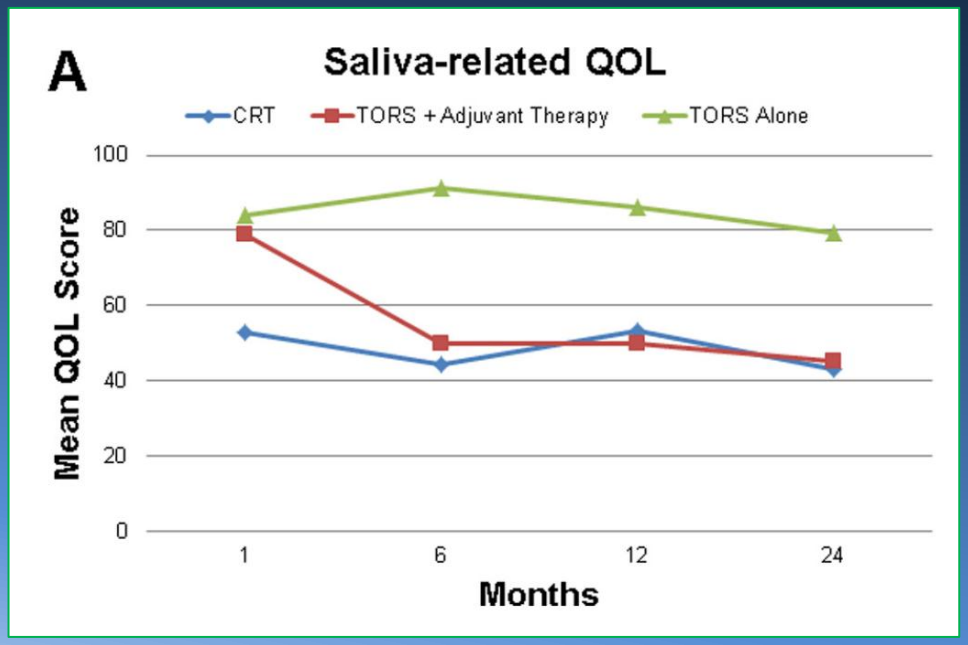
Characteristic	Transoral surgery + RT (%)	CRT (%)
Primary tumor size		
Tonsil	16 (52)	16 (52)
Base of tongue	15 (48)	15 (48)
T classification		
T1	14 (45)	14 (45)
T2	12 (39)	12 (39)
T3	5 (16)	5 (16)
N classification		
N1	5 (16)	5 (16)
N2a	10 (32)	9 (29)
N2b	10 (32)	11 (35)
N2c	6 (19)	6 (19)
HPV status		
Positive	20 (65)	20 (65)
Negative	11 (35)	11 (35)
Smoking history		
None	14 (45)	14 (45)
Yes, <10 pack-year	7 (23)	7 (23)
Yes, 10–40 pack-year	5 (16)	5 (16)
>40 pack-year	5 (16)	5 (16)
Sex		
Male	26 (84)	26 (84)
Female	5 (16)	5 (16)
KPS		
90	27 (87)	24 (77)
80	4 (13)	7 (23)

But that is not the complete picture…..

Oncologic outcomes and patient-reported quality of life in patients with oropharyngeal squamous cell carcinoma treated with definitive transoral robotic surgery versus definitive chemoradiation

D.C. Ling MD [a], B.V. Chapman MD [a], J. Kim MD [b], G.W. Choby MD [b], P. Kabolizadeh MD, PhD [a], D.A. Clump MD, PhD [a], R.L. Ferris MD, PhD, FACS [b], S. Kim MD [b], S. Beriwal MD [a], D.E. Heron MD, FACRO, FACR [a,b], U. Duvvuri MD, PhD [b,*]

[a] *Department of Radiation Oncology, University of Pittsburgh Cancer Institute, Pittsburgh, PA, United States*
[b] *Department of Otolaryngology, University of Pittsburgh Medical Center, Pittsburgh, PA, United States*

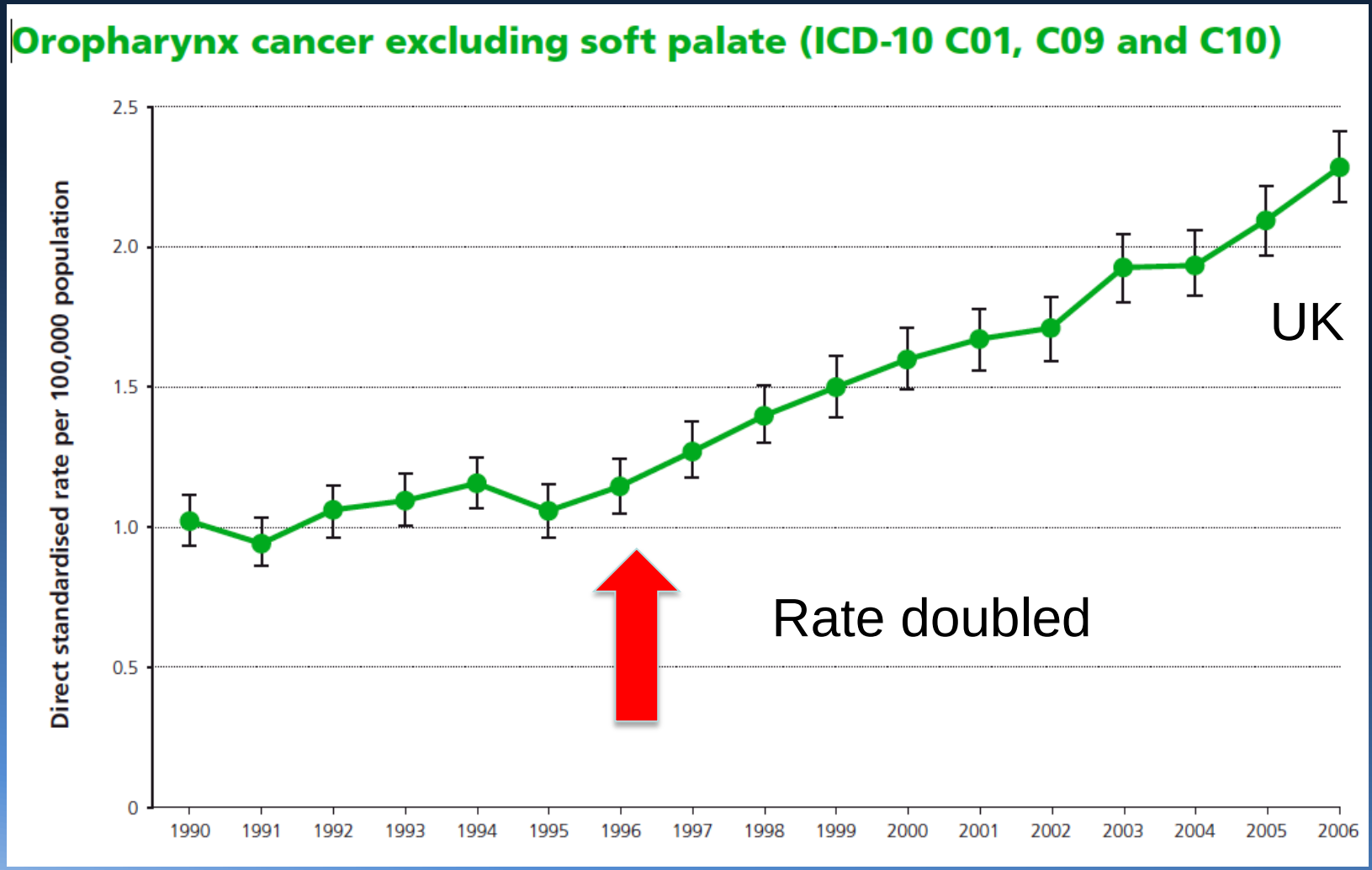


TORS only: 40
TORS+RT: 15
TORS + CRT: 37

University of Washington QoL: 1, 6, 12, and 24 months

Changing world and changing epidemiology

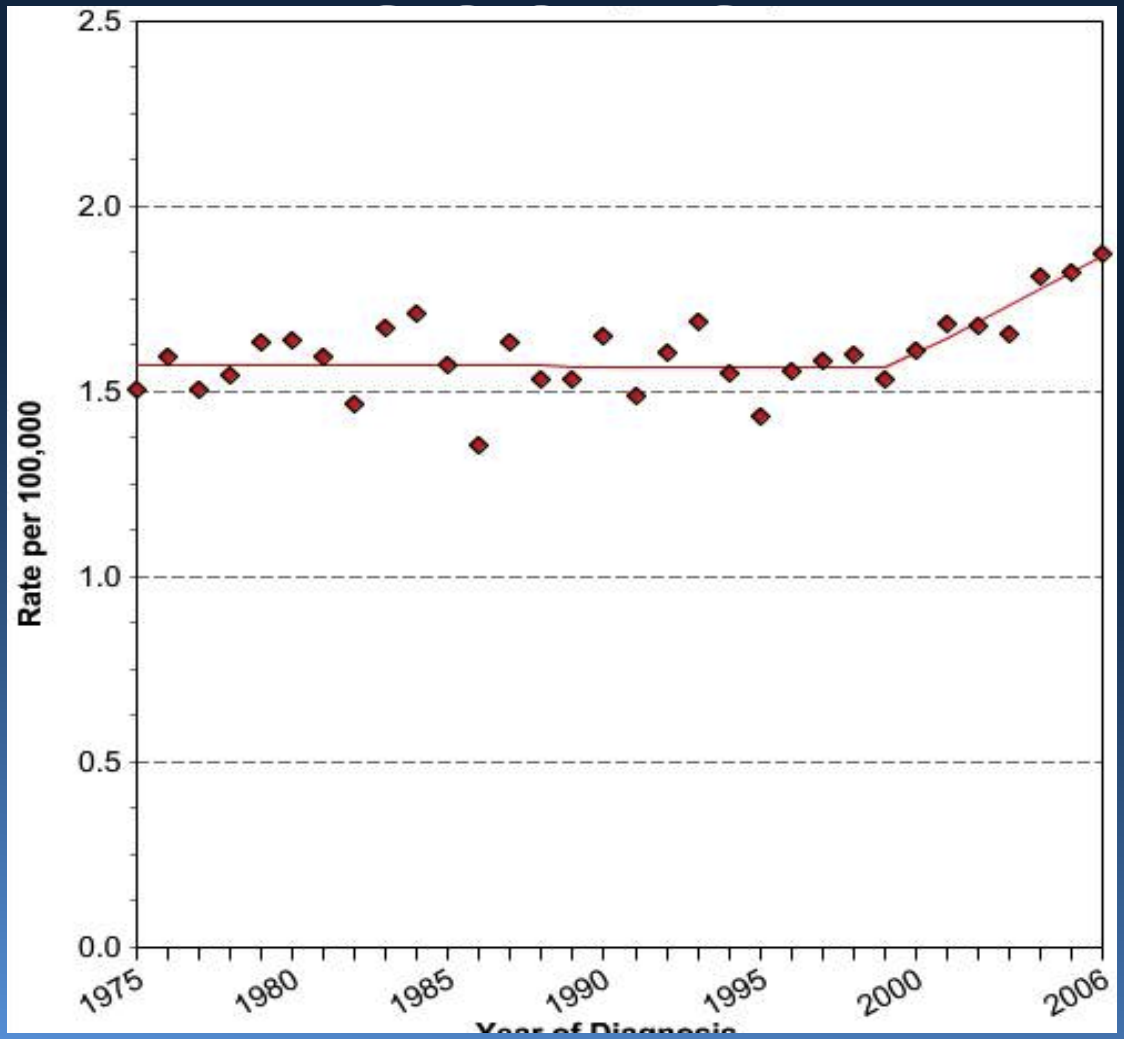
Rapidly rising incidence



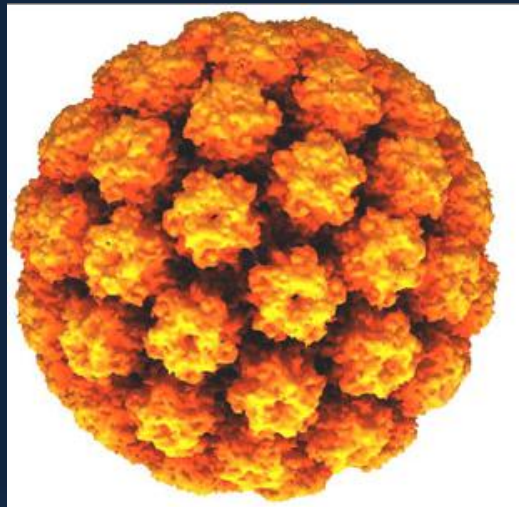
NCIN, 2010

Incidence of Oropharyngeal

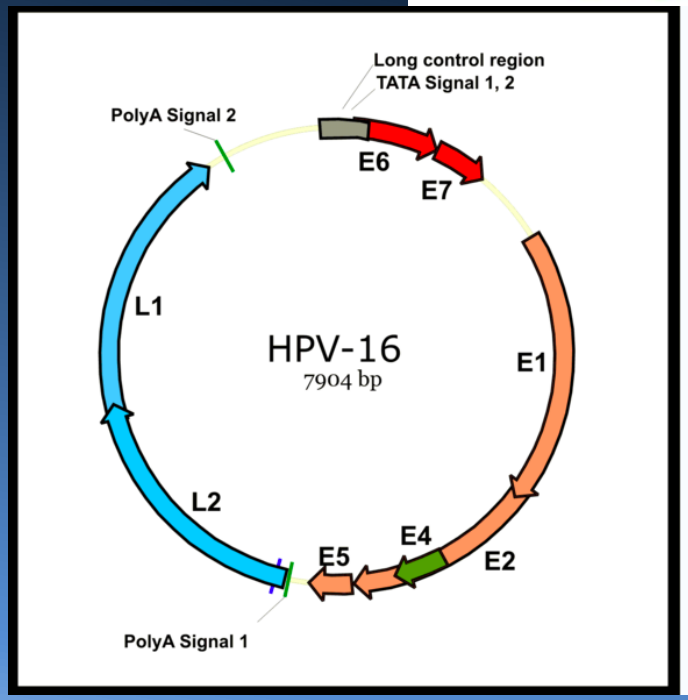
SEER data 1975-2006



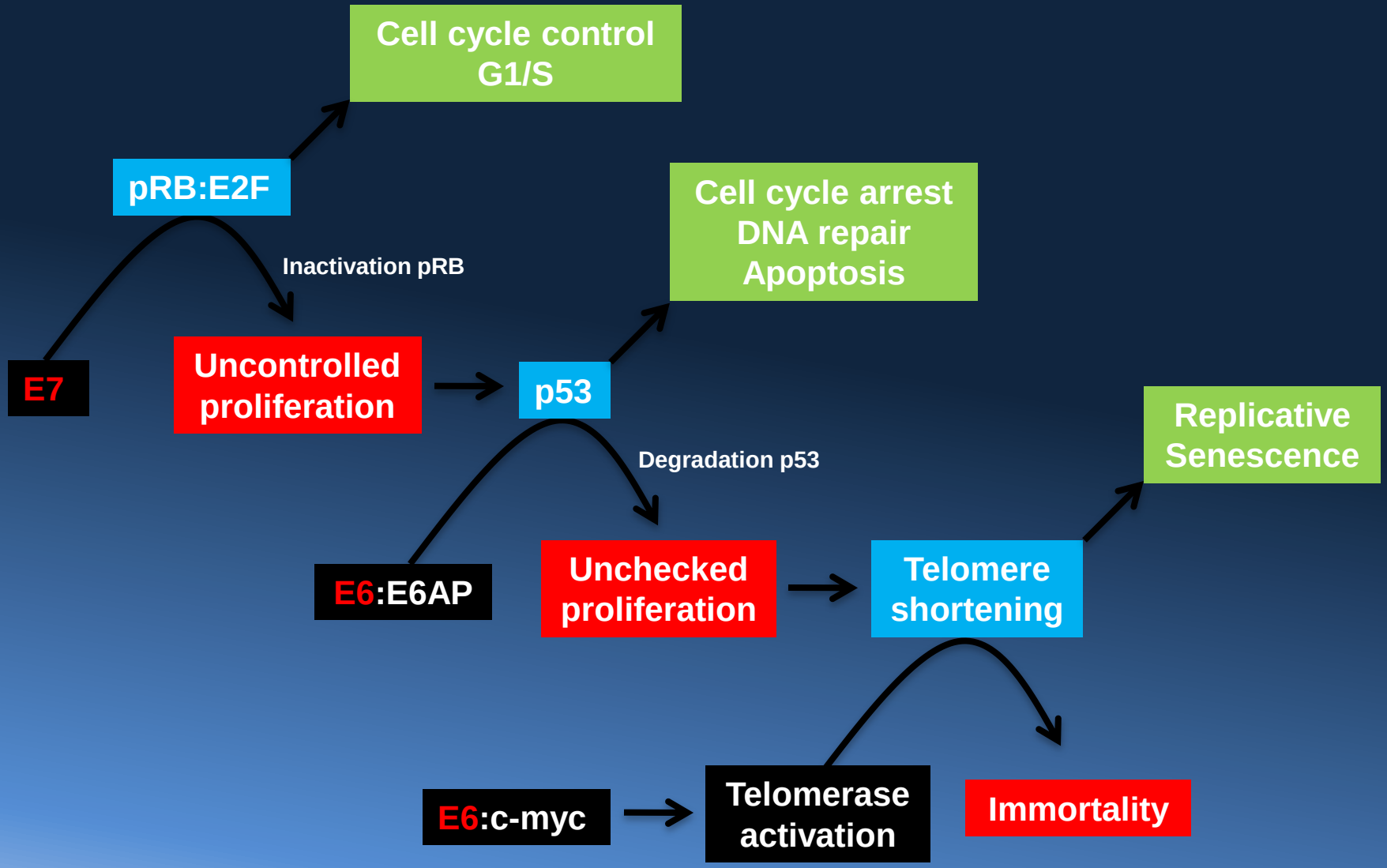
Human Papilloma Virus



- Double stranded circular DNA
- 72 L1 capsid proteins
- Orogenital transmission
- Many types
- Cervical and oropharyngeal SCC type 16 most common

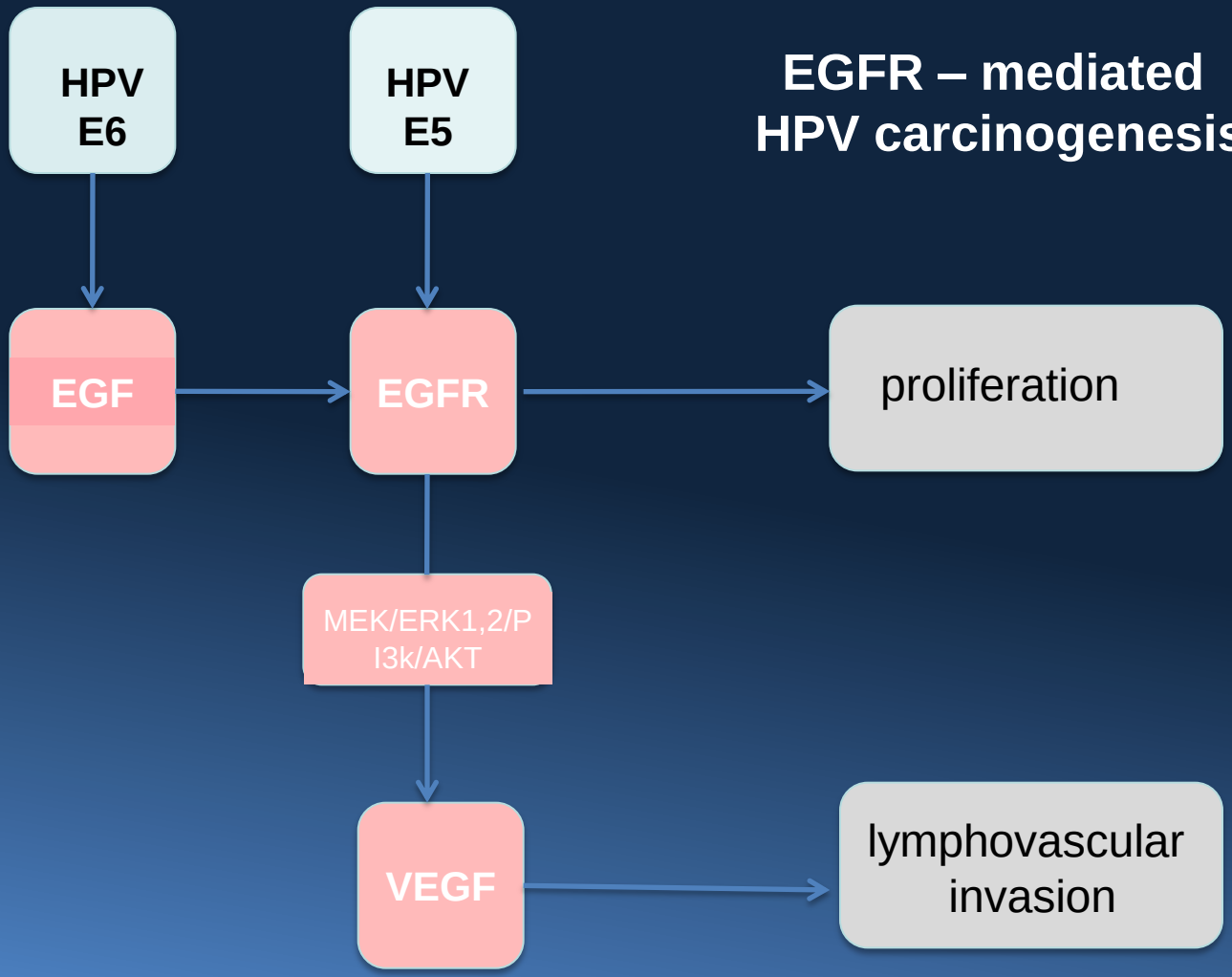


HPV Carcinogensis – effects of E6 & E7 on cell signalling



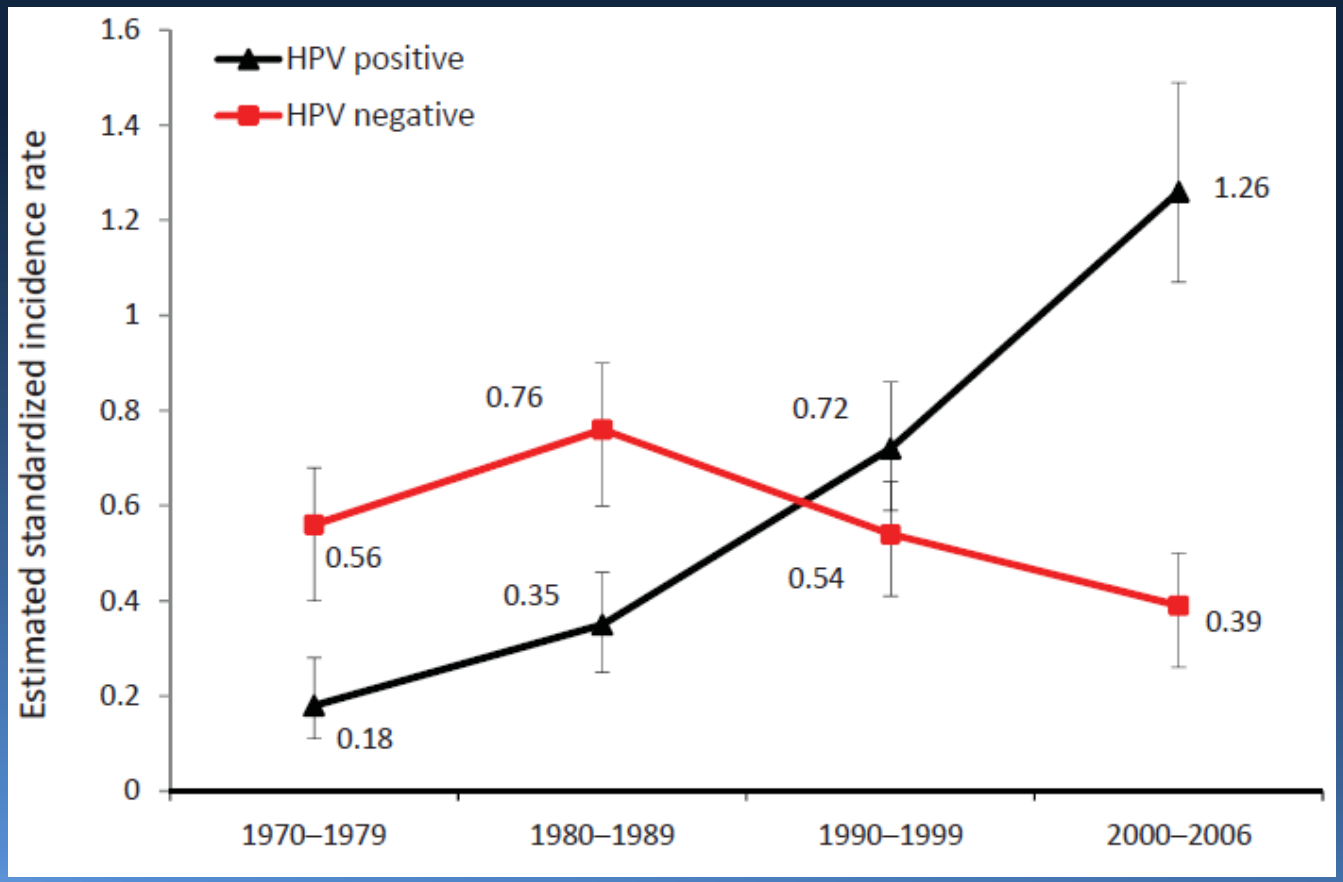
Munger et al., *J Virol* 2004; 78:11451011460

EGFR – mediated HPV carcinogenesis



Mathur 2005, Kim 2006
Rampias 2009

Incidence of HPV+ve and HPV-ve tonsillar cancer squamous cell carcinoma cases (Stockholm, Sweden, 1970–2006)

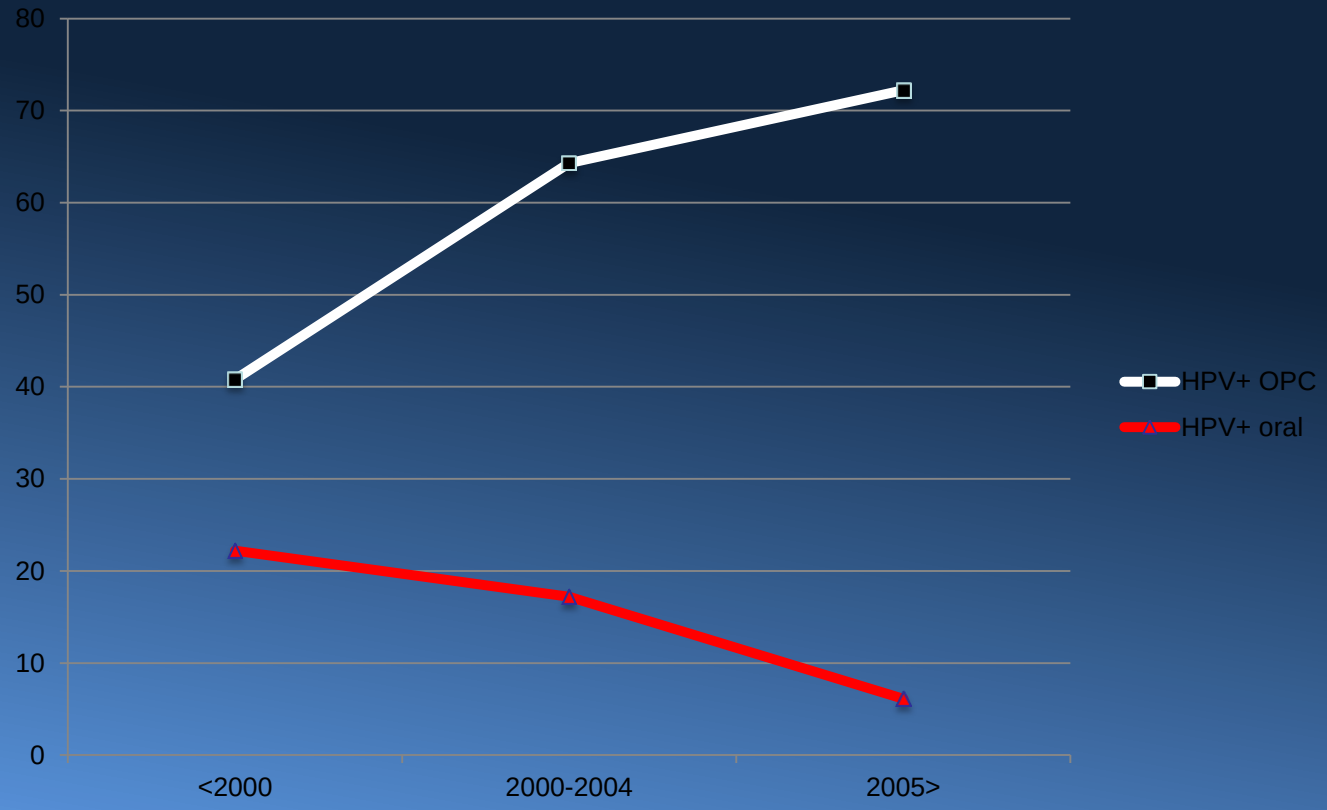


Näsman et al., IJC 2009; Ramqvist & Dalianis, Emert Inf Disease, 2010

HPV-related OPSCC increasing

Meta-analysis : HPV oropharyngeal and oral carcinoma by time

269 papers, 19,000 + patients



Global disease burden is increasing significantly

Mehanna, Head Neck 2013

Epidemic?

THE LANCET Oncology

The Lancet Oncology, Volume 11, Issue 8, Pages 781 - 789, August 2010
doi:10.1016/S1470-2045(10)70017-6 Cite or Link Using DOI

Published Online: 06 May 2010

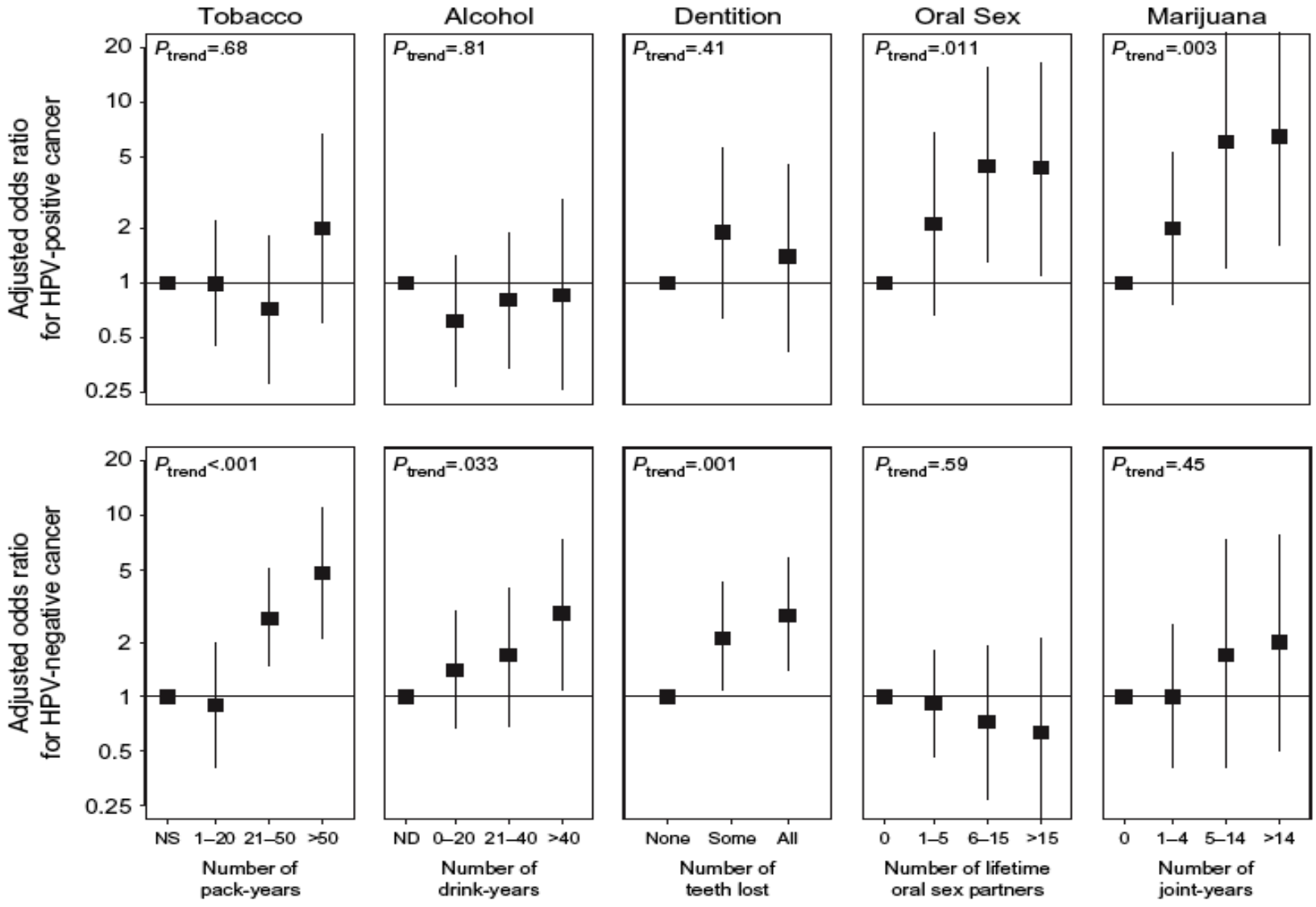
< Previous Article | Next Article >

HPV-associated head and neck cancer: a virus-related cancer epidemic

Dr Shanthi Marur MD [a], Gypsyamber D'Souza PhD [b], Prof William H Westra MD [c], Prof Arlene A Forastiere MD [a]

Summary

Risk factors



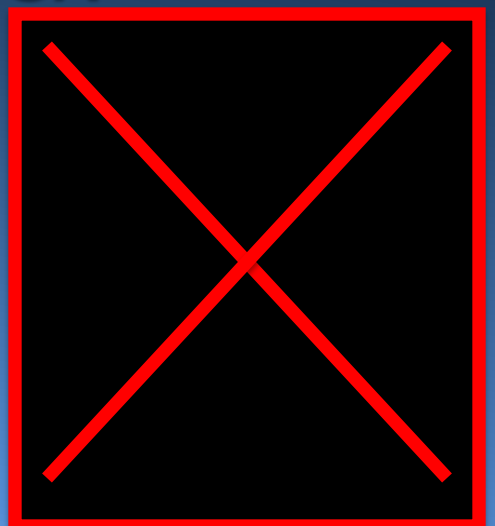
HPV +

HPV –

Gillison, M et al. J Natl Cancer Inst 2008;100: 407- 420

Risk factors – the 'good time' cancer

- Smoking- tobacco, marijuana
- Alcohol
- Viruses: HPV – orogenital sex



HPV HNC – a distinct disease entity

The molecular biology of head and neck cancer

C. René Leemans, Boudewijn J. M. Braakhuis and Ruud H. Brakenhoff

Feature	HPV-negative HNSCC	HPV-positive HNSCC
Incidence	Decreasing	Increasing
Aetiology	Smoking, excessive alcohol use	Oral sex
Age	Above 60 years	Under 60 years
Field cancerization	Yes	Unknown
TP53 mutations	Frequent	Infrequent
Predilection site	None	Oropharynx
Prognosis	Poor	Favourable

HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus.

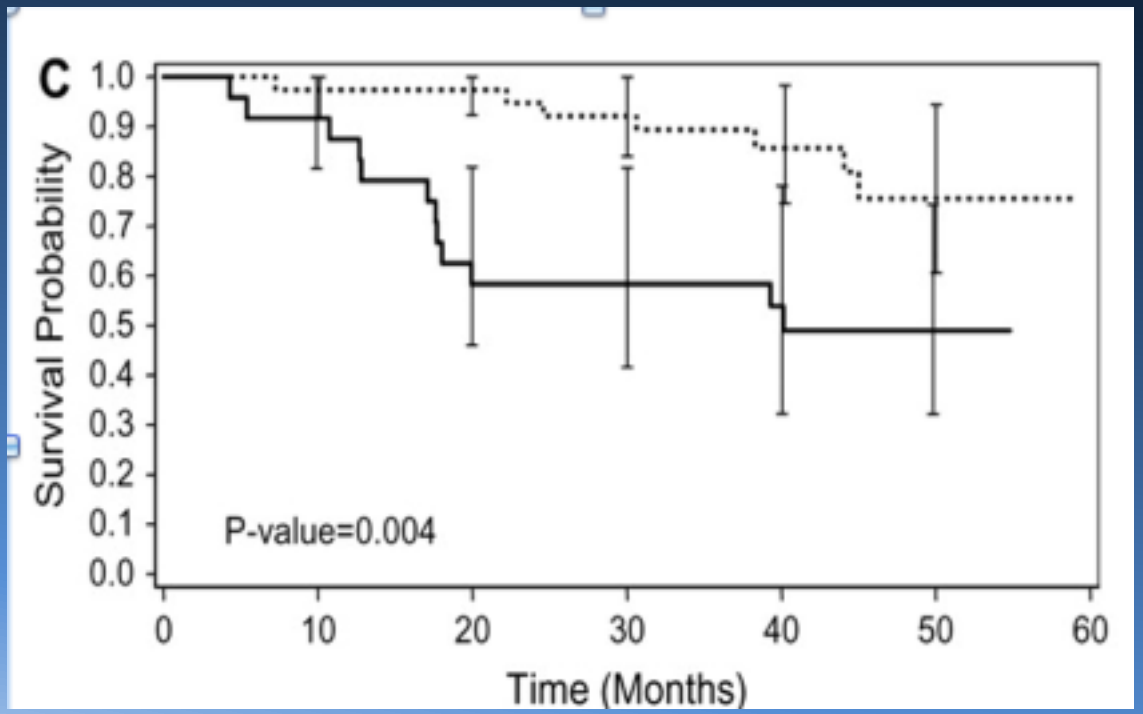
Leemans et al., Nature Reviews 2011

Good news …..

- Improved response to CRT

Metanalysis: HPV +ve 28% reduced risk of dying
49% reduced risk of local recurrence

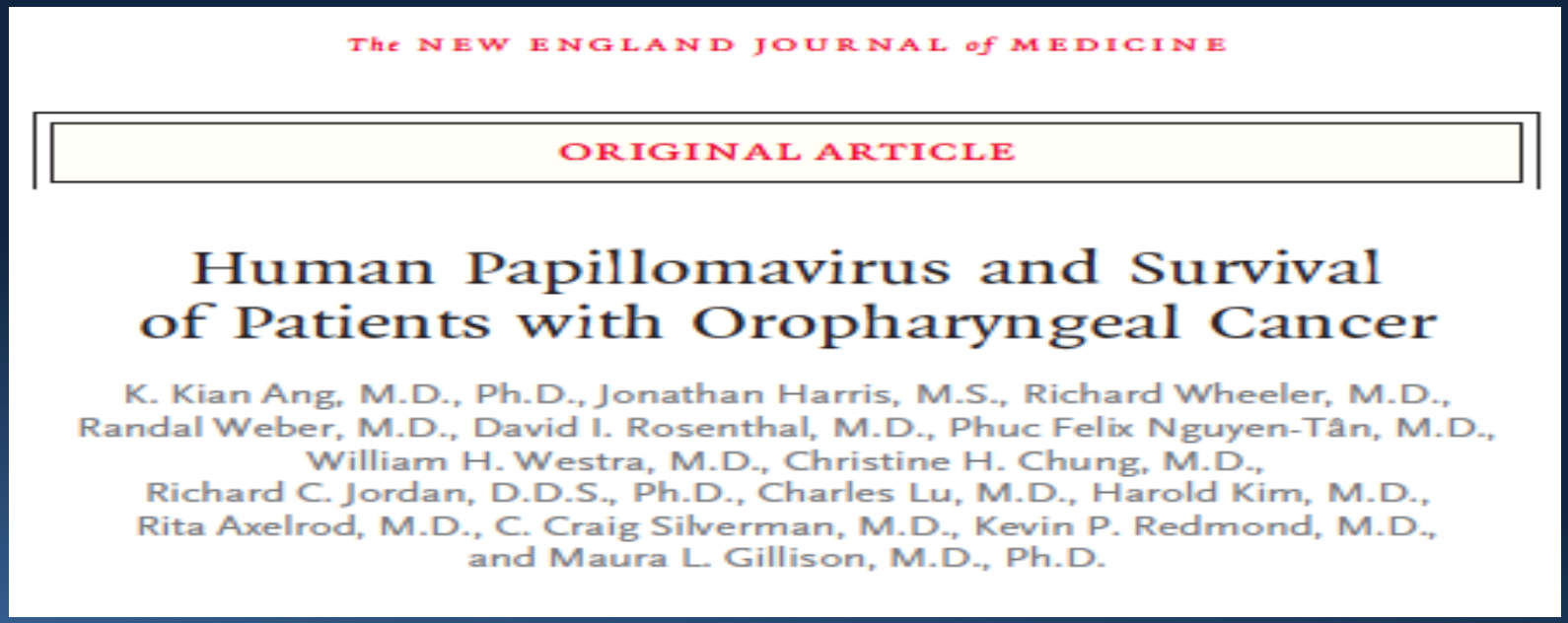
Ragin, *Int J Cancer*, 2007



2 yr OS :
95% vs 62%

Fakhry et al.
J. Natl Cancer Inst. 2008

CRT and HPV



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

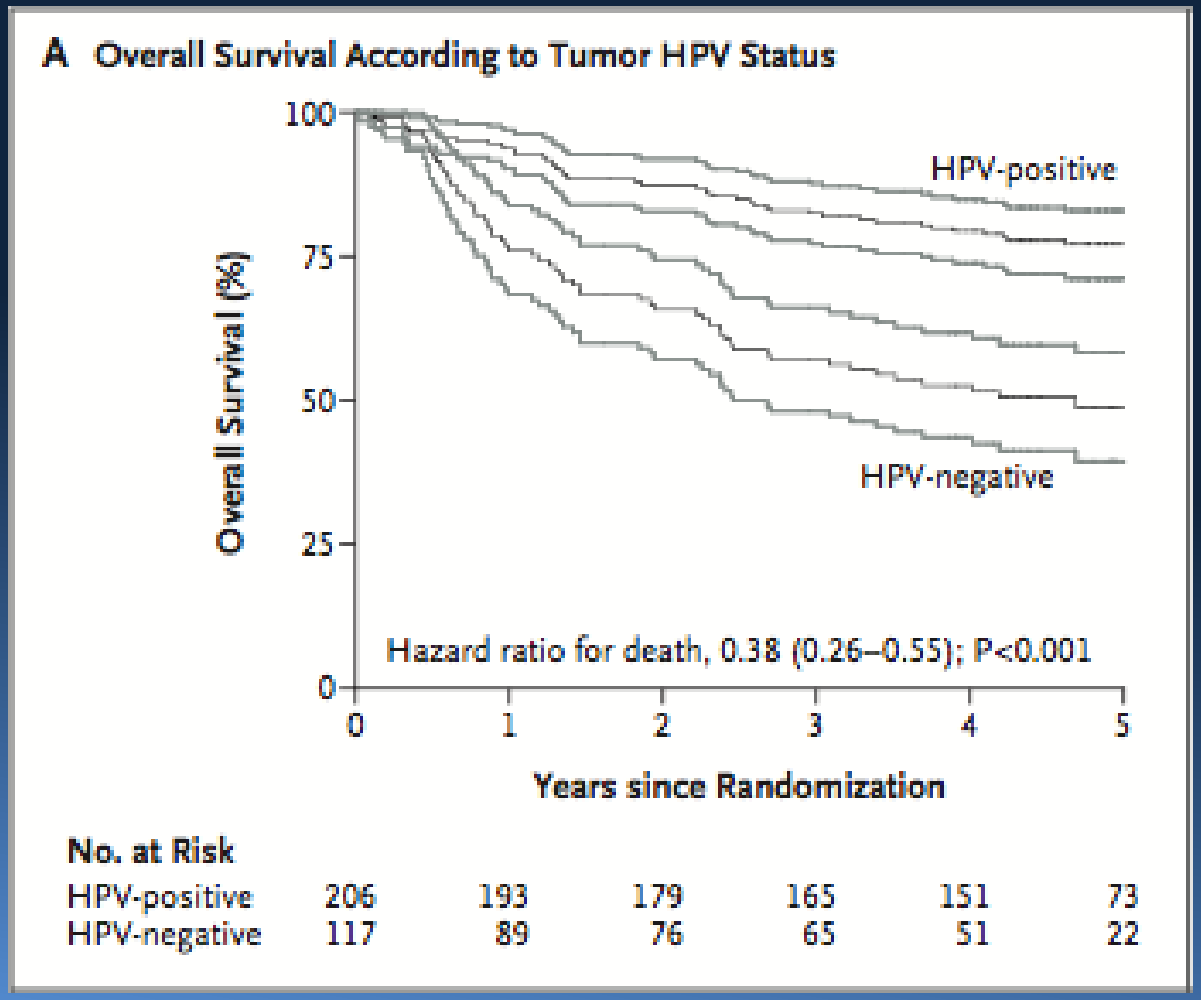
Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer

K. Kian Ang, M.D., Ph.D., Jonathan Harris, M.S., Richard Wheeler, M.D., Randal Weber, M.D., David I. Rosenthal, M.D., Phuc Felix Nguyen-Tân, M.D., William H. Westra, M.D., Christine H. Chung, M.D., Richard C. Jordan, D.D.S., Ph.D., Charles Lu, M.D., Harold Kim, M.D., Rita Axelrod, M.D., C. Craig Silverman, M.D., Kevin P. Redmond, M.D., and Maura L. Gillison, M.D., Ph.D.

- RCT: Cisplatin with standard fractionation vs accelerated fractionation
- 323 patients
- 78% Stage IV, 22% Stage III
- 81% T3 and T4, no T1

CRT and HPV

HR= 0.38
(0.26-0.55)

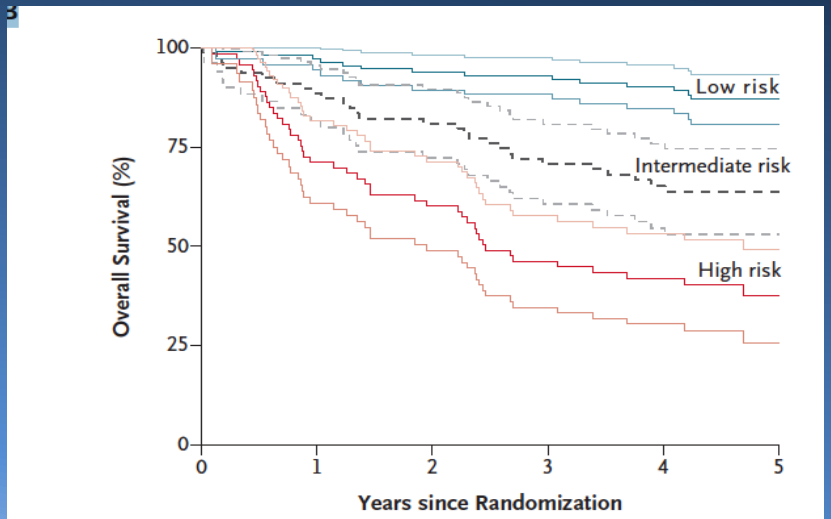


3 yr OS: HPV+ = 82.4% (95% CI, 77.2 to 87.6)
HPV- = 57.1% (95% CI, 48.1- 66.1)

Risk stratification in the new age

3 risk categories:

- Low risk: HPV+ / no or low smokers (50% patients)
  OS 3 yr 93%
- Intermediate: HPV+ + smokers+N2b-N3 and HPV- + low-no smoker + T2-3
  OS 3yr 70.8%
- High: HPV- /high smokers or low smoker+T4
  OS 3yr 46.3%



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

Ang, NEJM, 2010

The Laryngoscope

TRIOLOGICAL SOCIETY CANDIDATE THESIS

Prognostic Factors and Survival Unique to Surgically Treated p16+ Oropharyngeal Cancer

Bruce H. Haughey, MBChB, FRACS, FACS; Parul Sinha, MBBS, MS

TABLE IX.

Multivariate Cox Proportional Hazard Ratios for Disease-Free Survival in Models Based on Clinical T Stage.

Variables	HR (95% CI)	*P* Value
cT stage (T3-4 vs. T1-2)	3.03 (1.10-8.34)	.032
Smoker (ever vs. never)	4.19 (1.22-14.42)	.023
No. of nodes (0-1 vs. ≥2)	6.36 (1.72-23.47)	.005
No. of nodes (1-2 vs. ≥3)	7.06 (1.97-25.27)	.003*
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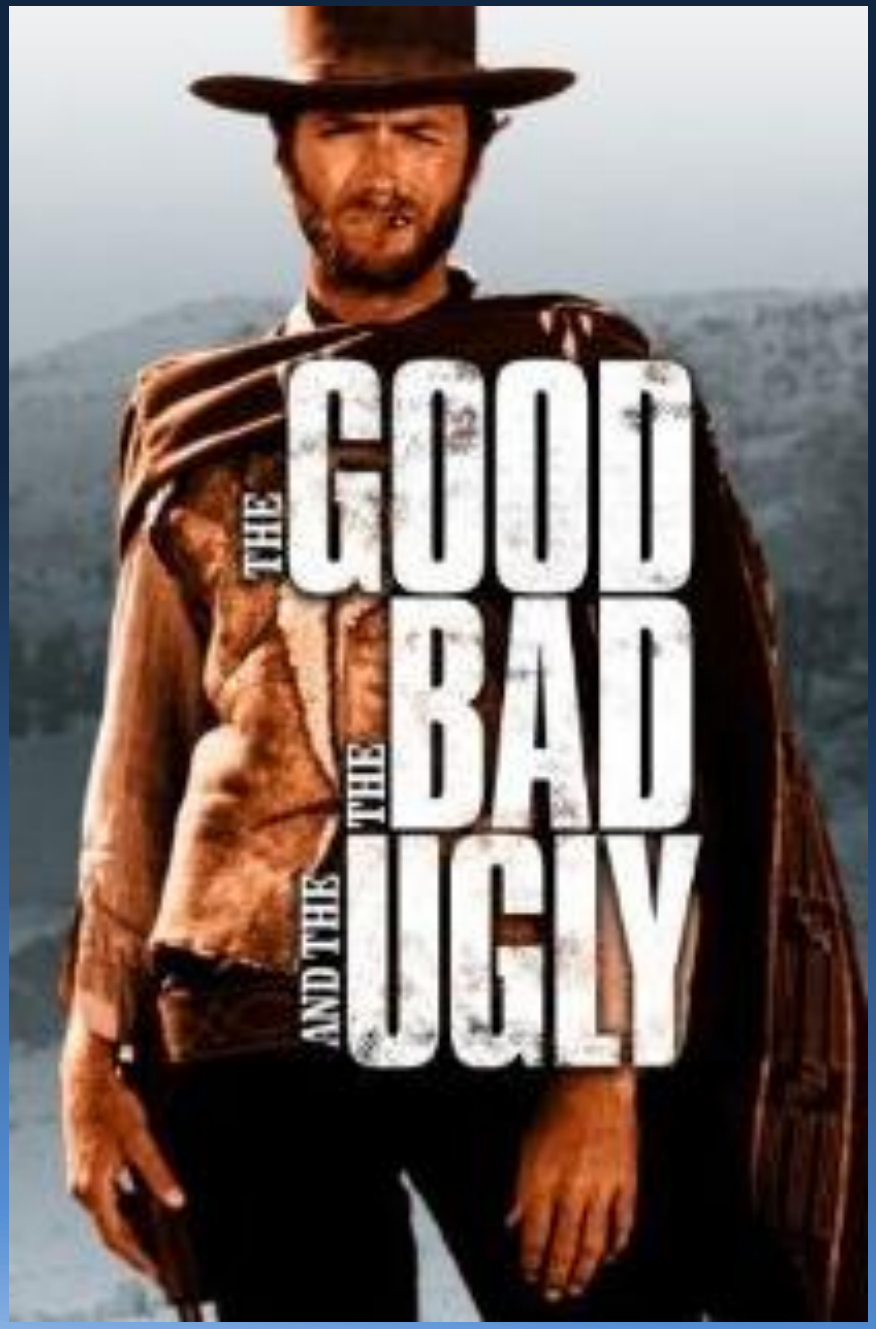
*Significance observed in models that excluded patients with no involved neck nodes (n = 153).

†Lost its significance in models with T stage.

HR = hazard ratio; CI = confidence interval; cT = clinical T stage; pN = pathological N stage, Rx = Therapy.

	3yr OS
Low	93%
Intermediate	70.8%
High	46.3%



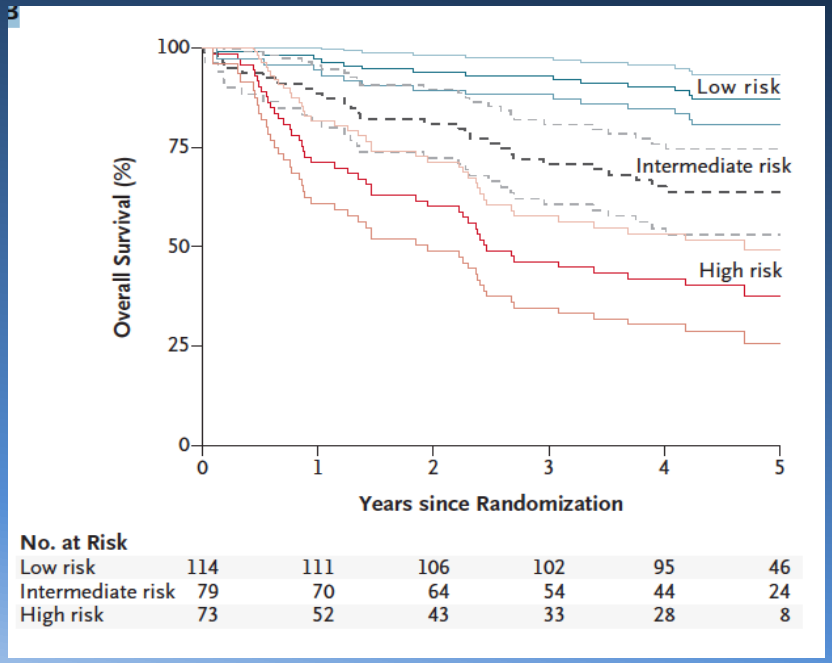
TNM 8th edition

Changing world and changing treatment paradigms

Excellent survival for low-risk OPC

3 risk categories:

- **Low risk: HPV+ / no or low smokers (50% patients)**
  OS 3 yr 93%
- Intermediate: HPV+ + smokers+N2b-N3 and
  HPV- + low-no smoker + T2-3
  OS 3yr 70.8%
- High: HPV- /high smokers or low smoker+T4
  OS 3yr 46.3%



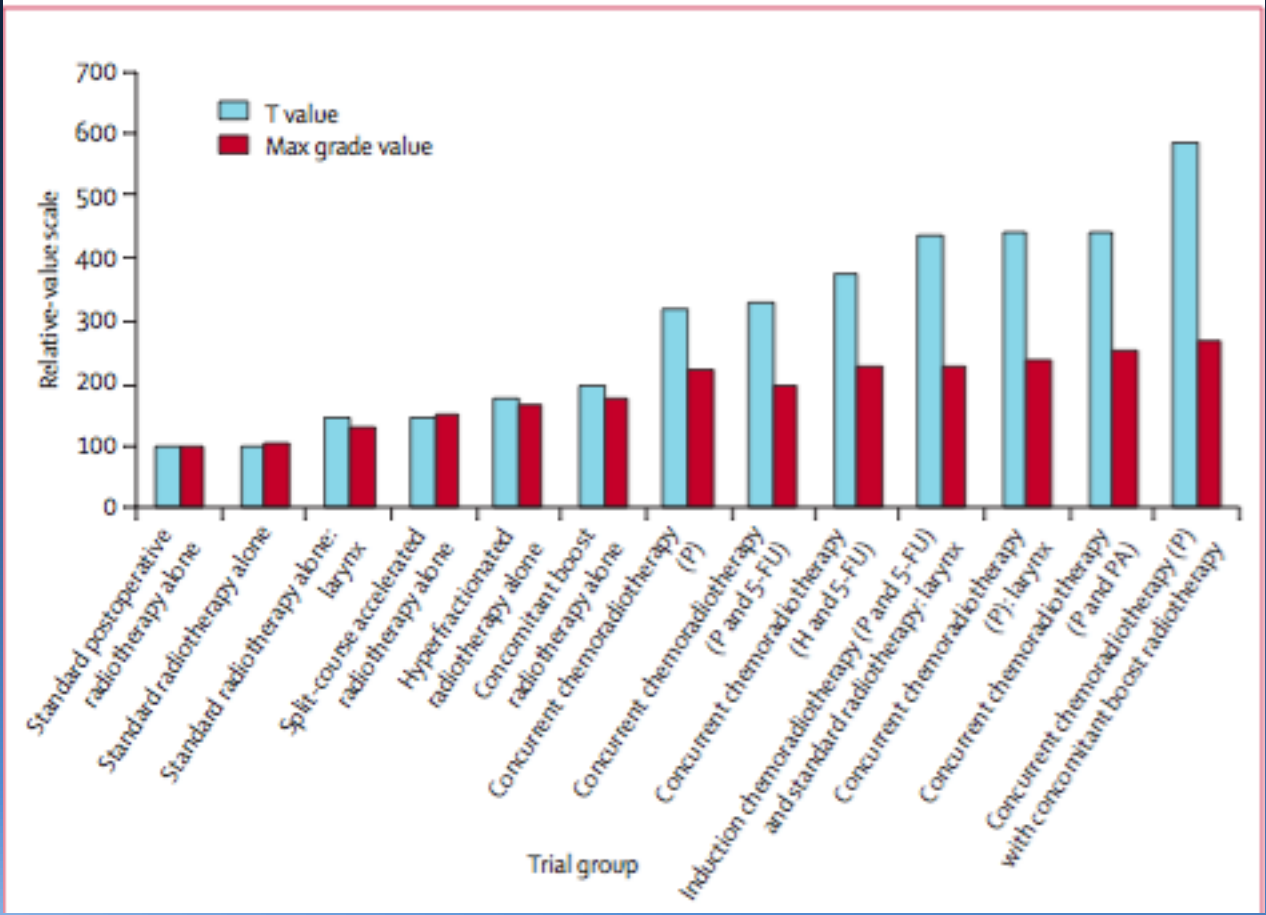
Ang, NEJM, 2010

Bad news


FIRST THE GOOD NEWS... TECHNICALLY THE OPERATION WAS A COMPLETE SUCCESS.....

CRT - toxicity

Higher survival rates in younger patients = living longer with morbidity



CRT - toxicity

Higher survival rates in younger patients = living longer with morbidity

Acute toxicity

- Grade 3-5 toxicity
  - Severe, life–threatening
- CRT: 202 events in 109 living pts =185%
- Double those treated with RT alone

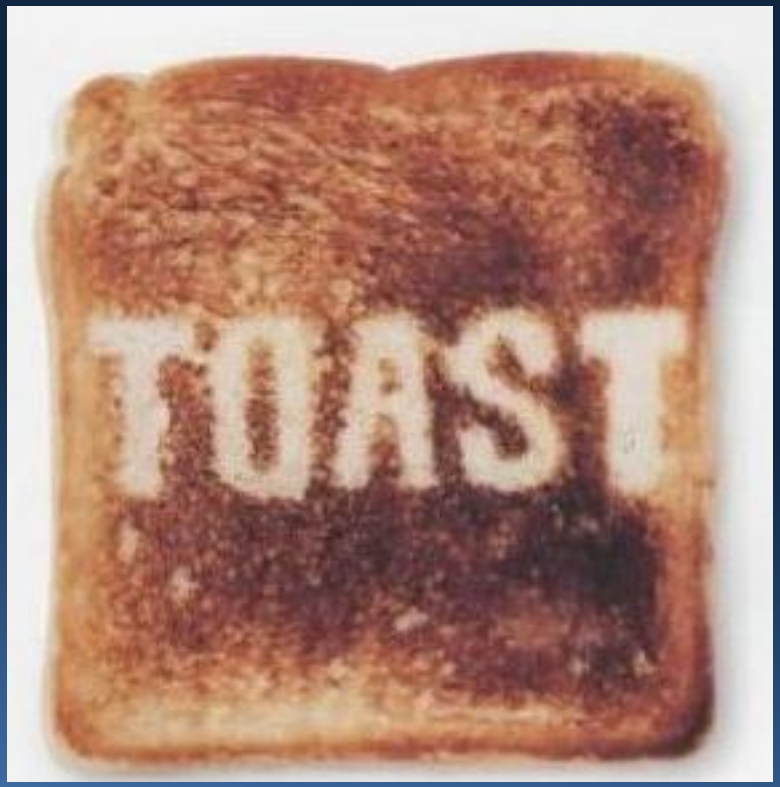
Calais, *JNCI,* 1999

Late toxicity- 5 yrs

- Grade 3-5 toxicity
  - Severe, life–threatening
- 66 % of 27 living pts with CRT
  - 56% swallowing problems
  - 56% xerostomia

Denis, *JCO*, 2004

Are we over-treating?



Are there any alternative treatment regimens with similar survival but less toxicity?

De-intensification

- Remove chemotherapy agent
- Do surgery
- Do surgery and reduce RT
- Less toxic chemotherapy agent

De-intensification

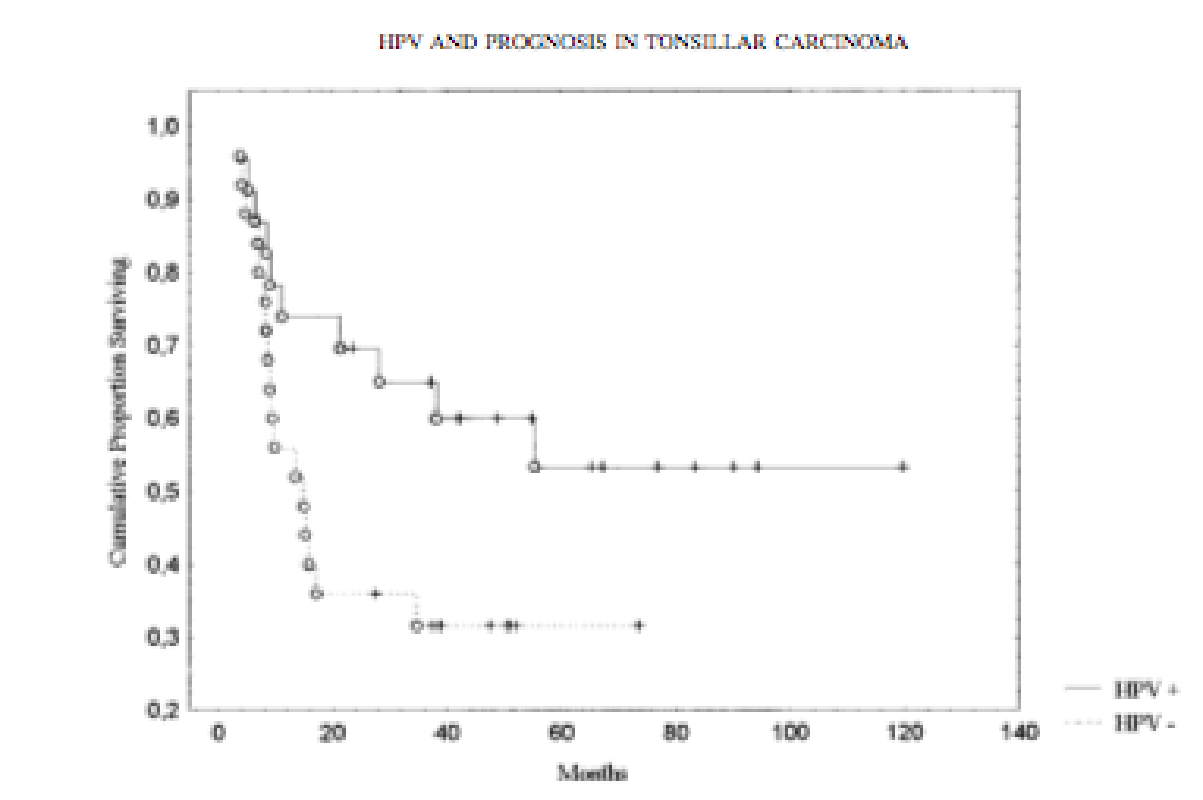
- Remove chemotherapy agent
- Do surgery
- Do surgery and reduce RT
- Less toxic chemotherapy agent

Increased radio-sensitivity

- Some early studies suggest that HPV+ve patients are more radiosensitive than HPV-ve patients (Mellin, *Int J Cancer*, 2000)

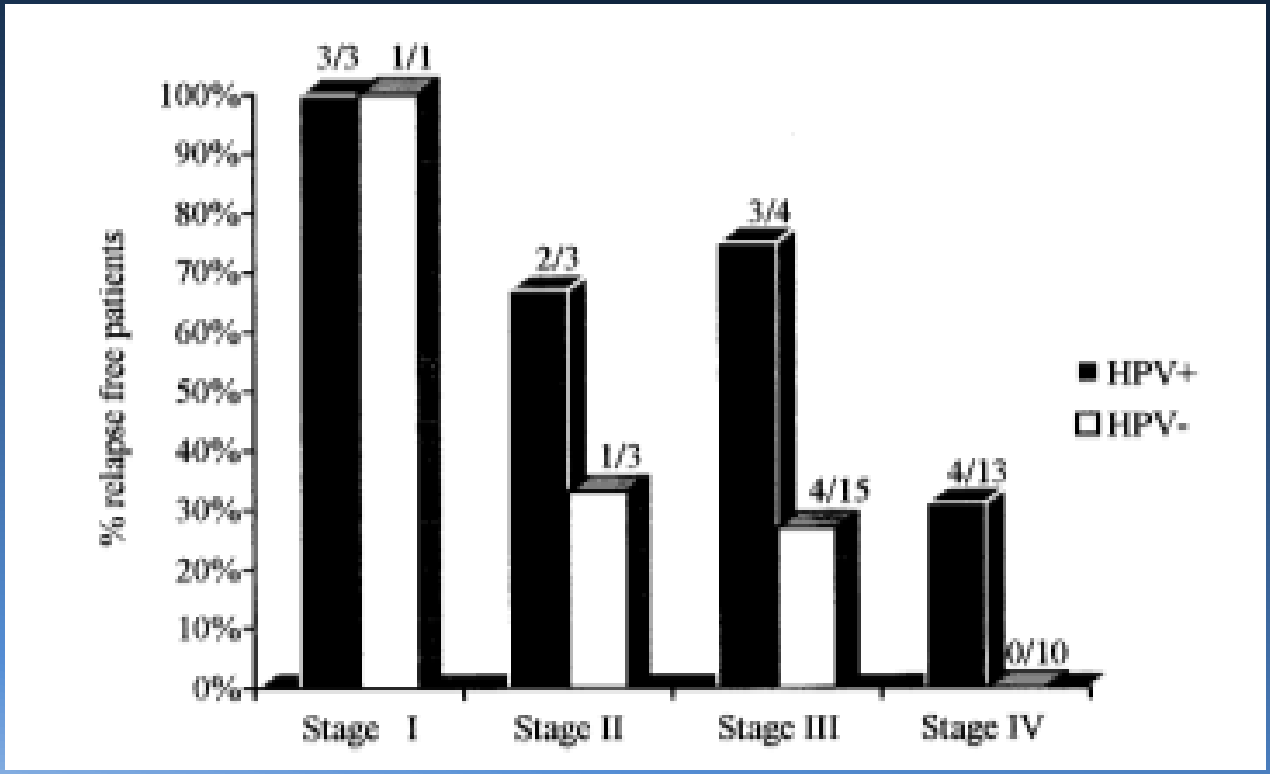
3 yr
cause specific
rate

= 65.3% vs
31.5%

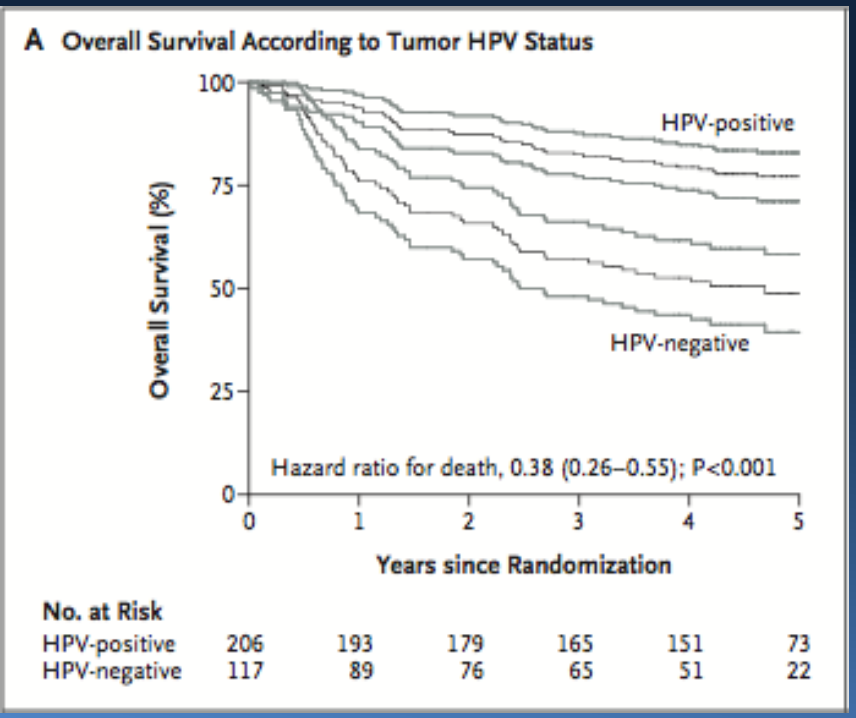


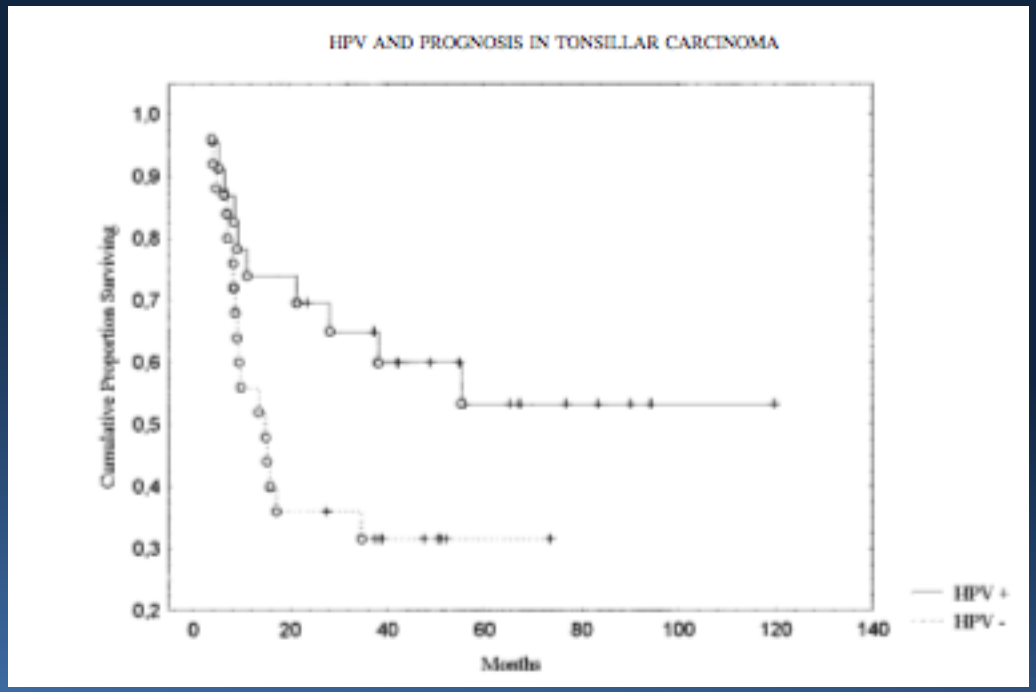
Increased radio-sensitivity

- Effect of HPV-related radiosensitivity only evident in stage II-IV (Mellin, *Int J Cancer*, 2000)



Increased radio-sensitivity





3 yr cause specific rate

65.3% vs 31.5%

82.4% vs 57.1%

Contents lists available at ScienceDirect

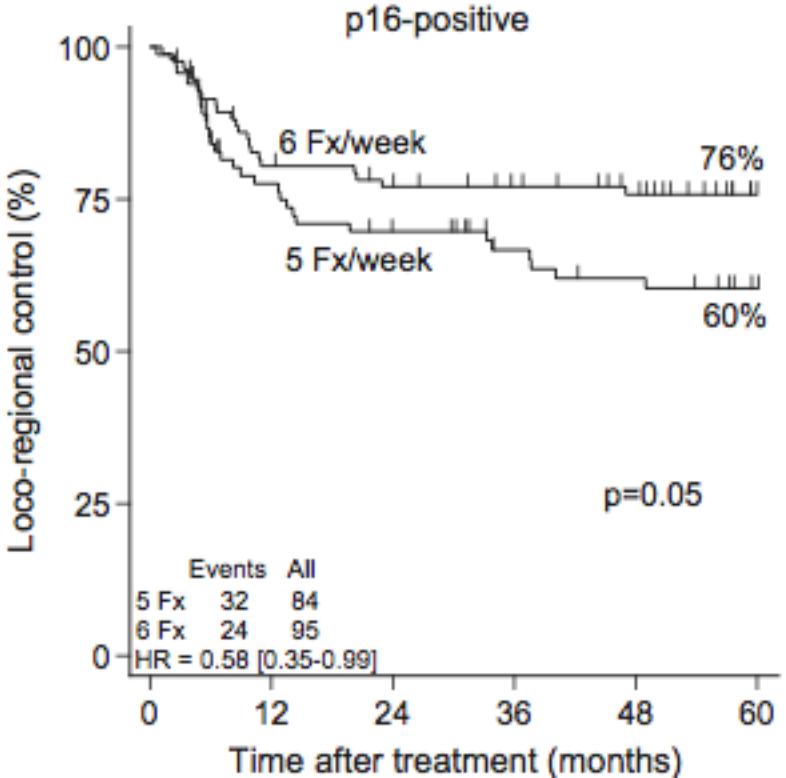
Radiotherapy and Oncology

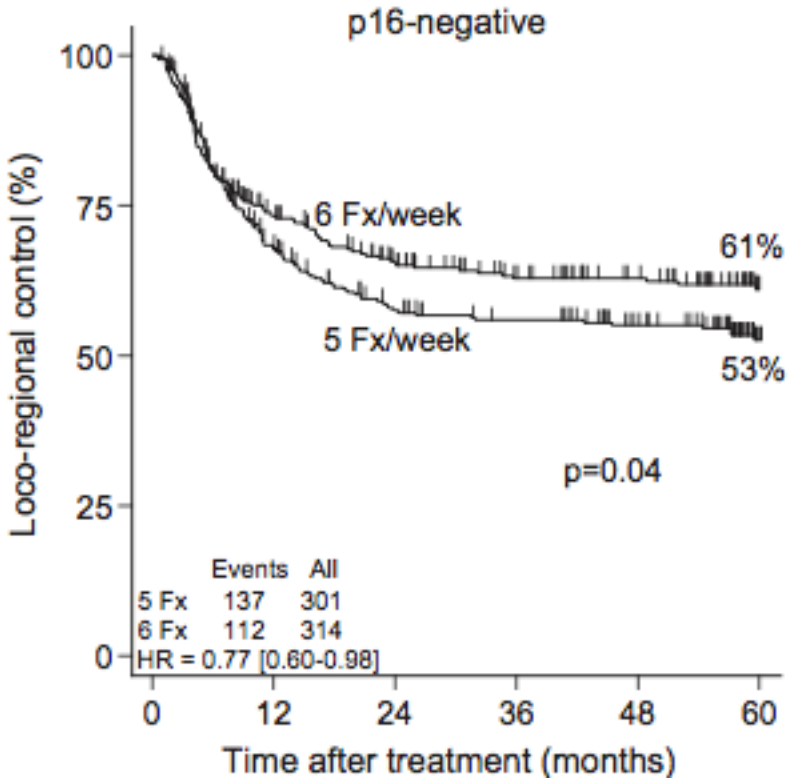
journal homepage: www.thegreenjournal.com

Phase III randomised trial

The influence of HPV-associated p16-expression on accelerated fractionated radiotherapy in head and neck cancer: Evaluation of the randomised DAHANCA 6&7 trial

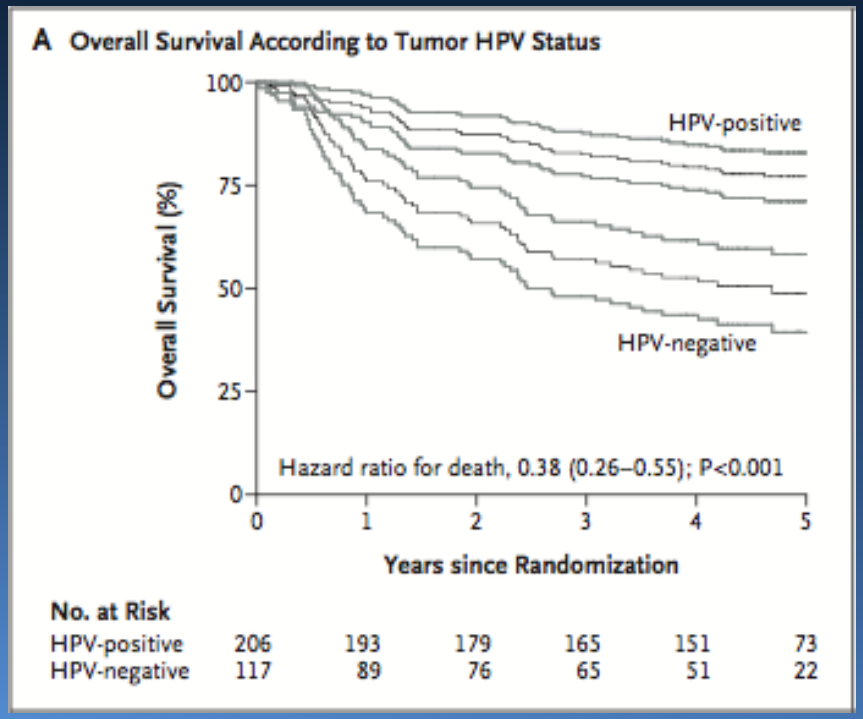
Pernille Lassen [a,*], Jesper G. Eriksen [a], Annelise Krogdahl [b], Marianne Hamilton Therkildsen [c], Benedicte P. Ulhøi [d], Marie Overgaard [e], Lena Specht [f], Elo Andersen [g], Jørgen Johansen [h], Lisbeth J. Andersen [i], Cai Grau [e], Jens Overgaard [a], On behalf of the Danish Head and Neck Cancer Group (DAHANCA)





Increased radio-sensitivity

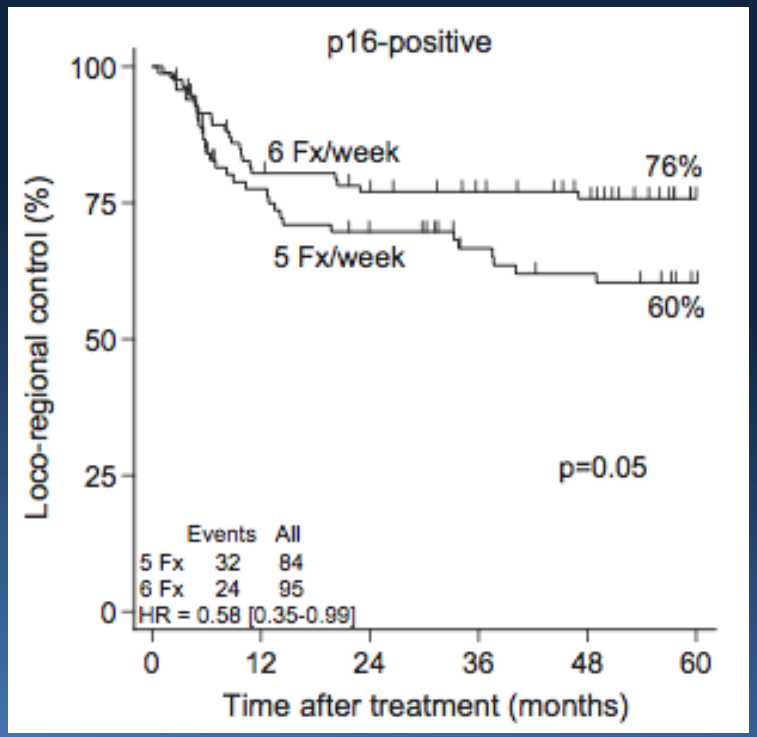
RT 6Fx vs 5Fx



3 yr cause specific rate

78% vs 70%

CRT



82.4%

CRT vs RT for HPV+ OPC

		Ang	Mellin	Lassen
Treatment		CRT	RT	Accelerated RT
RT dose		70G	64Gy	66-68Gy in 6F/wk
Stage III/IV		100%	80%	60%
3 yr survival		**82%**	**66%**	**78%**

Ang, 2010; Mellin, 2000

Risk of Distant Metastases in HPV+

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

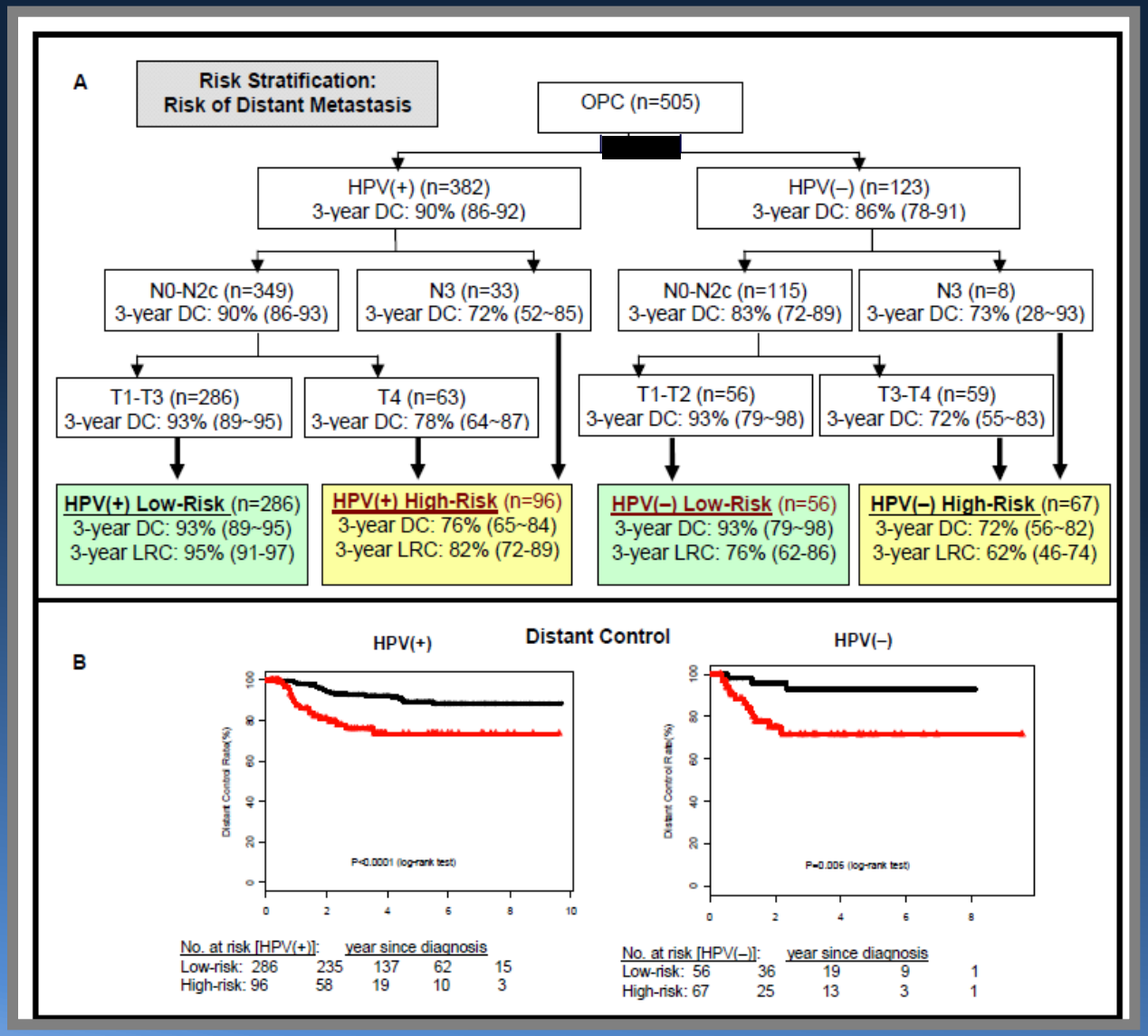
Deintensification Candidate Subgroups in Human Papillomavirus–Related Oropharyngeal Cancer According to Minimal Risk of Distant Metastasis

Brian O'Sullivan, Shao Hui Huang, Lillian L. Siu, John Waldron, Helen Zhao, Bayardo Perez-Ordonez, Ilan Weinreb, John Kim, Jolie Ringash, Andrew Bayley, Laura A. Dawson, Andrew Hope, John Cho, Jonathan Irish, Ralph Gilbert, Patrick Gullane, Angela Hui, Fei-Fei Liu, Eric Chen, and Wei Xu

Result – VII: DM Risk Stratification

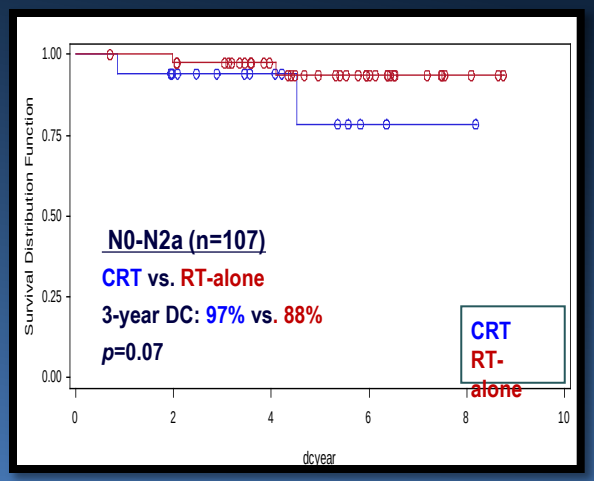
PMH 2001-2009:
- HPV(+): n=382
- HPV(-): n=123

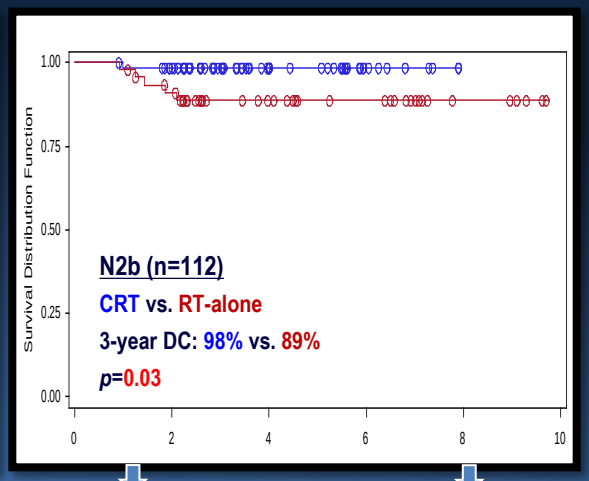
HPV(+) Low-risk:
- RT-alone: 150
- CRT: 136

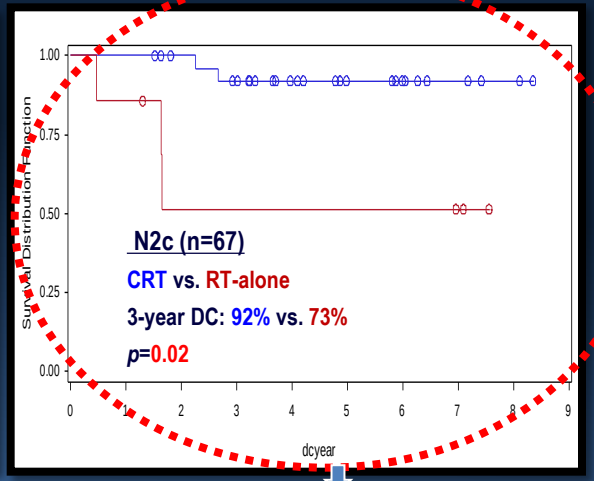


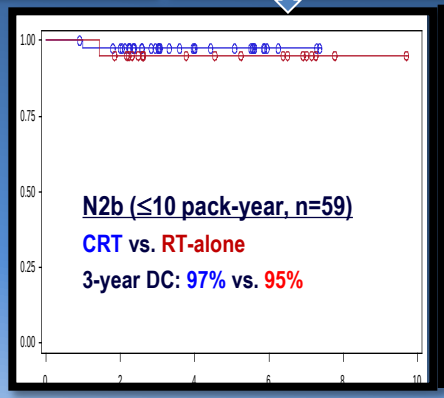
HPV(+) Higher Risk of DM Subgroup

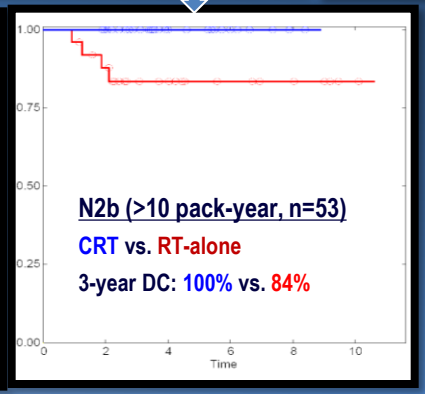
- Patients treated with RT alone had higher distant mets than those treated with CRT if
  - N3
  - N2c
  - N2b smokers >10 pack

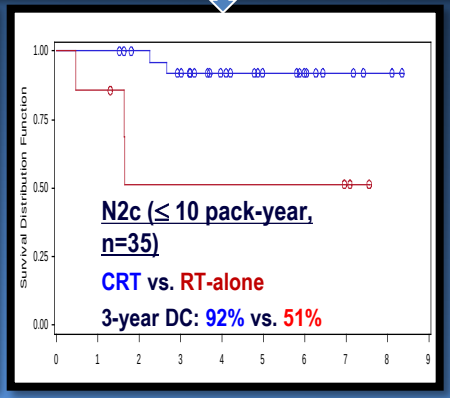












O'Sullivan 2013

- Beware de-intensifying treatment by removing chemotherapy in HPV+ patients with:
  - T4 disease,
  - N2c-N3 disease, and
  - N2b heavy smokers
- Can we decrease RT dose but keep Chemo?
  - Need to be cautious since no evidence

De-intensification

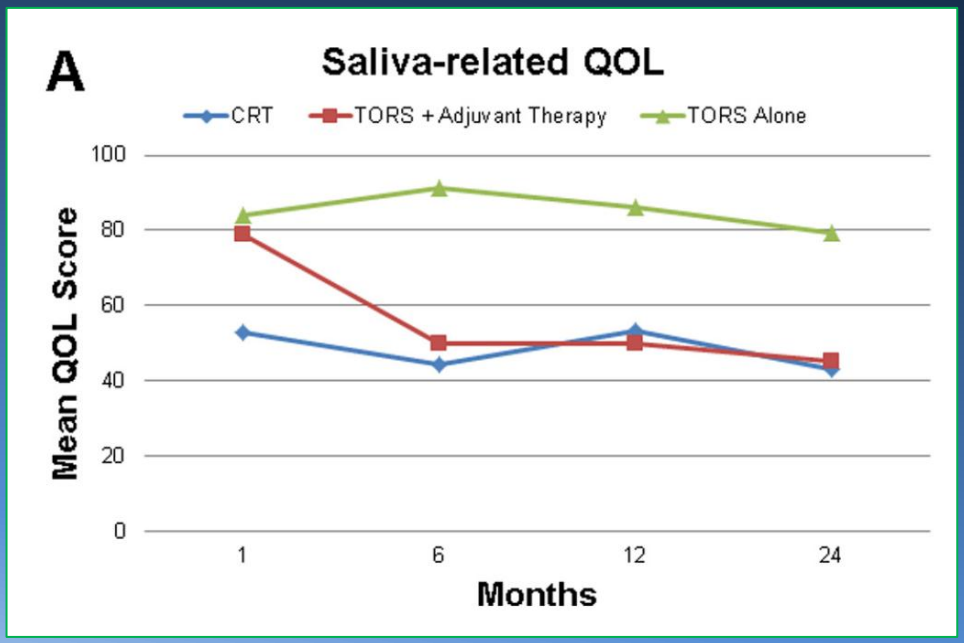
- Remove chemotherapy agent
- Do surgery
- Do surgery and reduce RT
- Less toxic chemotherapy agent

Best outcome for surgery is when done alone..

Oncologic outcomes and patient-reported quality of life in patients with oropharyngeal squamous cell carcinoma treated with definitive transoral robotic surgery versus definitive chemoradiation

D.C. Ling MD [a], B.V. Chapman MD [a], J. Kim MD [b], G.W. Choby MD [b], P. Kabolizadeh MD, PhD [a], D.A. Clump MD, PhD [a], R.L. Ferris MD, PhD, FACS [b], S. Kim MD [b], S. Beriwal MD [a], D.E. Heron MD, FACRO, FACR [a,b], U. Duvvuri MD, PhD [b,*]

[a] *Department of Radiation Oncology, University of Pittsburgh Cancer Institute, Pittsburgh, PA, United States*
[b] *Department of Otolaryngology, University of Pittsburgh Medical Center, Pittsburgh, PA, United States*



TORS only: 40
TORS+RT: 15
TORS + CRT: 37

University of Washington QoL: 1, 6, 12, and 24 months

Prognostic Factors and Survival Unique to Surgically Treated p16+ Oropharyngeal Cancer

Bruce H. Haughey, MBChB, FRACS, FACS; Parul Sinha, MBBS, MS

However Adjuvant therapy is Highly Effective

Multivariate Cox Proportional Hazard Ratios for Disease-Free Survival in Models Based on Clinical T Stage.

Variables	HR (95% CI)	*P* Value
cT stage (T3-4 vs. T1-2)	3.03 (1.10-8.34)	.032
Smoker (ever vs. never)	4.19 (1.22-14.42)	.023
No. of nodes (0-1 vs. ≥2)	6.36 (1.72-23.47)	.005
No. of nodes (1-2 vs. ≥3)	7.06 (1.97-25.27)	.003*
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*Significance observed in models that excluded patients with no involved neck nodes (n = 153).

†Lost its significance in models with T stage.

HR = hazard ratio; CI = confidence interval; cT = clinical T stage; pN = pathological N stage, Rx = Therapy.

TRANSORAL ROBOTIC SURGERY AND HUMAN PAPILLOMAVIRUS STATUS: ONCOLOGIC RESULTS

Marc A. Cohen, MD,[1] Gregory S. Weinstein, MD,[1] Bert W. O'Malley, Jr, MD,[1] Michael Feldman, MD,[2] Harry Quon, MD[1,3]

[1] Department of Otorhinolaryngology–Head and Neck Surgery, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania. E-mail: gregory.weinstein@uphs.upenn.edu
[2] Department of Pathology, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania
[3] Department of Radiation Oncology, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania

Accepted 27 April 2010
Published online 6 December 2010 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/hed.21500

50 patients → 74% HPV+

83% of HPV+ pts had nodes, 44% had ECS

27% received post op RT

57% received post op CRT

Selection of patients suitable for TOLS/TORS

The Laryngoscope

TRIOLOGICAL SOCIETY CANDIDATE THESIS

Prognostic Factors and Survival Unique to Surgically Treated p16+ Oropharyngeal Cancer

Bruce H. Haughey, MBChB, FRACS, FACS; Parul Sinha, MBBS, MS

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*Significance observed in models that excluded patients with no involved neck nodes (n = 153).

†Lost its significance in models with T stage.

HR = hazard ratio; CI = confidence interval; cT = clinical T stage; pN = pathological N stage, Rx = Therapy.

Pre-treatment selection of cases

- Proportion of patients upstaged Nodal stage to N2b+ on surgery → need RT or CRT

Clinical stage	Upstaged	Upstaged to N2b+
N0	6%	0
N1	50%	30%
N2a	25%	25%

N0 most likely to avoid RT or CRT

Pre-treatment selection of cases

- Proportion of patients with nodal disease who have ECS→ need RT or CRT

Clinical stage	% ECS
N0	0%
N1	29%
N2	55%
N3	60%

Sinha, Cancer, 2012

N0 most likely to avoid RT or CRT

Pre-treatment selection of cases

- Patients with positive margins or >1 node likely to have RT/ CRT

Stage	% pos margins	% >1 node	% ECS	% soft tiss mets	% RT only	% CRT
Overall	7	56	80	52	43	40
T1	4	52	77	58	48	31
T2	7	58	76	55	47	42
T3	12	58	96	65	31	46
T4	14	64	92	67	29	64

T1 and T2 are most likely to avoid RT or CRT

Selection of cases most eligible for TORS/TOLS

Those most likely to avoid RT or CRT –
T1N0, T2N0, ?T1N1

Proportion of eligible patients who **underwent surgery** in hands of an **enthusiast**

Stage	% of total cohort
T1N0	2%
T2N0	4%
T1N1	8%
T2N1	5%

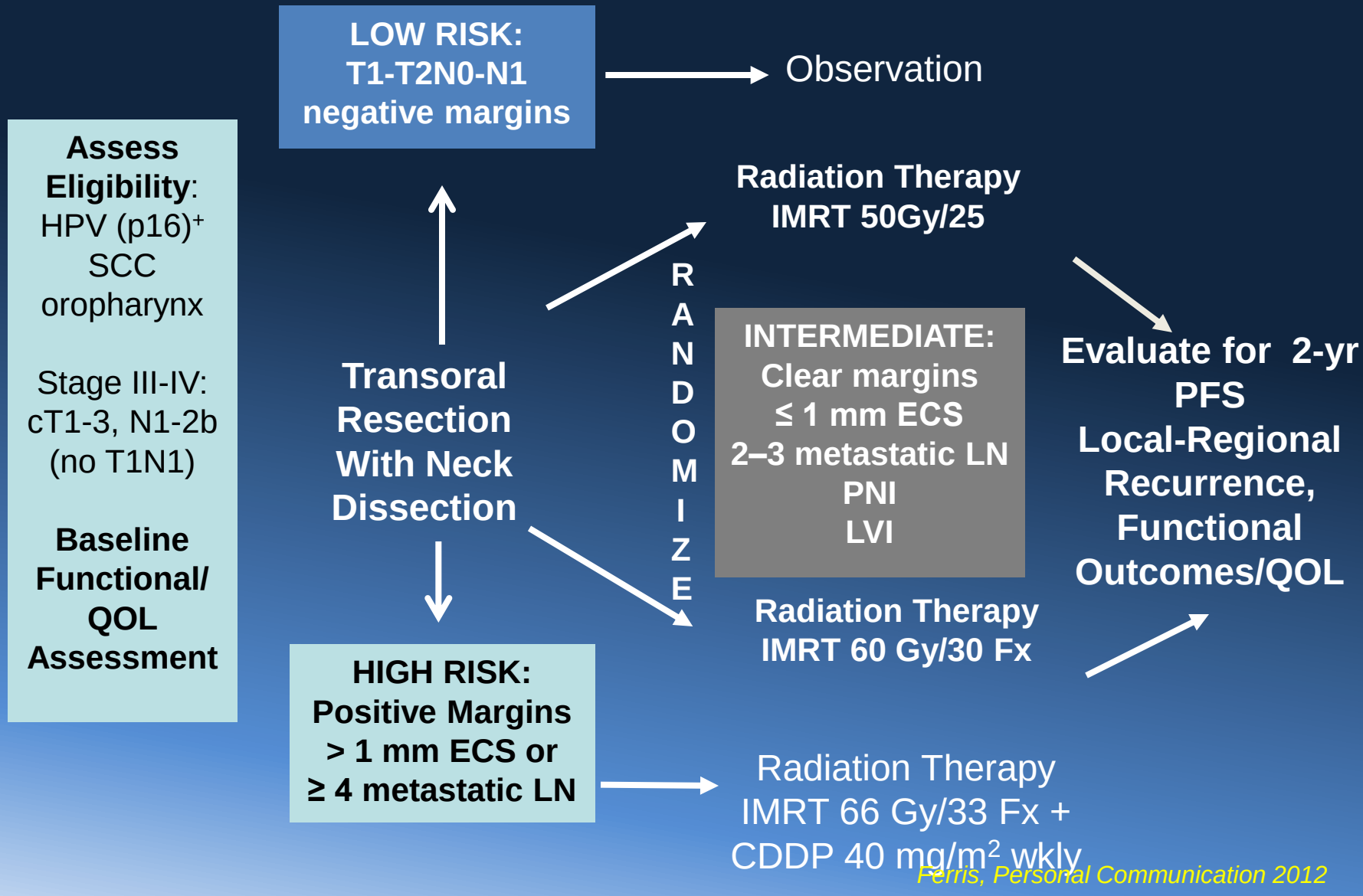
TOLS/TORS for low-risk HPV+ OPC

- Distant mets higher if treated with RT alone compared to CRT in N2b smokers, N2c and N3 disease
- Adjuvant treatment (RT/CRT) improves OS, DFS in TORS (Haughey 2012)
  - Removal of RT/CRT may be dangerous
- 40% get triple therapy (surgery+RT+chemo)
- Only 17% are spared adjuvant treatment
  - Need to identify them eg T1NO, T2N0

De-intensification

- Remove chemotherapy agent
- Do surgery
- Do surgery and reduce RT
- Less toxic chemotherapy agent

Proposed ECOG 3311 P16+ Trial – Low Risk OPSCC: Personalized Adjuvant Therapy Based on Pathologic Staging of Surgically Excised HPV+ Oropharynx Cancer



Ferris, Personal Communication 2012

WCTU
WALES CANCER TRIALS UNIT
UNED YMCHWIL CANSER CYMRU

Post-oper**a**tive adjuvant **t**reatment for **H**PV-positive tum**o**ur**s**

PATHOS

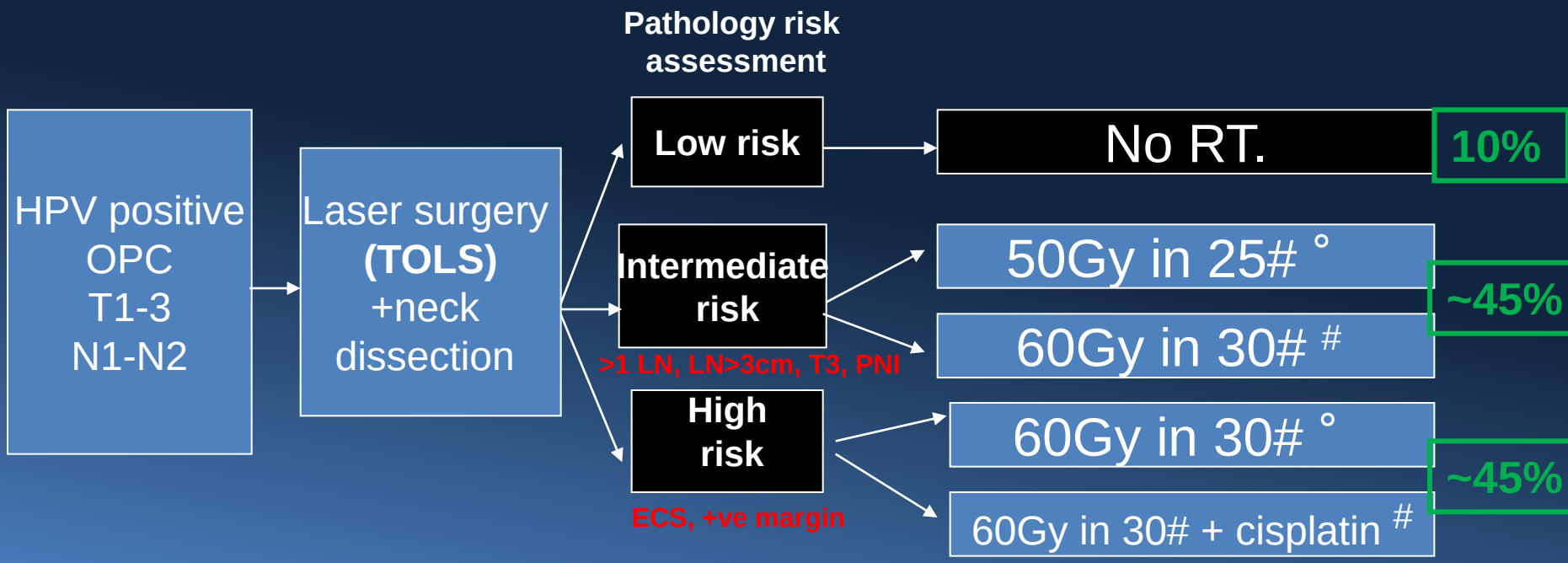
Mererid Evans, Terry Jones, Max Robinson, Chris Hurt
Joanne Patterson, Kate Hutcheson

H&N CSG 1st March 2013

PATHOS trial

- Randomized, multicentre, phase II/III

° Test arm, #comparator



- Endpoints: phase II – swallowing function; phase III – survival

De-intensification

- Remove chemotherapy agent
- Do surgery
- Do surgery and reduce RT
- Less toxic chemotherapy agent

De-ESCALaTE HPV

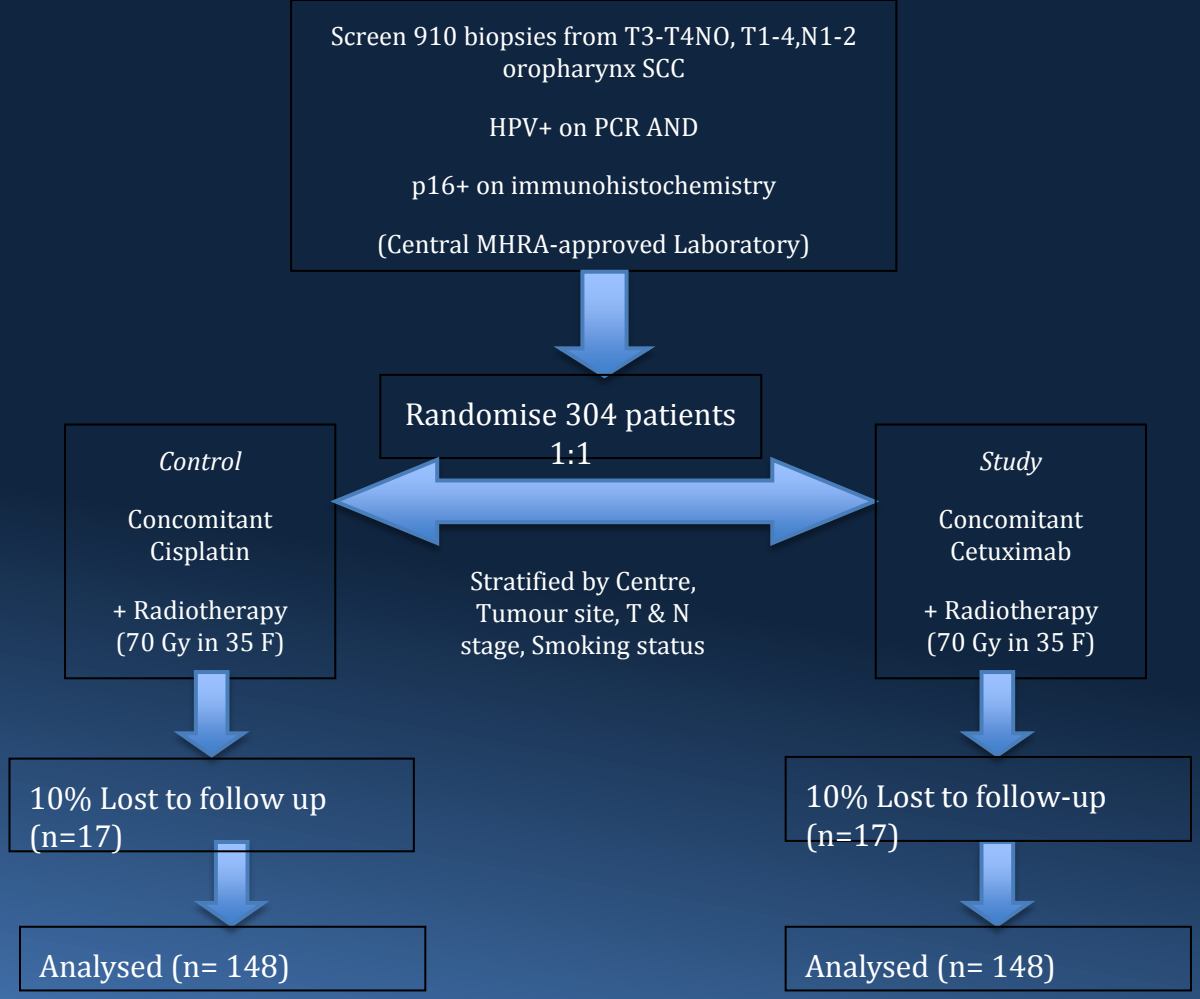
Determination of EGFR-inhibitor versus Standard CRT early And Late Toxicity Events in HPV – positive Oropharyngeal SCC

De-ESCALaTE HPV

CI: Hisham Mehanna

TEAM

- Chief Investigator: Hisham Mehanna
- CTU Lead: Janet Dunn
- CTU Trial Coordinator: Tessa Fulton-Lieuw
- Trial Statistician: Chris McConkey
- Nursing Advisor: Annie Young
- Pharmacy Advisor: Mojid Khan
- Translational Science Advisor: Catharine West
- Health Economics Advisor: Alastair Gray
- RT QA Lead: Chris Nutting
- RT Advisors: Mererid Evans & Andrew Hartley
- RT QA Physics Advisor: Margaret Bidmead
- HPV Diagnostics Advisor: Max Robinson
- Medical Oncology Lead: Martin Forster
- Oncology Advisor: Chris Boshoff
- RTTQA Co-ordinator: Liz Miles



Follow-up: 2 years

***Primary outcomes*:**

Severe Toxicity (Acute and Late) : using CTCAE grading, including *skin rashes*, mucositis

Secondary outcomes:

Health economics using EQ-5D, Early toxicity, Quality of life: using EORTC general and head neck specific modules, Swallowing: using MDADI questionnaire and gastrostomy - dependency rates, Mortality (cause of death), disease free survival, recurrence, metastases.

RTOG 1016: A Randomized Phase III Trial of Chemoradiotherapy With Cisplatinum or Cetuximab in p16 Positive Oropharynx Cancer

Stratify: HPV, Smoking, Stage

ELIGIBILITY

Stage

III, IVA, B

Resectable

P16+

Oropharynx

Cancer

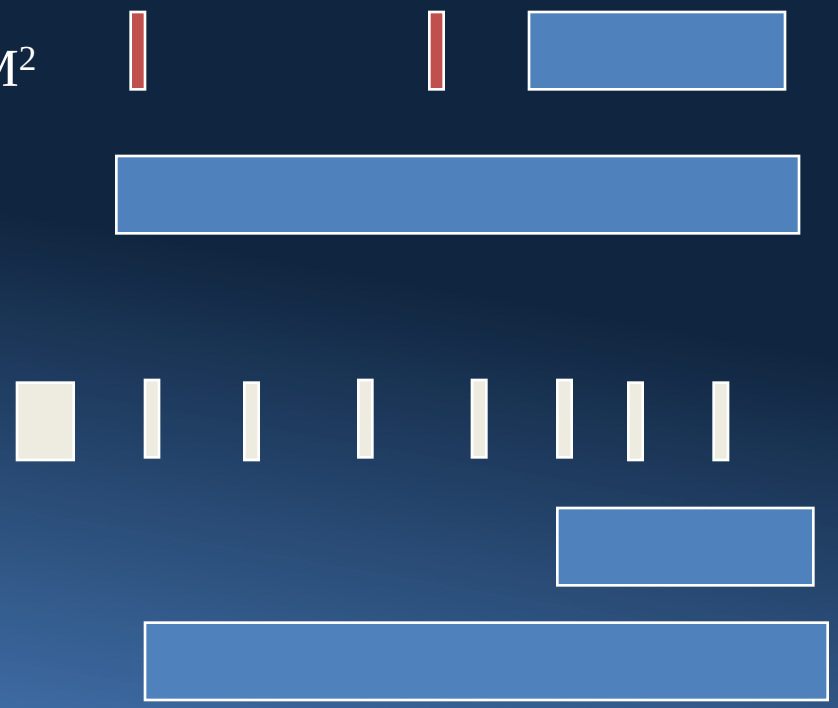
RANDOMIZE

P - 100 mg/M^2

XRT

C225 400/250 mg

XRT



70 Gy in 35 Fxs

LOW and INT RISK OPC

CI: Trotti, Gillison

Low

3yr OS

ONLY 20% OPSCC patients in most countries Outside North America

Interm… 60%

…gh 46.3% 20%

Vast majority of patients in most countries Outside North America

Aim of management: better survival → Need to escalate treatment

Failure mainly locoregional

- Data from RTOG 0129.
- Differences in survival between the low, intermediate and high-risk groups:
  - mainly due to differences in 3 years LRC
  - Low risk: 90.4%,
  - Intermediate risk: 80.9%
  - High risk: 57.3%

Options for improving locoregional control

- Add induction chemotherapy
- Add more RT – intensification of RT?
- Add surgery
- Other regimens?

Comparing **A**lternative treatment **Re**gimens for intermediate and high risk oropharyngeal cancer
CompARe

CI: Prof. Hisham Mehanna

University of Birmingham

Chief investigator:
Hisham Mehanna

National leads:
Arm 1: Mehmet Sen
Arm2: John Chester
Arm 3: Paul Sanghera
Arm 4: Vin Paleri
Arm 5: Martin Forster

RT QA:
Andrew Hartley (lead)
Hoda Booz
Andrew Chan
Tom Roques

CTU:
Claire Gaunt
Charlotte Firth

RTQA group: Liz Miles
Huiqi Yang Rada Zotova

Path: Max Robinson

Surgery QA: Jim McCaul

SAEs:
Bernie Foran – RT
Hoda Booz- RT
Anthony Kong - Chemo
Kevin Harrington - chemo
Statistics:
Cindy Billingham
Piers Gaunt

Deescalate liaison:
Janet Dunn

Health economics:
Andrew Sutton

Qualitative study:
Jenny Donovan
Marcus Jepson

CompARE

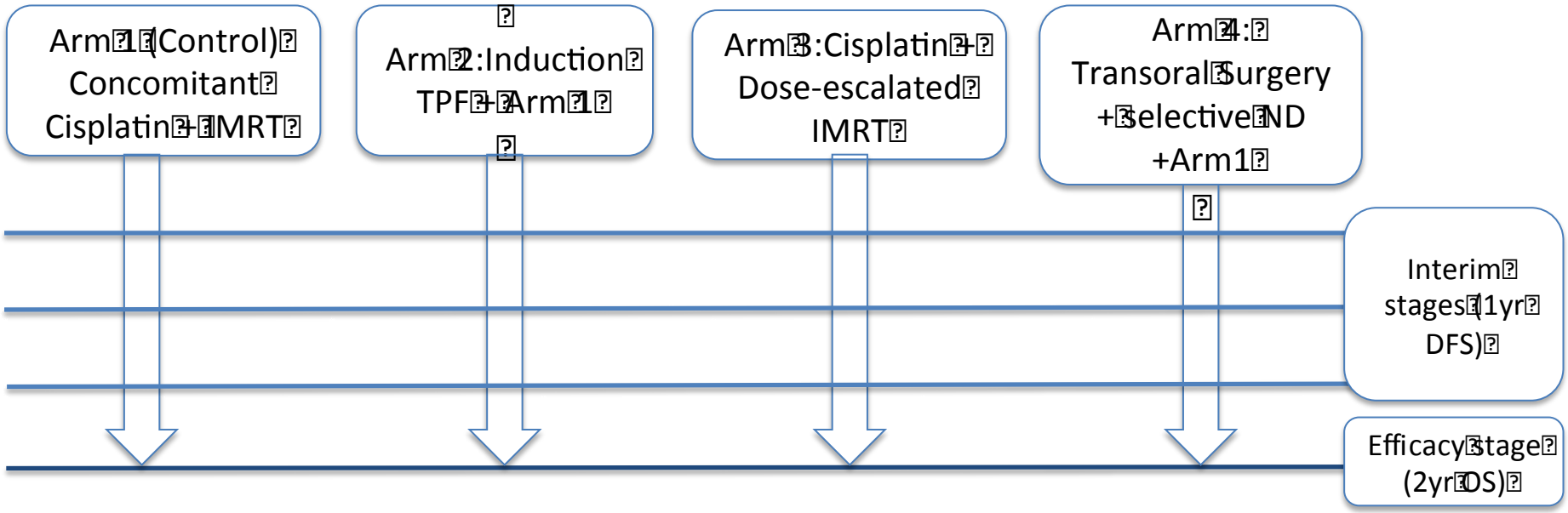
Population

Intermediate or high risk OPC, >18yrs, ECOG PS 0-1, Fit for surgery and chemotherapy.

RANDOMISE to ARMS 1-4 or ARMS 1-3 only

Stratify Intermediate vs High risk & Centre.

Adjust for Site (Tonsil vs Base of Tongue) and size (T1-3 vs T4) of tumour and nodes (N0-2A vs N2B-3)



Primary Outcome

Overall survival (2 years)

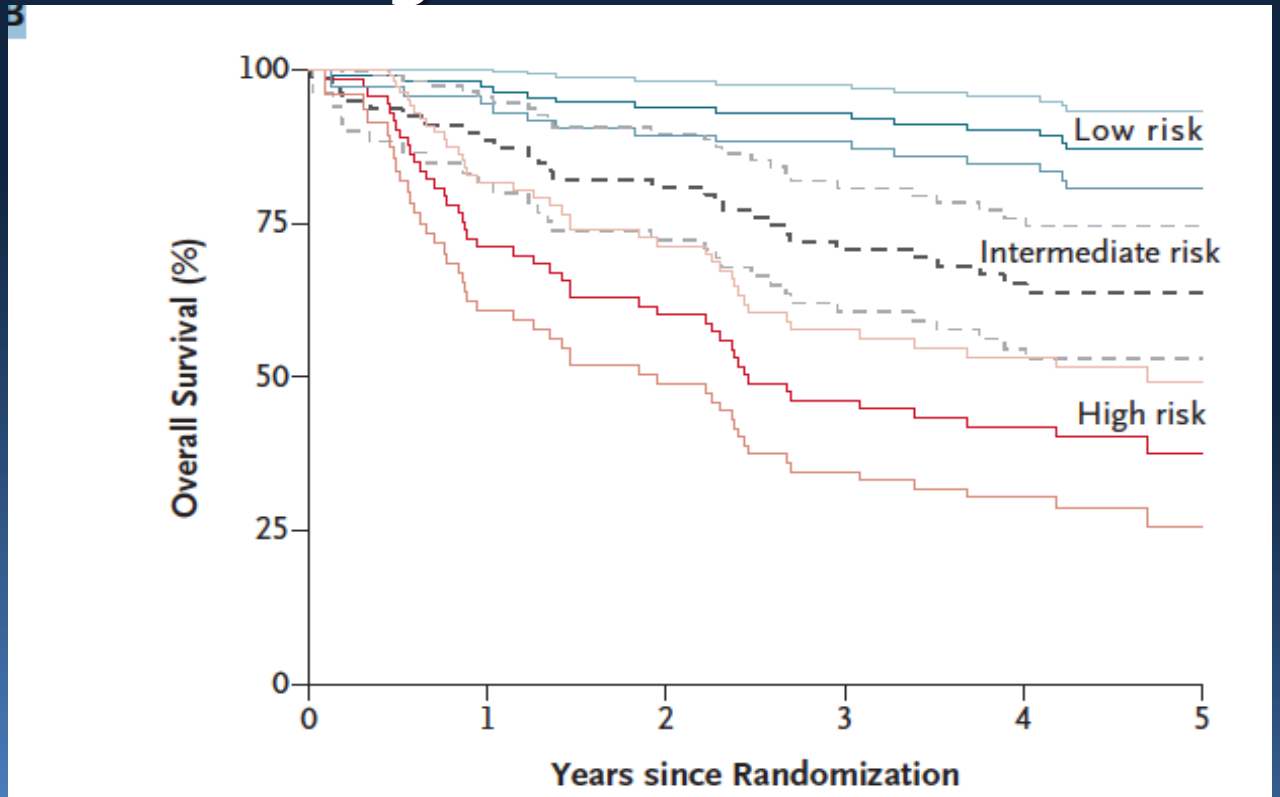
Secondary Outcomes

Disease free survival, Acute and Late severe toxicity using CTCAE, QoL using EORTC QLQ-C30 & HN35, & MDADI (for swallowing), Cost-effectiveness using EQ-5D, Surgical complications, Molecular markers

Individualised treatment selection

Risk factors in the new age

3 risk categories:



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

Ang, NEJM, 2010

Biomarkers with prognostic effect

CLINICAL REVIEW

David W. Eisele, MD, *Section Editor*

Prognostic biomarkers of survival in oropharyngeal squamous cell carcinoma: systematic review and meta-analysis

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Biomarker classifiers to predict prognosis following treatment of oropharyngeal carcinoma

PredicTr-OPC

CI: Prof Hisham Mehanna
Institute of Head and Neck Studies and Education

Conclusions

- HPV+OPSCC different disease entity with good prognosis
  - Need to study alternative treatments with less toxicity
  - Need to improve patients selection using treatment response classifiers

Conclusions

- Low risk HPV+OPSCC different disease entity with very good prognosis
  - Need to study alternative treatments with less toxicity
- Intermediate and high risk HPV+ OPSCC → poor prognosis
  - Need better treatments
- Need to further improve patients selection using treatment response classifiers

Do not change management of OPSCC patients without evidence

Enroll your patients into appropriate clinical trials

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Patients

Collaborators

Institute of Head and Neck Studies and Education

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Clinical trials and effectiveness

Experimental and translational medicine

Quality of life