



HPV oropharyngeal cancer: an overview

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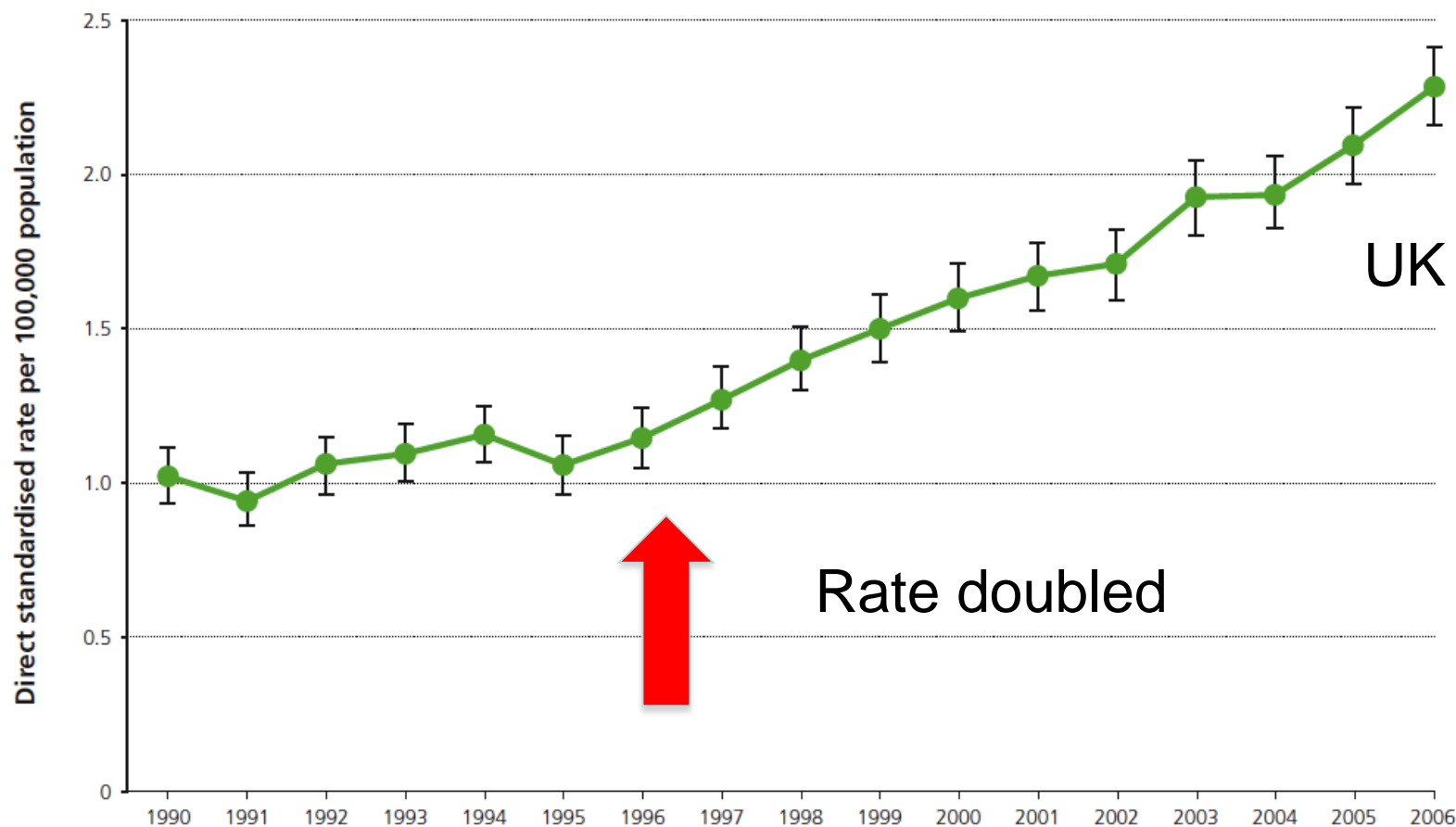
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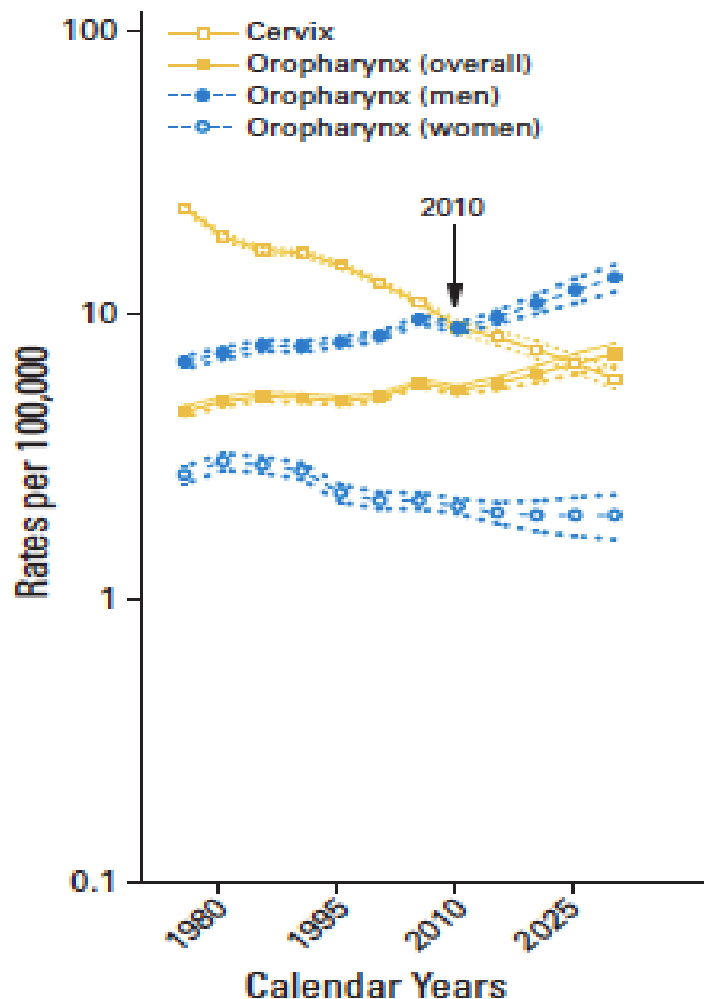
UNIVERSITY OF
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Rapidly rising incidence

Oropharynx cancer excluding soft palate (ICD-10 C01, C09 and C10)

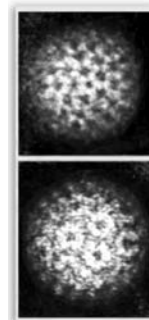
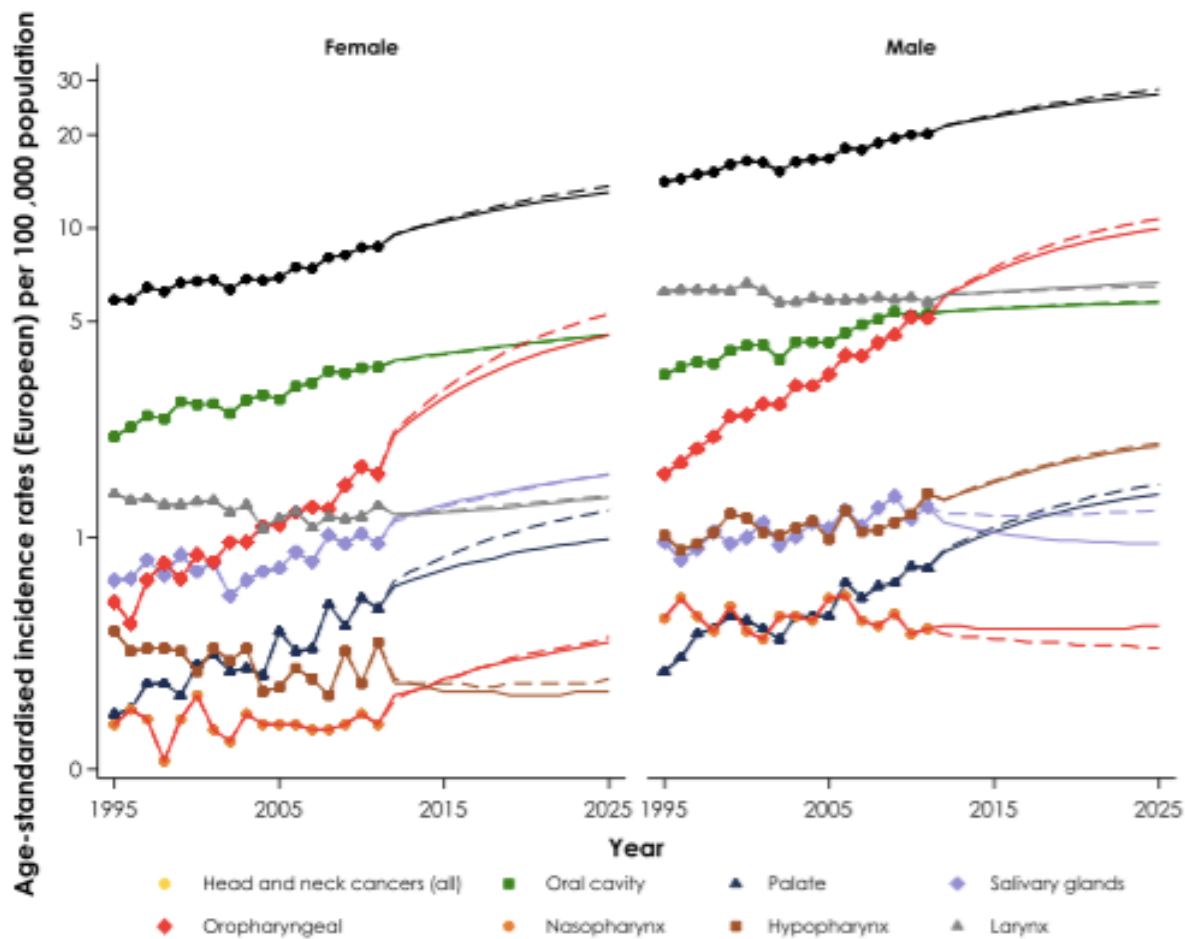


Oropharyngeal cancer projections USA



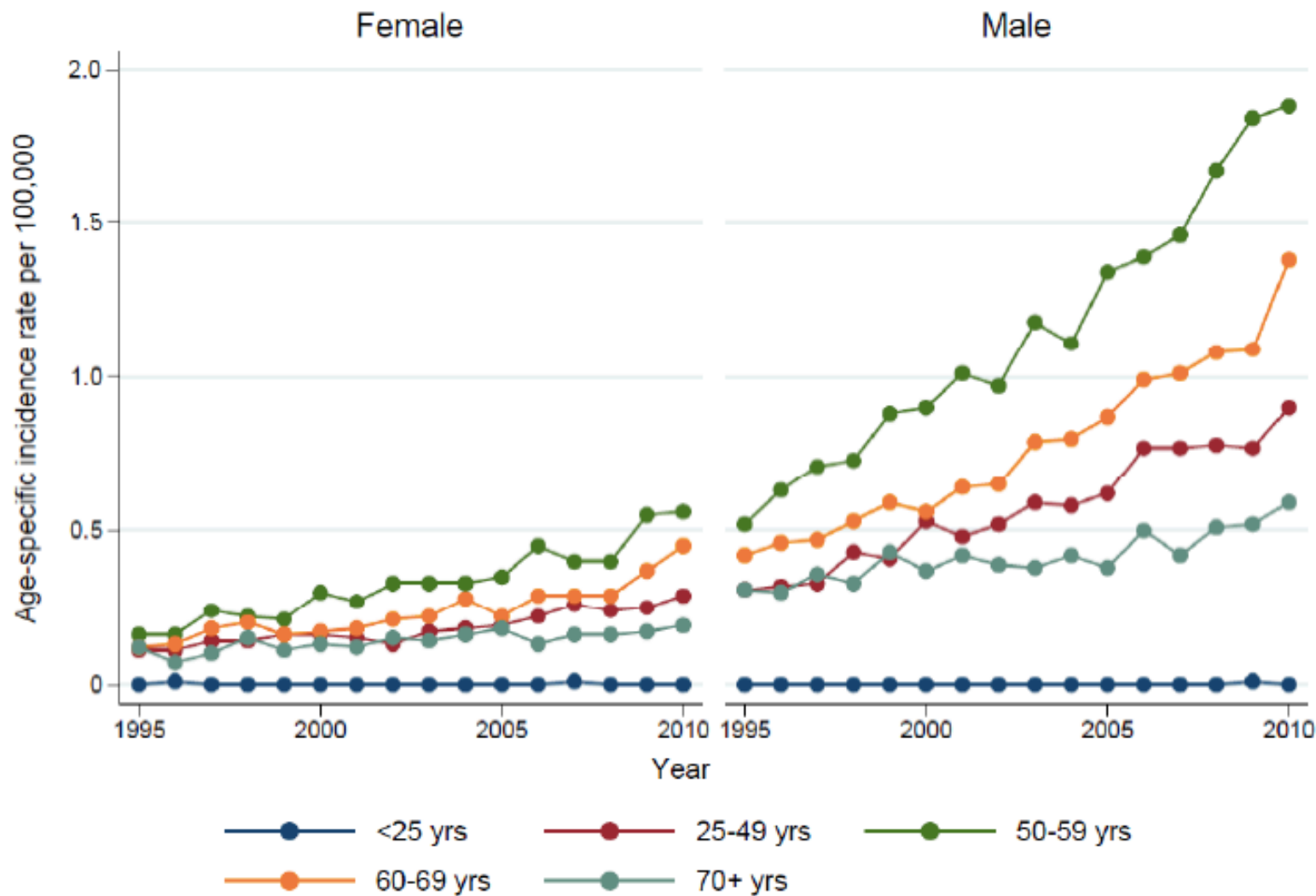
Chaturvedi JCO 2011

OPSCC increasing



Louie, Mehanna, Sasieni, Oral Onc, 2015

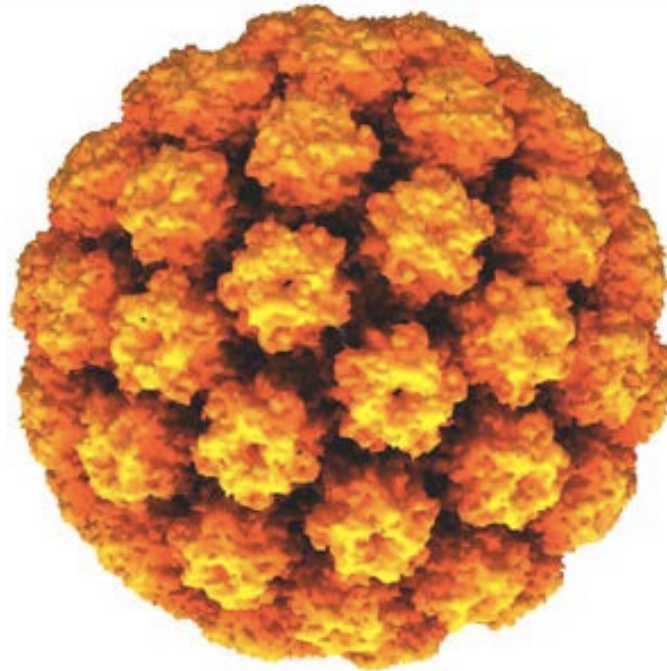
OPC projections by age



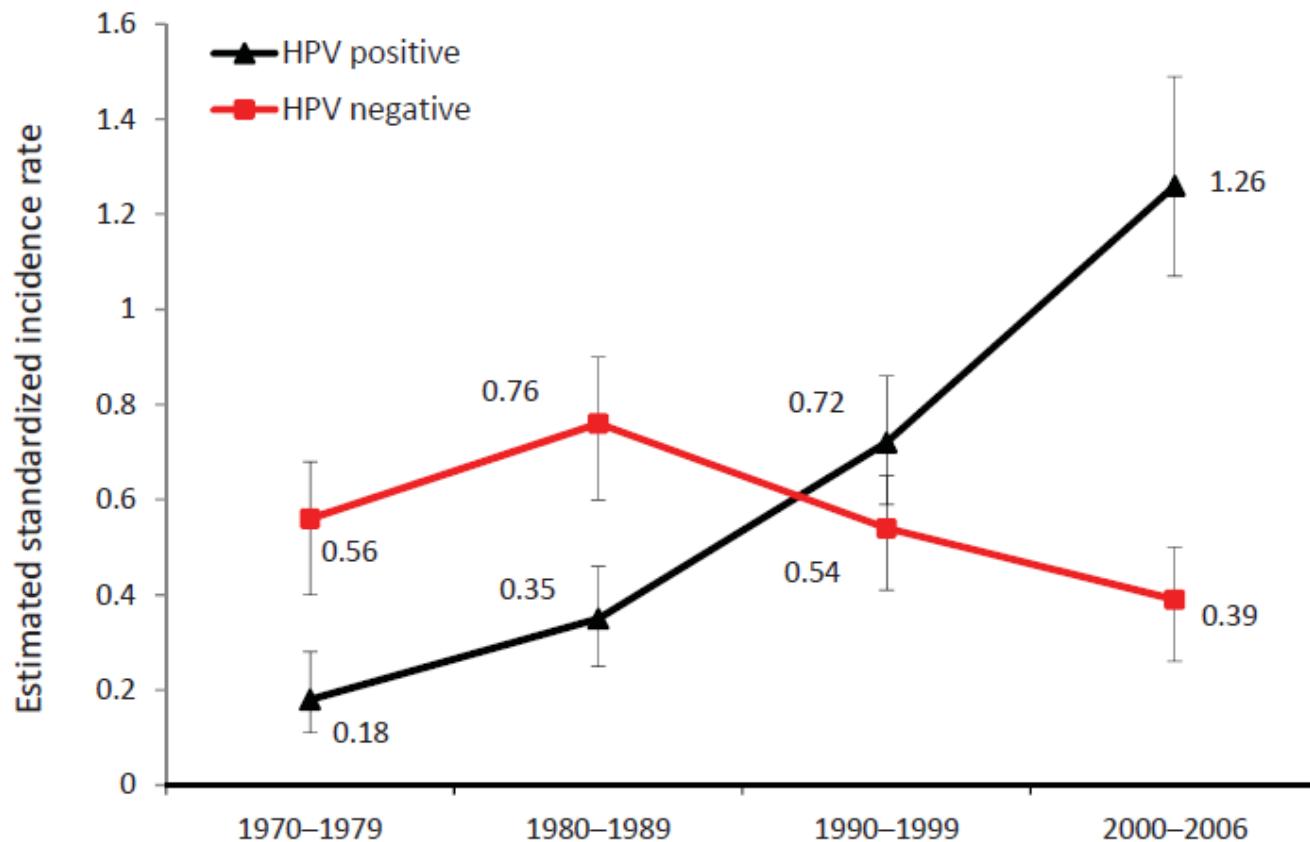
Louie, Mehanna, Sasieni, Oral Onc, 2015

Figure 2. Incidence of oropharyngeal cancers by sex and age-group

Human Papilloma Virus

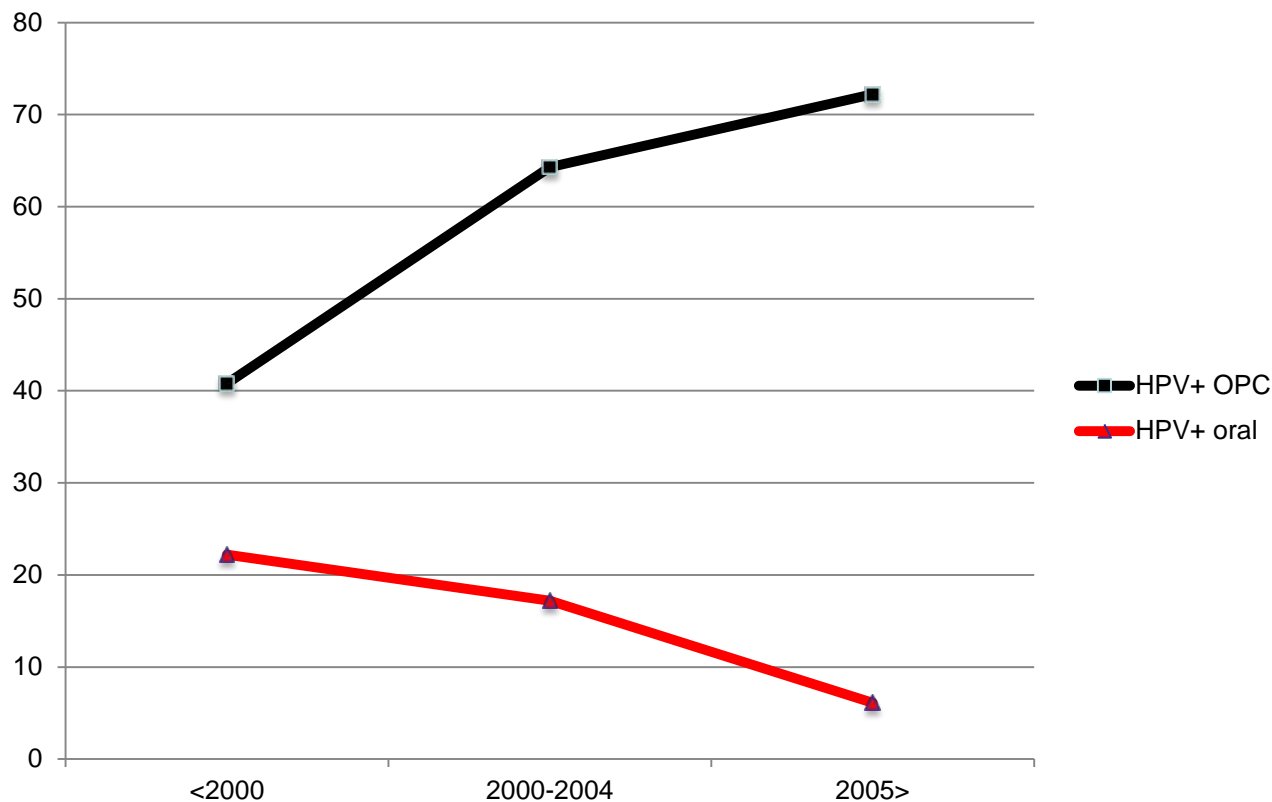


Incidence of HPV+ve and HPV-ve tonsillar cancer squamous cell carcinoma cases (Stockholm, Sweden, 1970–2006)



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?

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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](#)

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Published Online: 06 May 2010

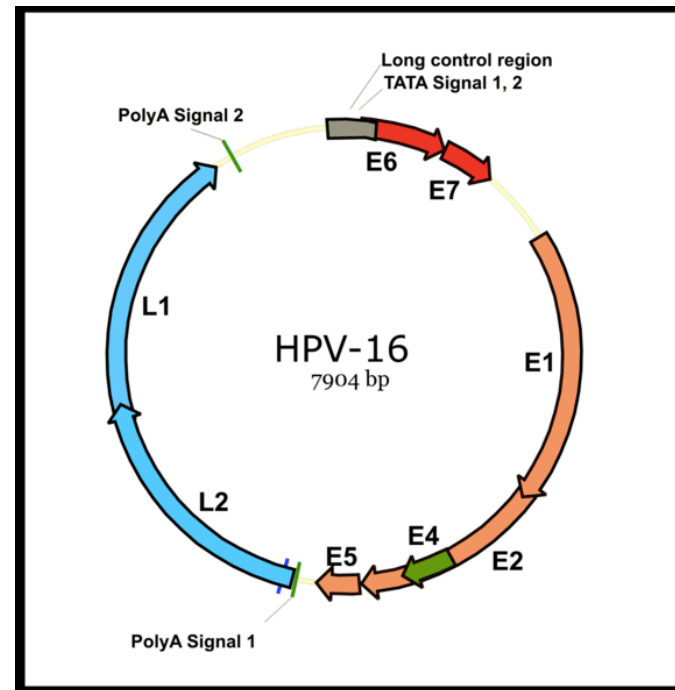
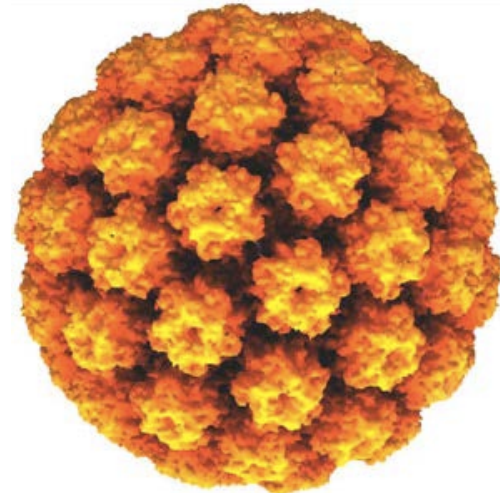
HPV-associated head and neck cancer: a virus-related cancer epidemic

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

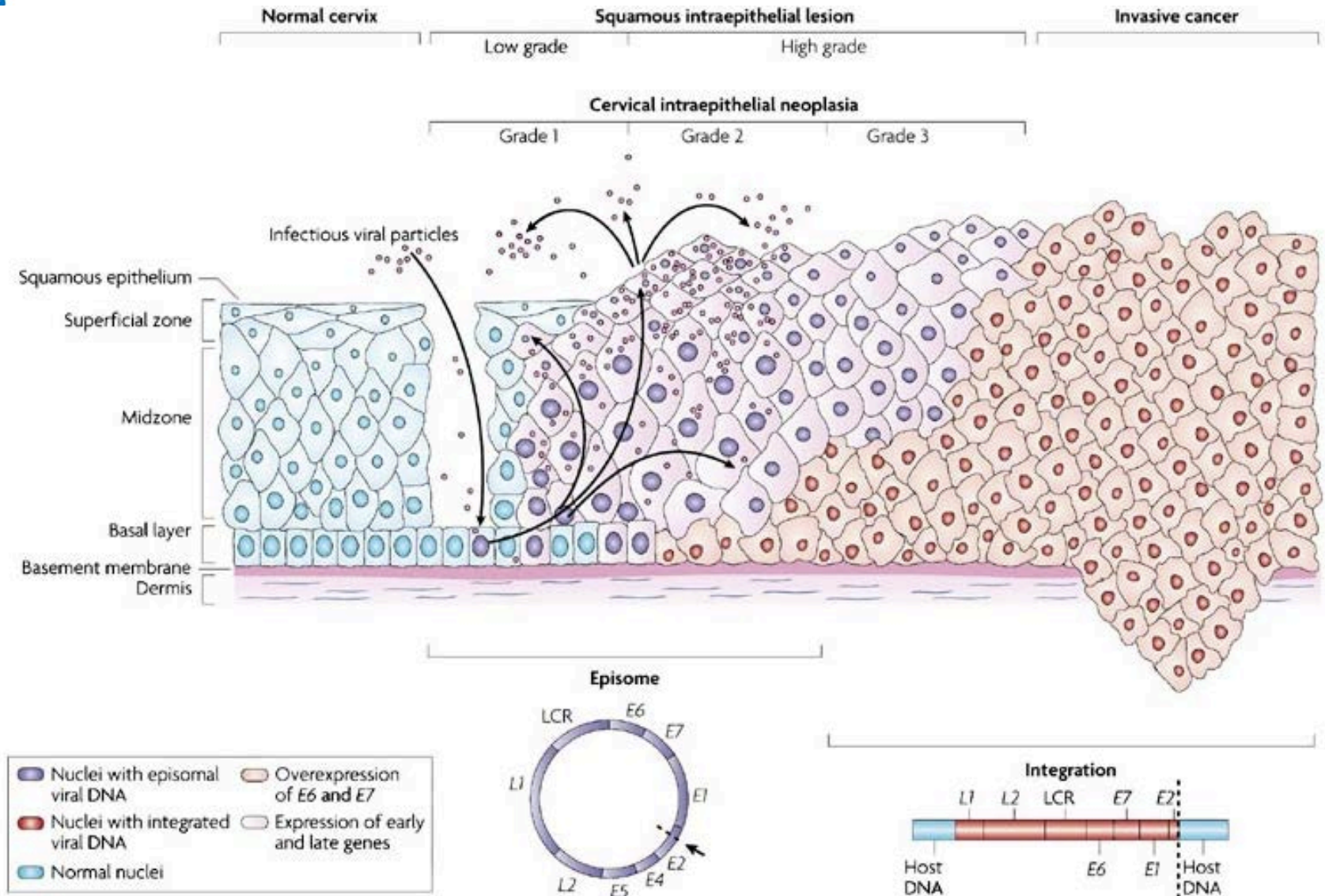
Summary

Human Papilloma Virus

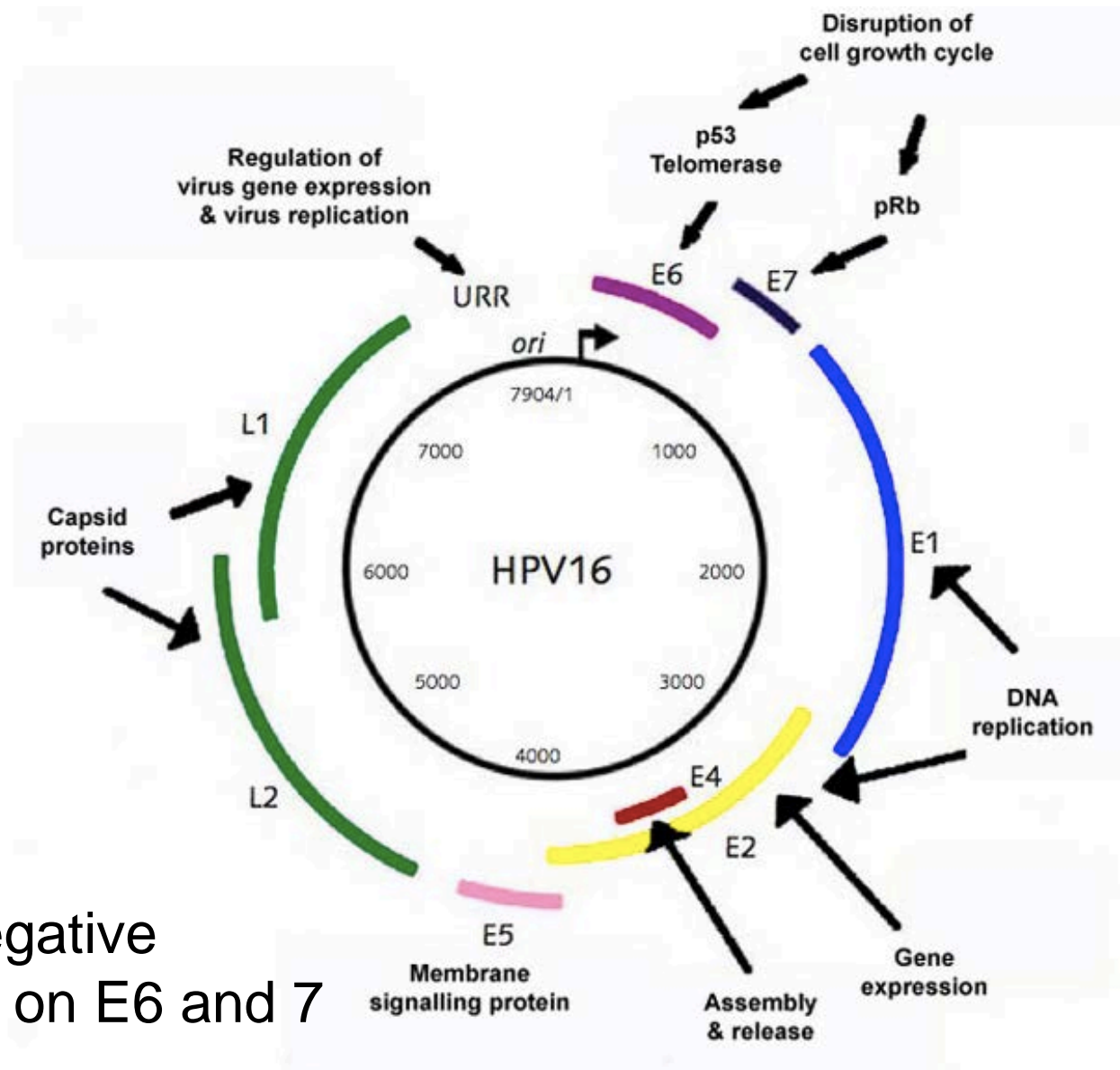
- Double stranded circular DNA
- 72 L1 capsid proteins
- >170 types
- Cervical and oropharyngeal SCC type 16 most common
- Can survive cold and dry
- Orogenital transmission
- Hand – genital transmission



How does it cause infection?

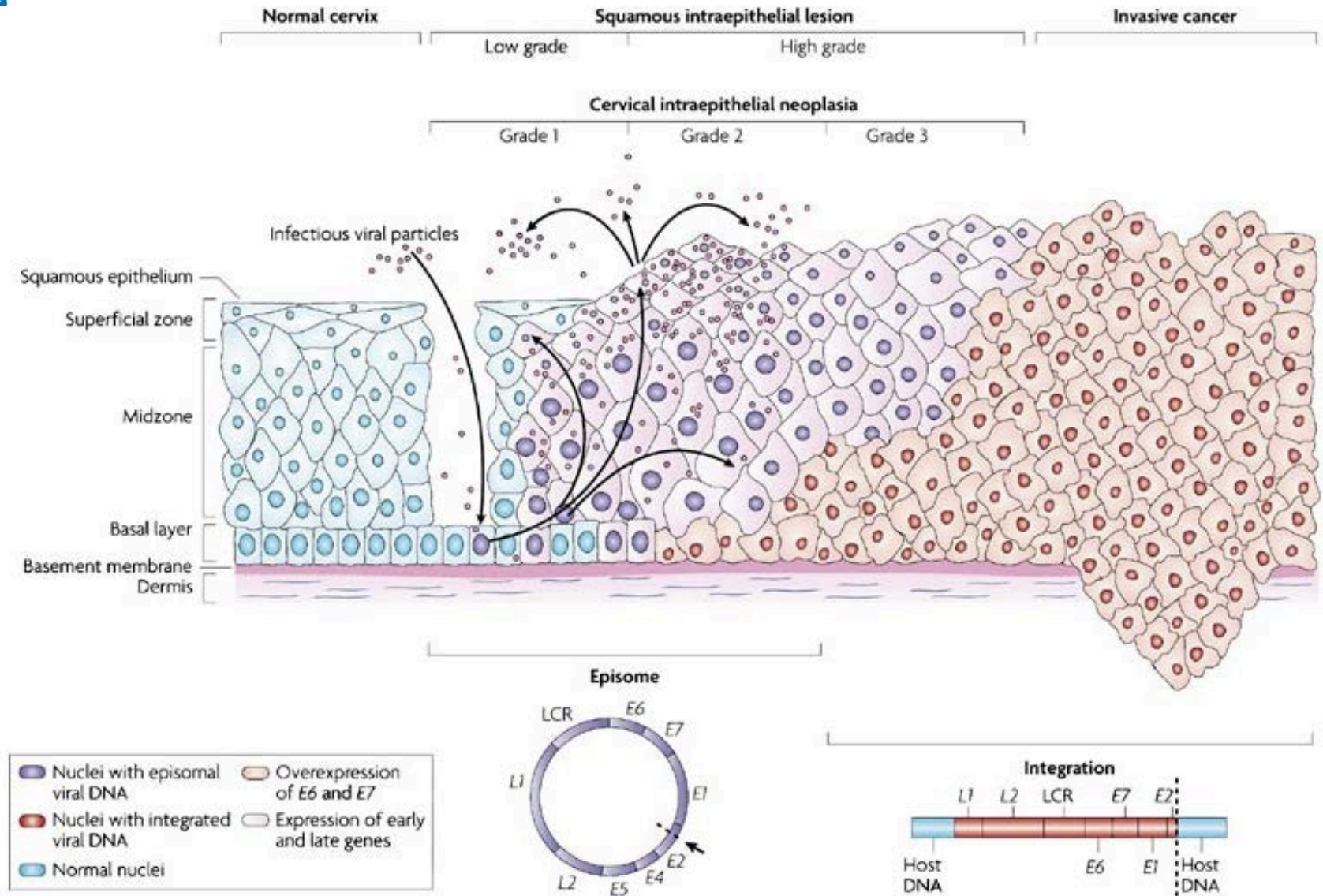


How does it replicate and spread?

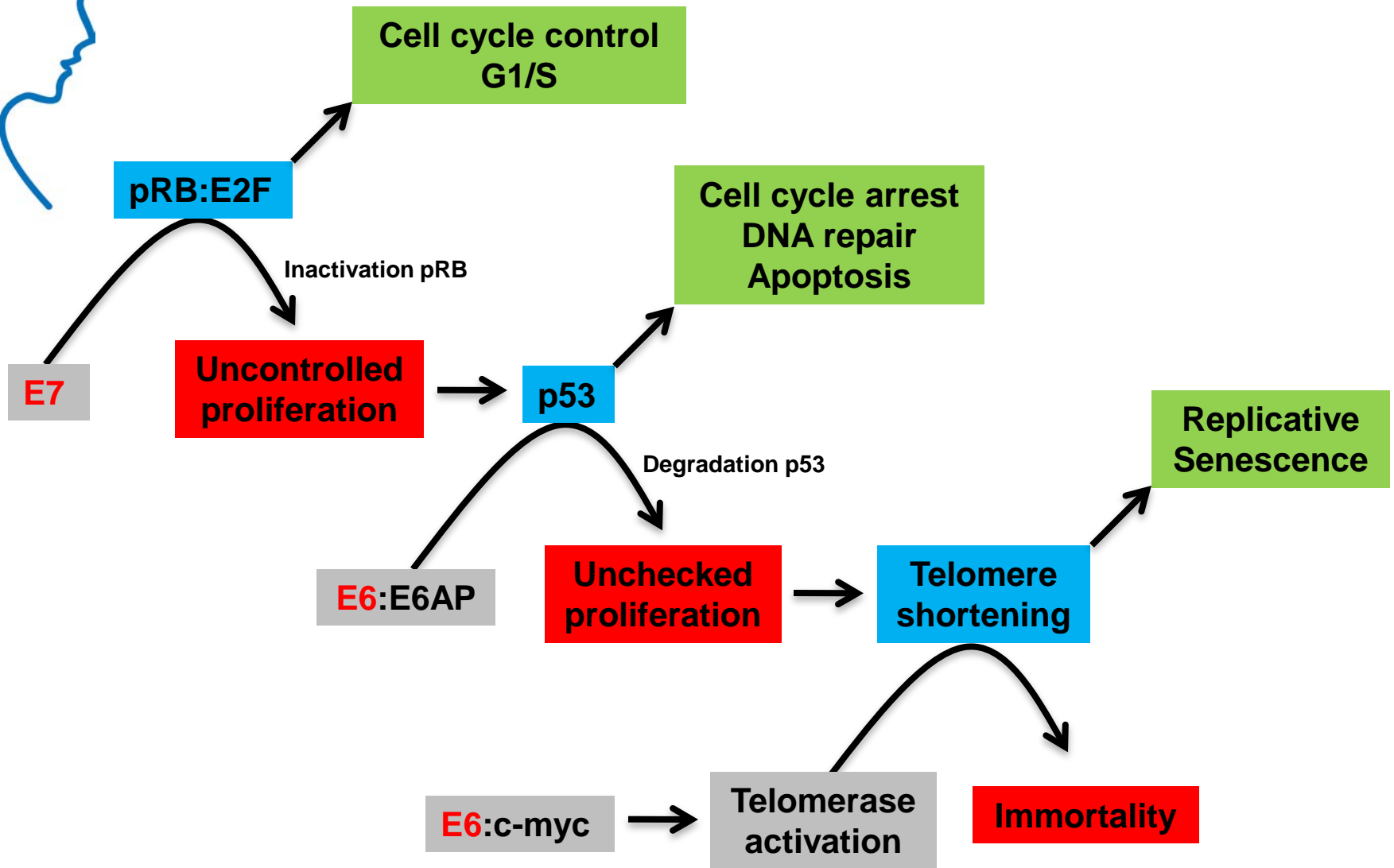


E2 has negative
Feedback on E6 and 7

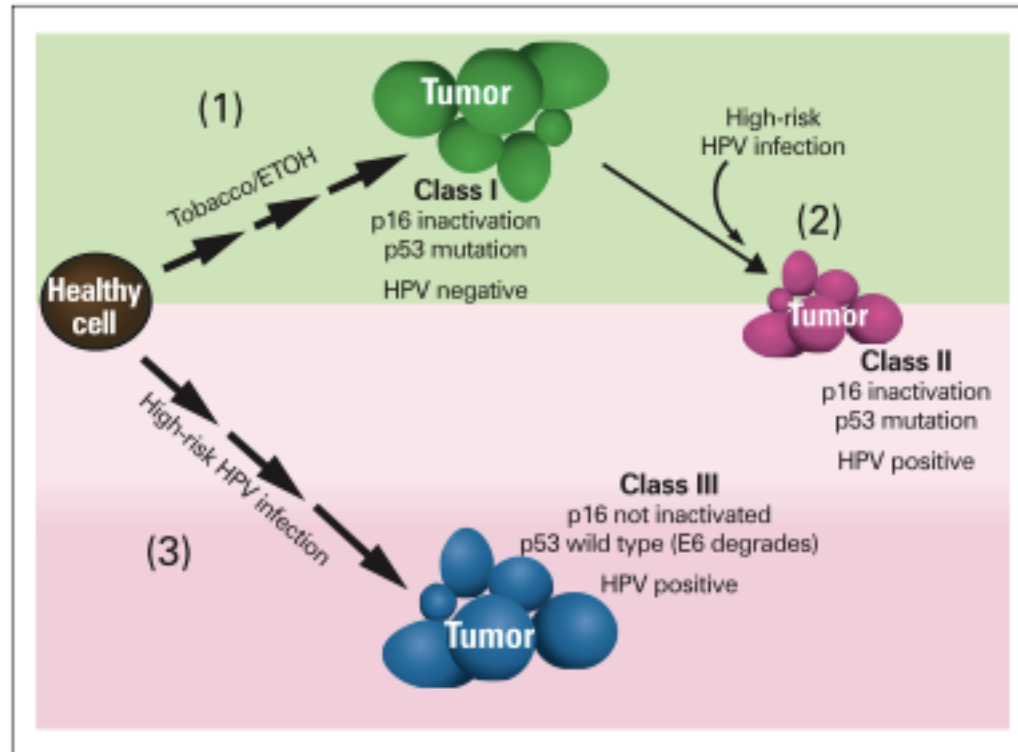
How does it cause cancer?



HPV Carcinogenesis – effects of E6 & E7 on cell signalling



Interaction between HPV and smoking



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Case–Control Study of Human Papillomavirus and Oropharyngeal Cancer

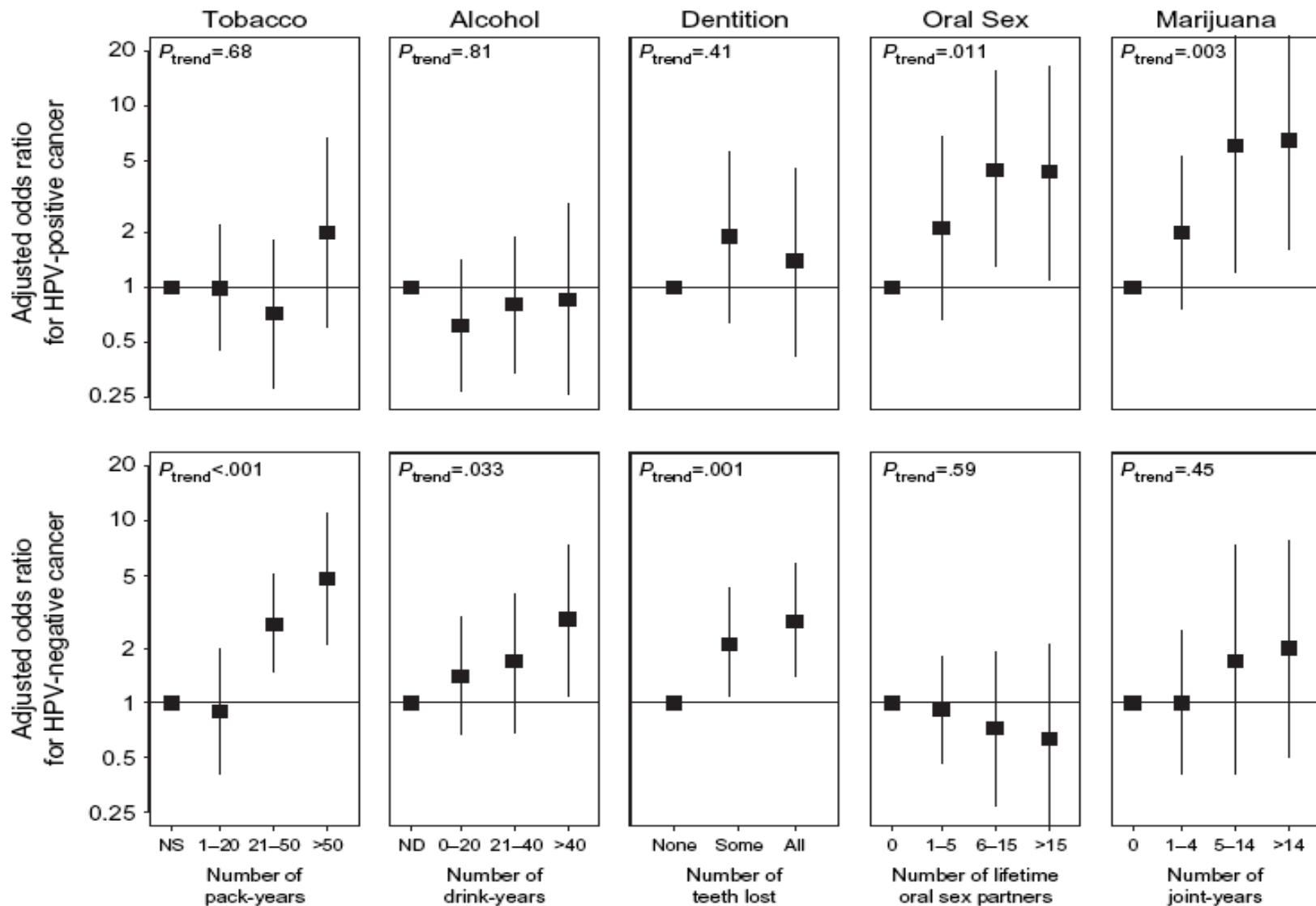
Gypsyamber D'Souza, Ph.D., Aimee R. Kreimer, Ph.D., Raphael Viscidi, M.D., Michael Pawlita, M.D., Carole Fakhry, M.D., M.P.H., Wayne M. Koch, M.D., William H. Westra, M.D., and Maura L. Gillison, M.D., Ph.D.

Risk factors for HPV-OPSCC

Table 2. Associations of Oropharyngeal Cancer with Sexual Behaviors.*

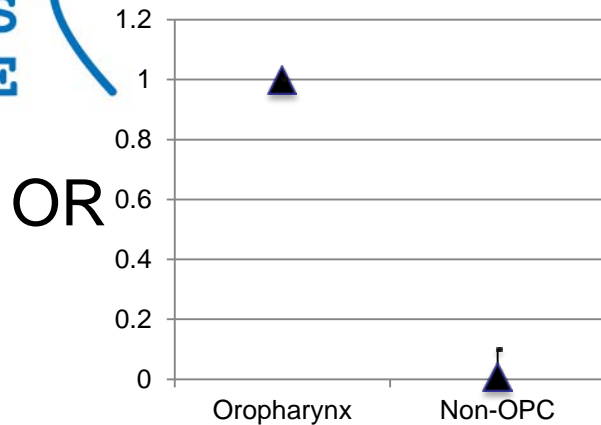
Sexual Behavior	Patients with Oropharyngeal Cancer (N= 100)	Control Patients (N= 200)	Adjusted Odds Ratio (95% CI) [†]	
			All Patients	HPV-16+ Patients [‡]
	<i>number (percent)</i>			
Lifetime no. of vaginal-sex partners				
0–5	31 (31)	108 (54)	1.0	1.0
6–25	41 (41)	63 (32)	2.2 (1.2–4.0)	2.7 (1.4–5.5)
≥26	28 (28)	29 (14)	3.1 (1.5–6.5) [§]	4.2 (1.8–9.4) [¶]
Lifetime no. of oral-sex partners				
0	12 (12)	38 (19)	1.0	1.0
1–5	46 (46)	110 (55)	1.9 (0.8–4.5)	3.8 (1.0–14.0)
≥6	42 (42)	52 (26)	3.4 (1.3–8.8)	8.6 (2.2–34.0) ^{**}
Anal sex				
No	55 (55)	129 (64)	1.0	1.0
Yes	45 (45)	71 (36)	1.3 (0.8–2.2)	1.6 (0.9–2.8)
Casual-sex partner ^{††}				
No	42 (42)	120 (60)	1.0	1.0
Yes	58 (58)	80 (40)	1.7 (1.0–3.0)	2.4 (1.2–4.7)

Risk factors

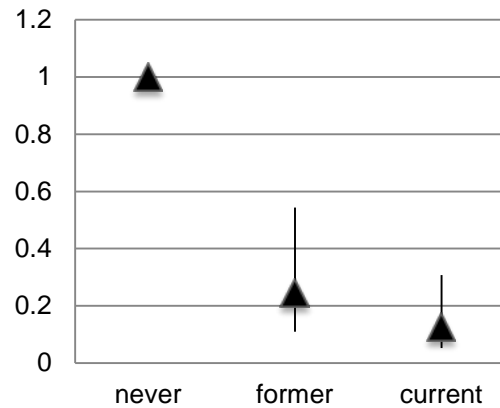


Risk factors for HPV positivity

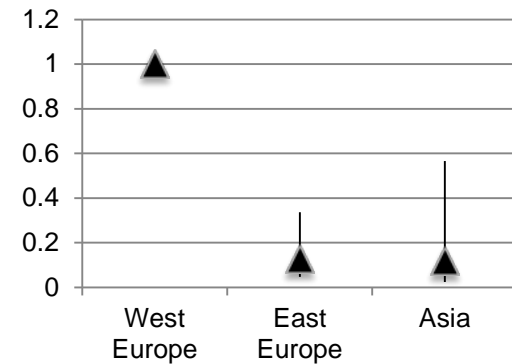
Tumour site



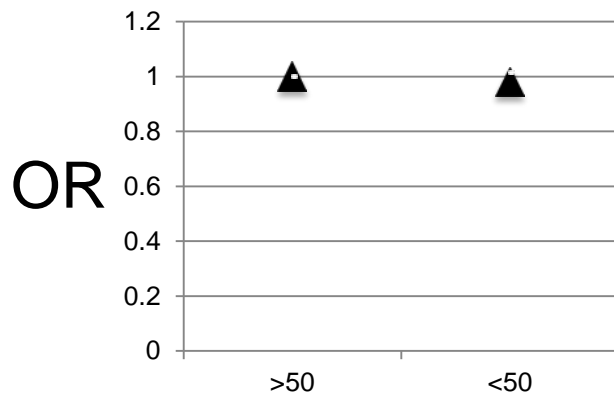
Smoking status



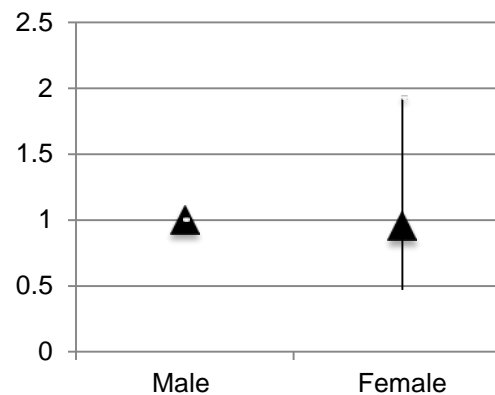
Geographic region



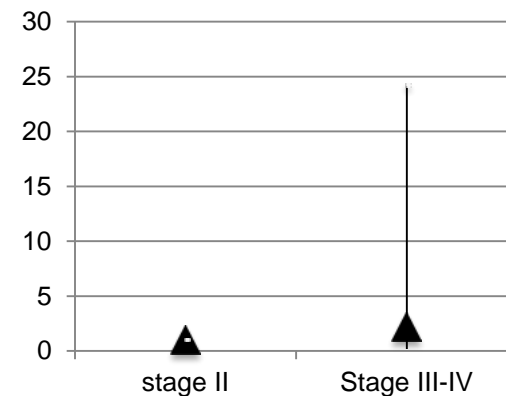
Age



Gender



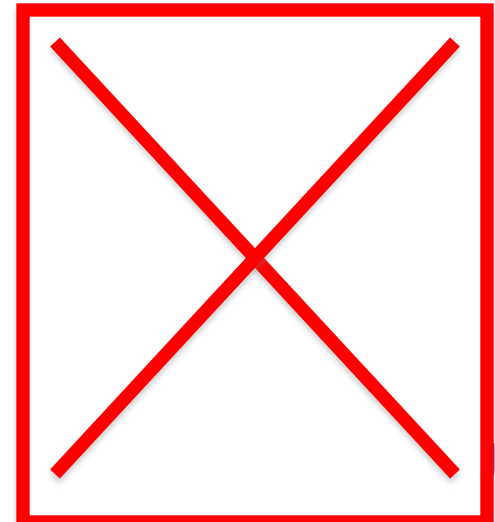
Tumour stage



Predictive of HPV+ity

Not predictive of HPV+ity

Risk factors – the ‘good time’ cancer



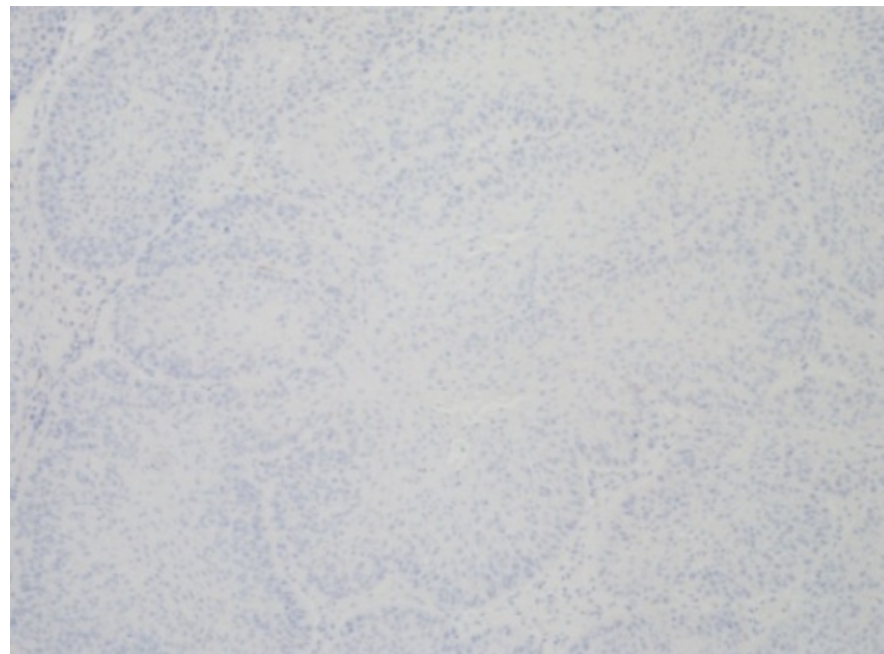
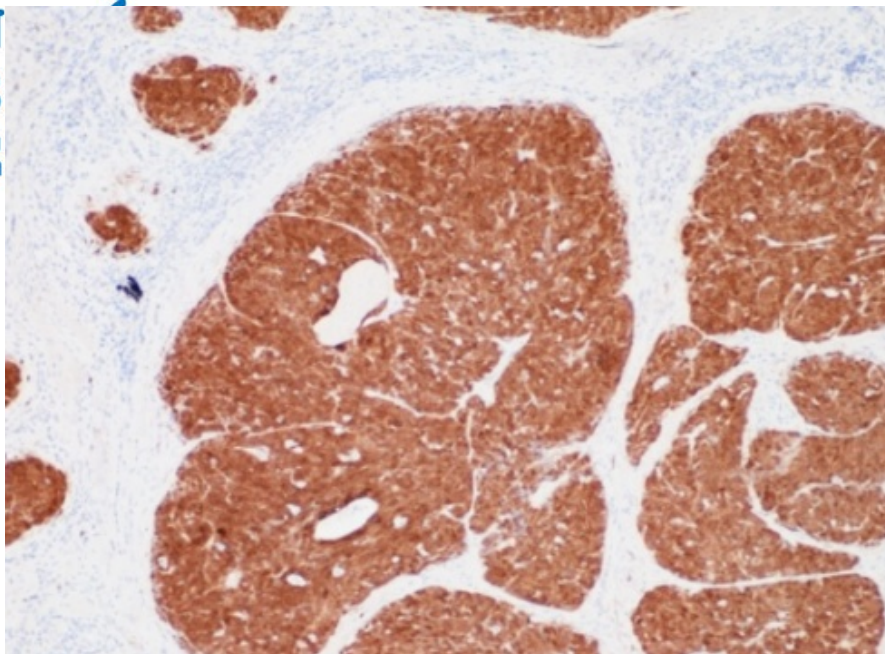
Diagnosis

MCHUMOR by T. McCracken



"Off hand, I'd say you're suffering from an arrow through your head, but just to play it safe, I'm ordering a bunch of tests."

Interpretation of p16 immunohistochemistry



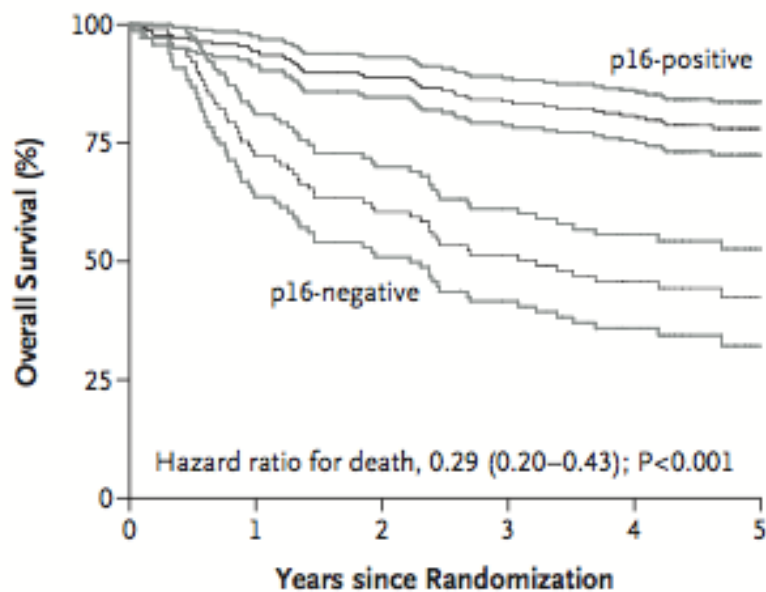
High interobserver agreement

**Thavaraj et al. *J Clin Pathol* 2011;64:308-312
Intraclass correlation 0.986 (95% CI 0.982-0.990. $p < 0.0001$)**

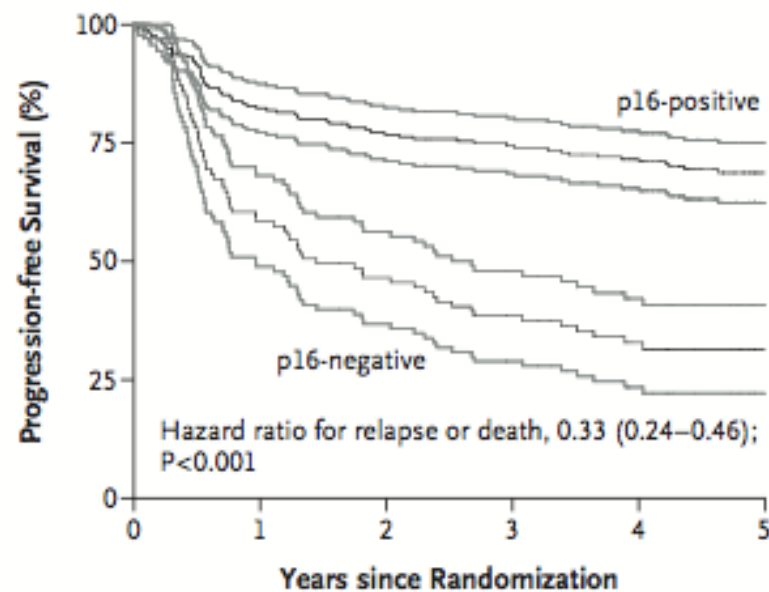
**Jordan et al. *Am J Surg Pathol* 2012;36:945-954
Kappa scores > 0.90**

p16 immunohistochemistry

C Overall Survival According to p16 Expression



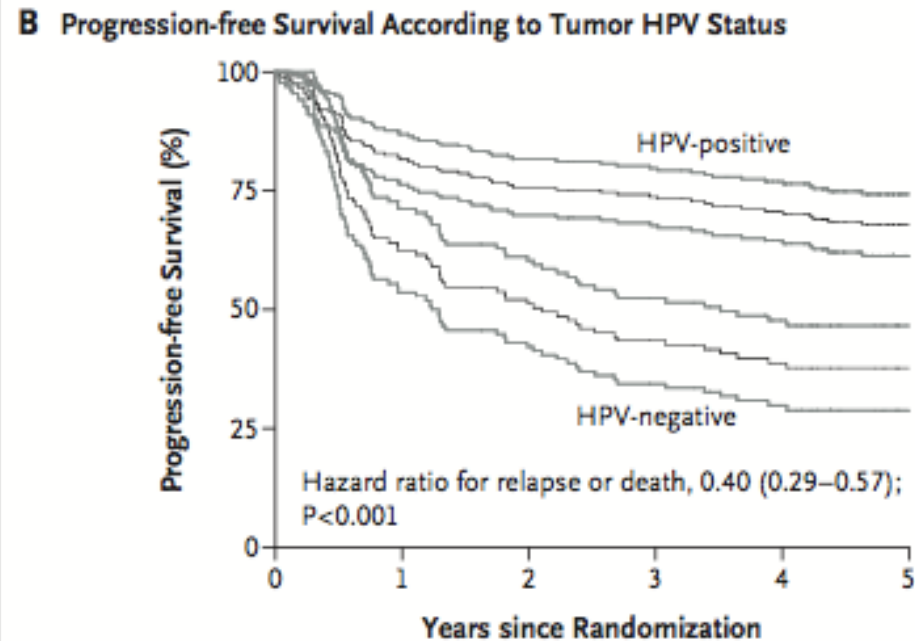
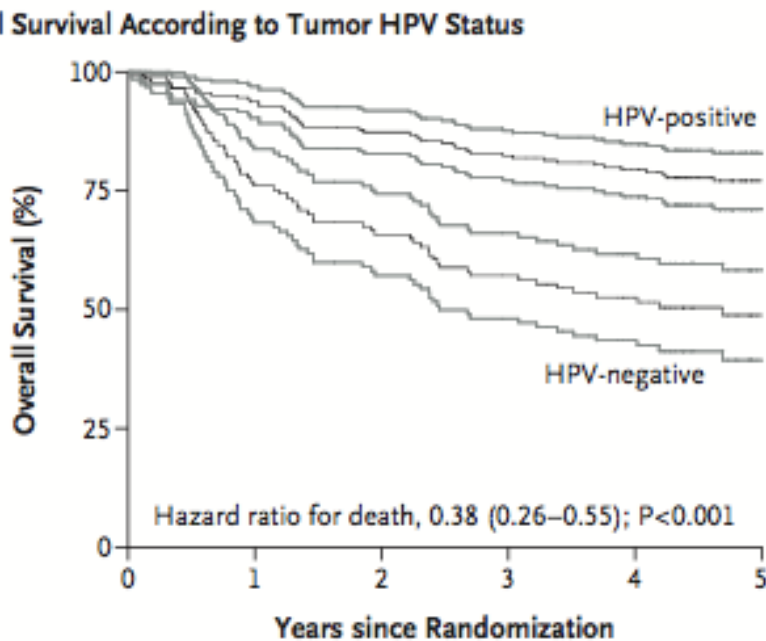
D Progression-free Survival According to p16 Expression



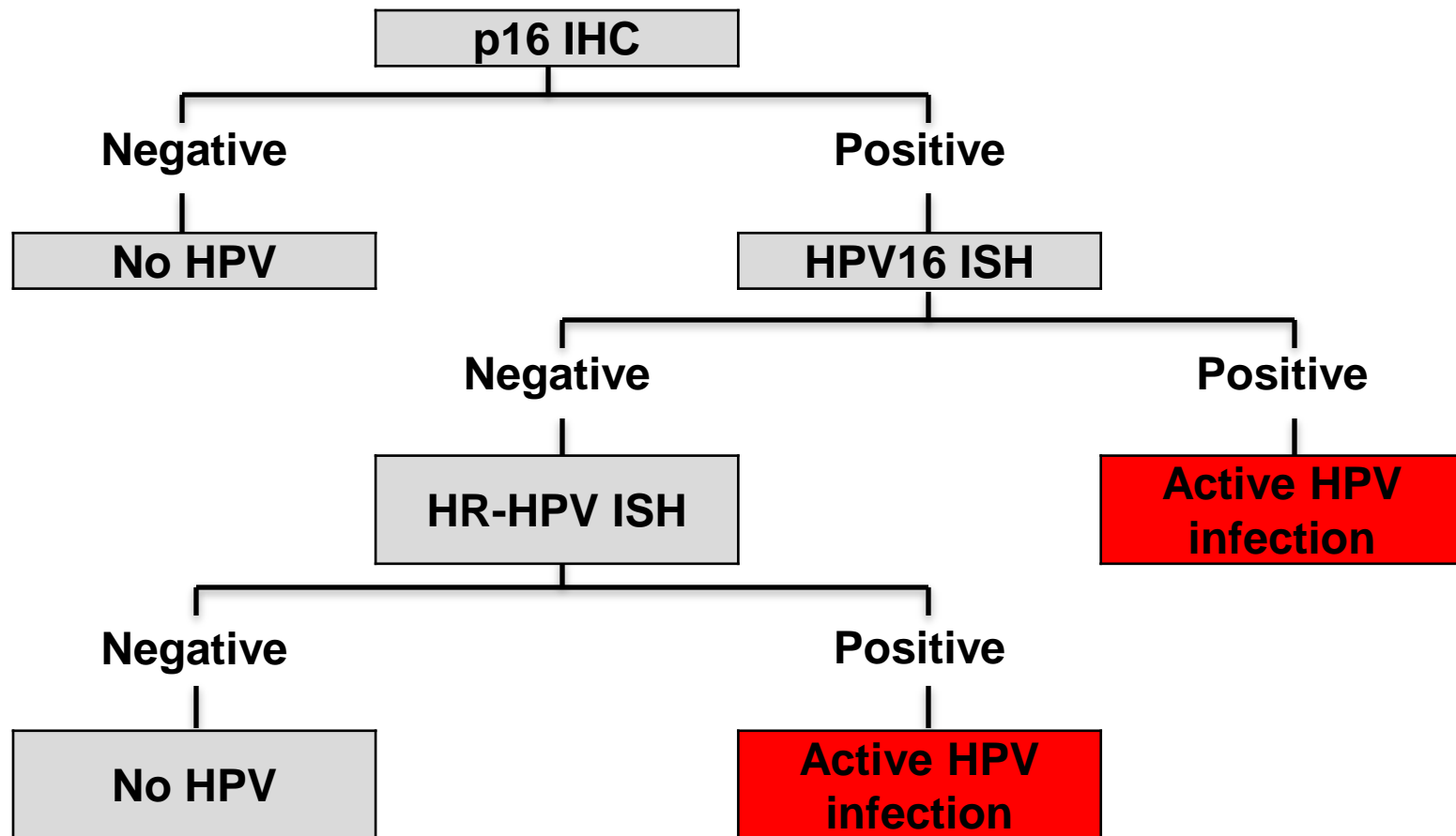
Ang, NEJM, 2010

HPV DNA

- HPV DNA testing by :
 - PCR to HPV L1 G5+/G6+ or E6 DNA 16 and other high risk types
 - DNA in-situ hybridisation
- HPV DNA status is prognostic



Algorithm for the detection of HPV in FFPE head and neck biopsies



p16 IHC & high risk HPV ISH has acceptable sensitivity & specificity for oncogenic HPV infection

HPV test	Sensitivity	Specificity
HR-HPV ISH	88%	88%
p16 IHC	94%	82%
p16 IHC & HPV ISH	88%	90%
P16 IHC & HPV PCR	97%	94%

Reference test mRNA on fresh frozen biopsies

Schache et al. *Clin Cancer Res* 2011

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

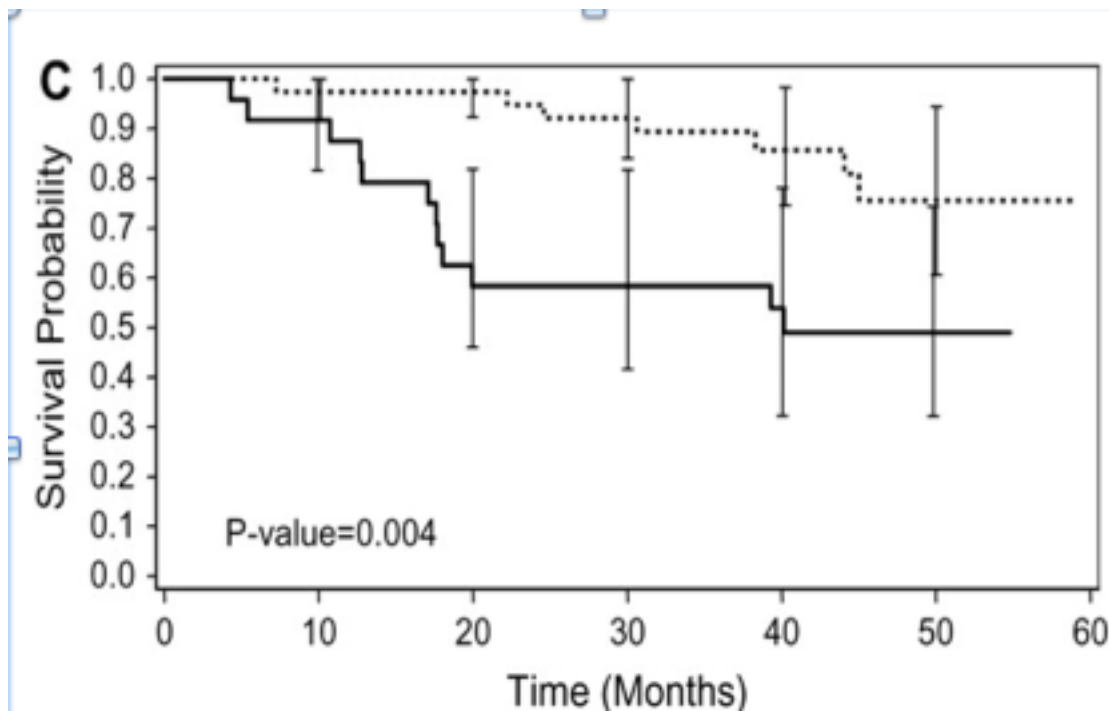
www.inhanse.org

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

Risk stratification in the new age

3 risk categories:

- Low risk: HPV+ / no or low smokers (50% patients)

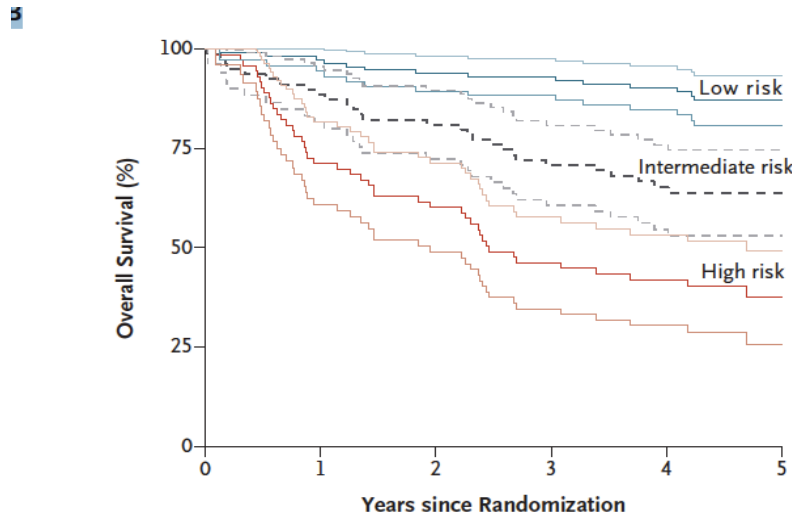
OS 3 yr 93%

- 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%



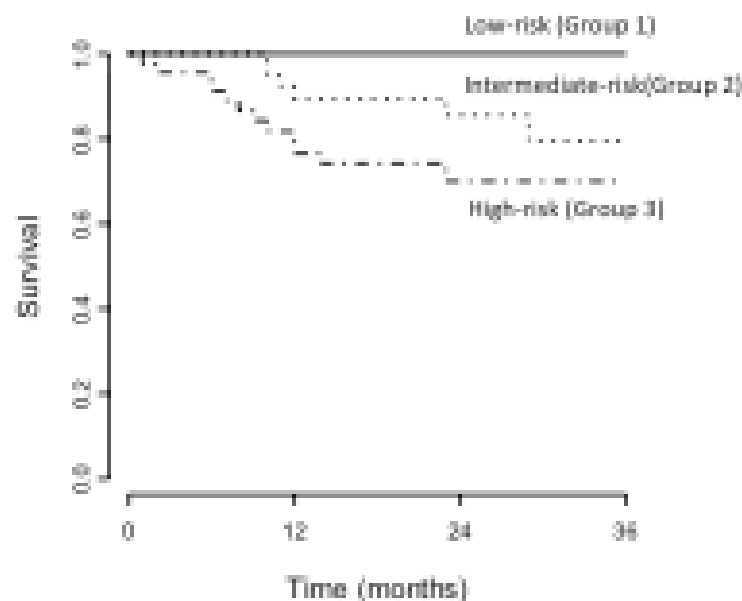
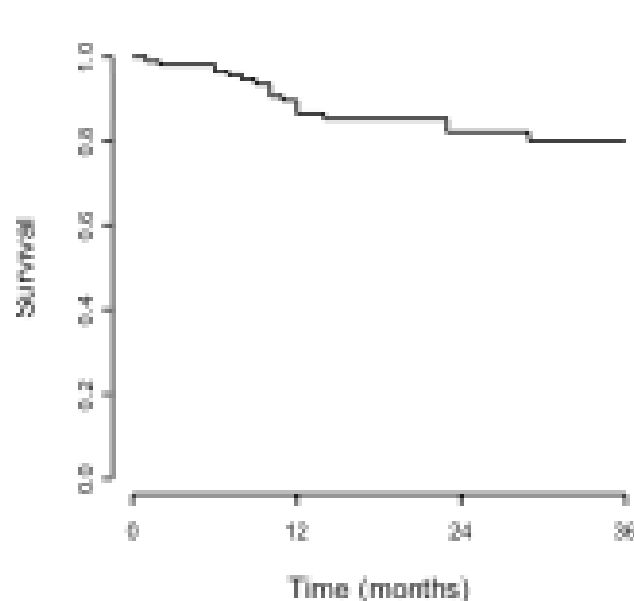
No. at Risk						
Low risk	114	111	106	102	95	46
Intermediate risk	79	70	64	54	44	24
High risk	73	52	43	33	28	8

Ang, NEJM, 2010

original article

Annals of Oncology
doi:10.1093/annonc/mdr544**Tumor stage, human papillomavirus and smoking status affect the survival of patients with oropharyngeal cancer: an Italian validation study**

R. Granata¹, R. Miceli², E. Orlandi³, F. Perrone⁴, B. Cortelazzi⁴, M. Franceschini³, L. D. Locati¹, P. Bossi¹, C. Bergamini¹, A. Mirabile¹, L. Mariani², P. Olmi³, G. Scaramellini⁵, P. Potepan⁶, P. Quattrone⁷, K. K. Ang⁸ & L. Licitra^{1*}



120 OPC patients



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

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

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*
pN stage (N2a+ vs. N0-2a)	3.8 (1.1-13.30)	.032
Adjuvant Rx (any vs. none)	0.21 (0.06-0.71)	.012 [†]
cT stage (T4 tonsil vs. T1-3 tonsil)	4.93 (1.46-16.65)	.010
cT stage (T4 tonsil vs. T1-3 tongue base)	8.26 (2.27-29.99)	.001

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

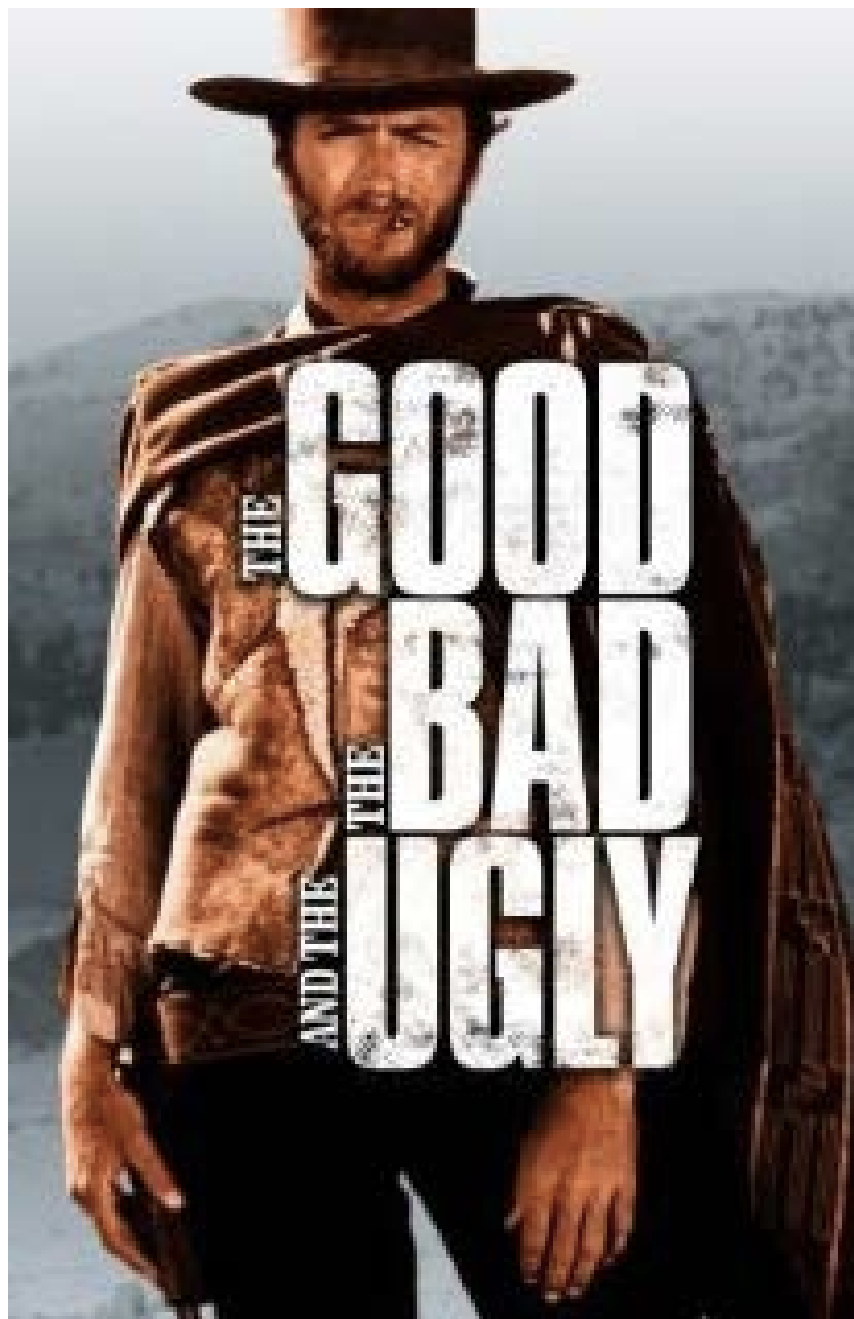
[†]Lost its significance in models with T stage.

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

Low

Intermediate

High



3yr OS

93%

70.8%

46.3%

Behaviour HPV+ different to HPV-

- Loco-regional control:
 - HPV+ higher than HPV-
 - 3 yr regional control=94% vs 84% in Toronto series
 - Responsible for improved survival in HPV+

Huang et al, Oral Onc, 2013

– RTOG 0129	3yr-LRC
• Low risk	90.4%
• Intermediate	80.9%
• High	57.3%

Ang, personal comm

Behaviour HPV+ different to HPV-

Distant control

Oral Oncology 49 (2013) 79–85



Contents lists available at SciVerse ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology



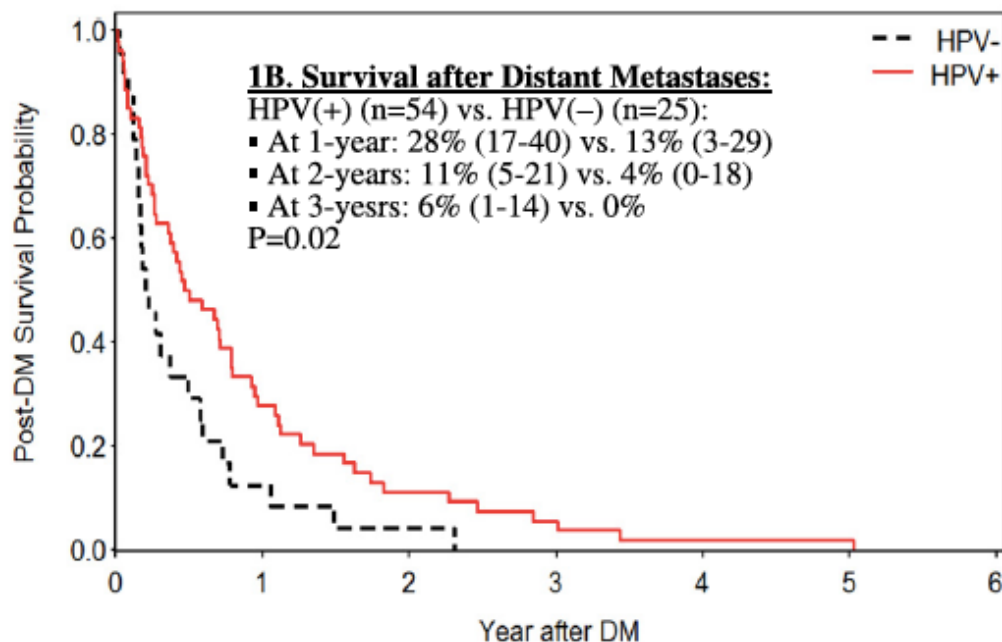
Natural course of distant metastases following radiotherapy or chemoradiotherapy in HPV-related oropharyngeal cancer ☆

Shao Hui Huang^a, Bayardo Perez-Ordóñez^b, Ilan Weinreb^b, Andrew Hope^a, Christine Massey^c, John N. Waldron^a, John Kim^a, Andrew J. Bayley^a, Bernard Cummings^a, B.C. John Cho^a, Jolie Ringash^a, Laura A. Dawson^a, Lillian L. Siu^d, Eric Chen^d, Jonathan Irish^e, Patrick Gullane^e, Angela Hui^f, Fei-Fei Liu^{a,f}, Xiaowei Shen^c, Wei Xu^c, Brian O'Sullivan^{a,*}

Behaviour HPV+ different to HPV-

- Distant control
 - HPV+ similar to HPV-
 - 3yr 89% vs 85% ; 5yr 87% vs 85%
 - Higher percentage of distant failure only in patients who fail in HPV+ (48%) vs HPV-ve (27%)
 - Distant failure occurs later in HPV+
 - HPV- all within 2.1 years
 - HPV+ 20% after yr 2 and 13% after yr 3
 - HPV+ longest within 5.3years
 - Distant failure occurs in different sites
 - HPV–ve: lung (commonest 22/25), liver, bone
 - HPV+: lung (commonest 42/54), skin, brain, intra-abdominal LNs, skeletal muscle, pancreas, axilla, spleen, kidney, peri-cardial LN

- Survival rate after DM
 - Longer for HPV+
 - 2yr survival after DM = HPV+ 11% vs HPV-ve 4%
 - HPV+ patients with oligometas to lung who were treated (pall chemo, Rt or resection) appeared to have longer survival





Interm

**Vast majority of patients in most countries
Outside North America**

**Aim of management: better survival
→ Need to escalate treatment**

46.3% 20%

60%

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%
- Data from Huang, O'Sullivan 2013
 - Distant control (DC): HPV+ similar to HPV-
 - 3yr DC 89% vs 85%
 - 5yr DC 87% vs 85%

Options for improving locoregional control

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

HPV+ high risk?

Expectation



CompARE

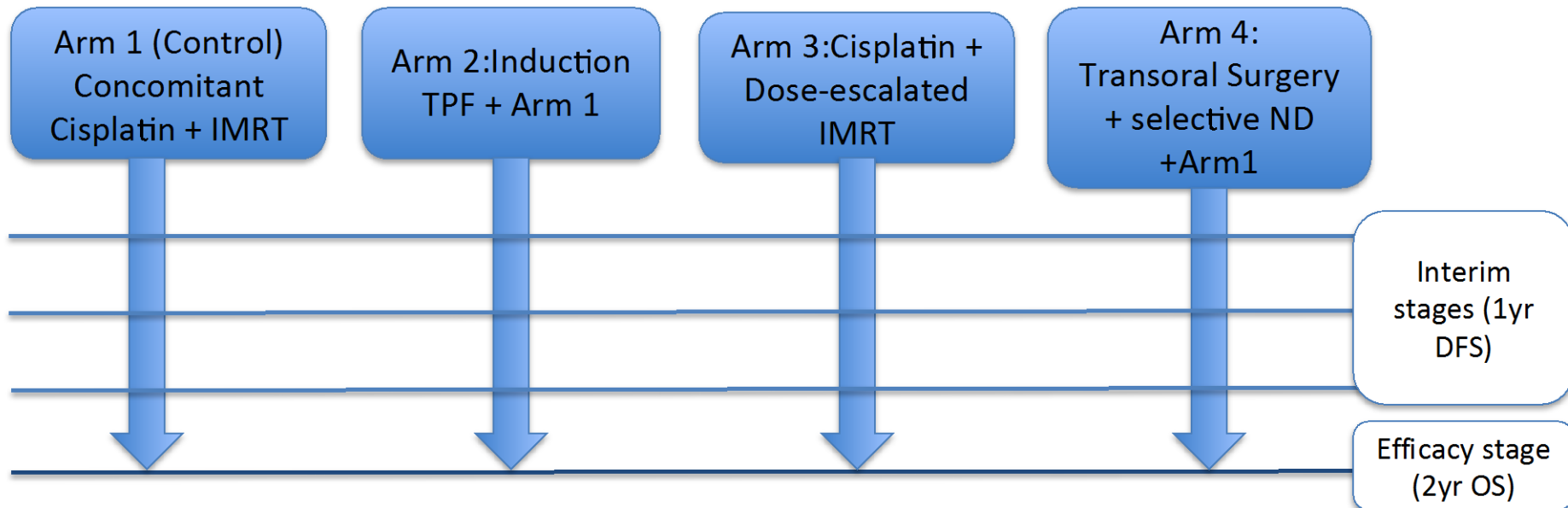
Population

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

Low

3yr OS

**ONLY 20% OPSCC patients in most countries
Outside North America**

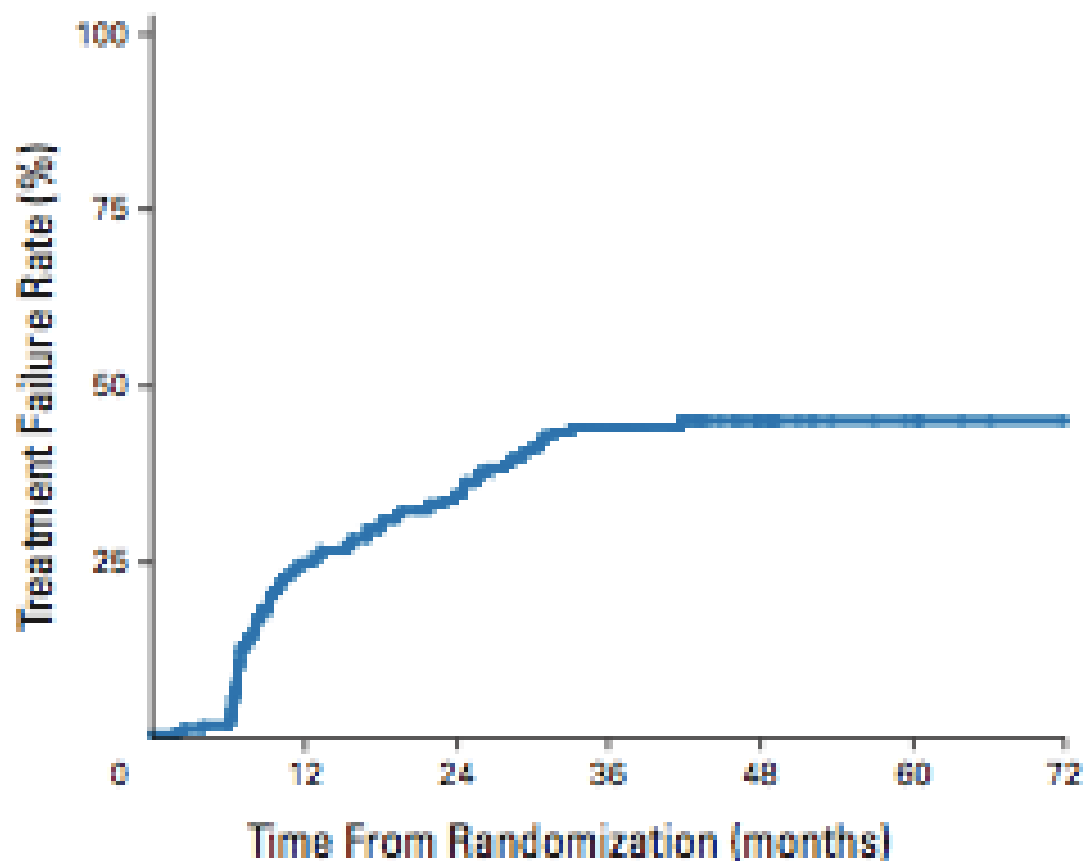


Bad news



CRT - toxicity

Higher survival rates in younger patients = living longer with morbidity



Are we over-treating?



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



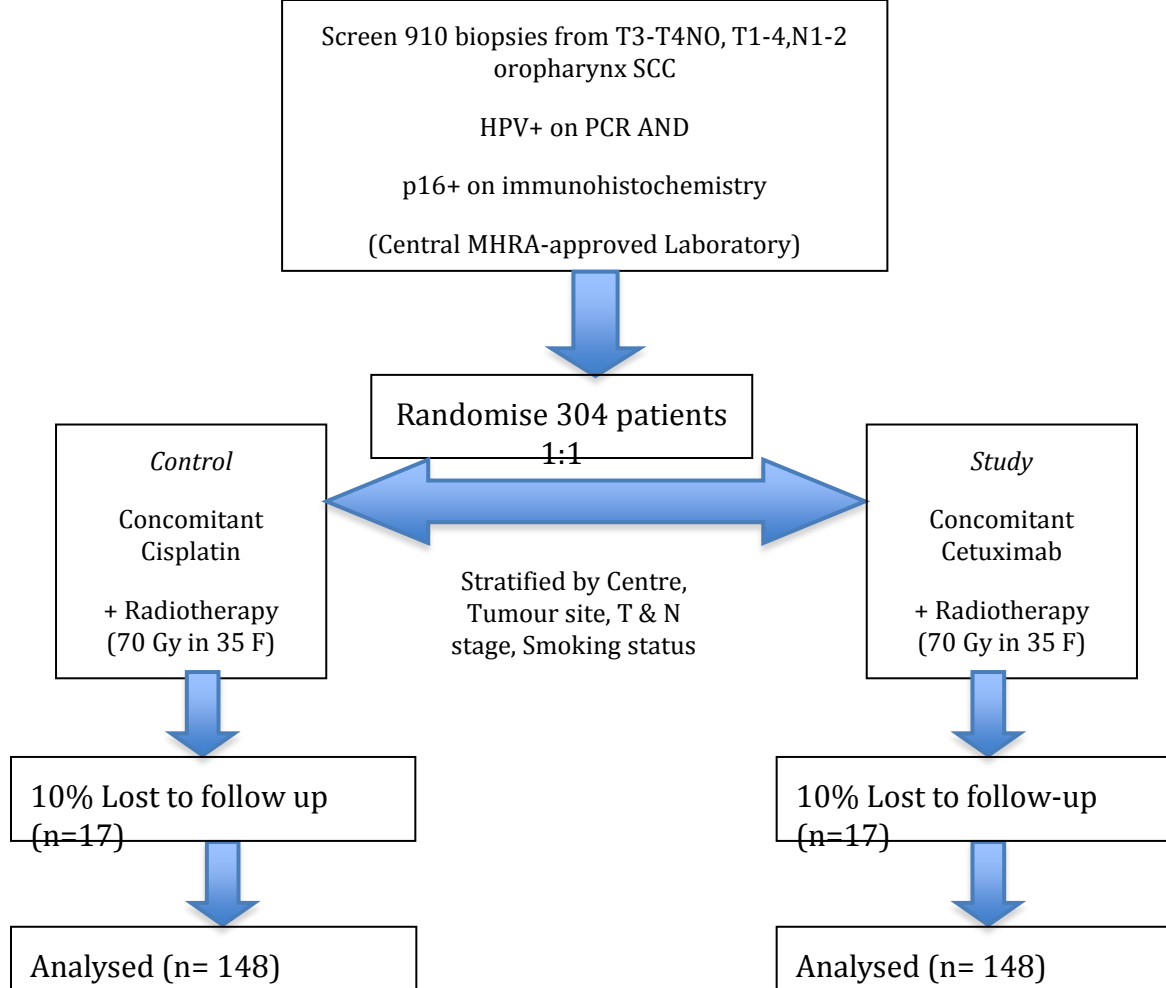
De-ESCALaTE HPV

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

De-ESCALaTE HPV

CI: Hisham Mehanna





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 Cisplatin or Cetuximab in p16 Positive Oropharynx Cancer

Stratify: HPV, Smoking, Stage

ELIGIBILITY

**Stage III, IVA, B
Resectable
P16+
Oropharynx
Cancer**

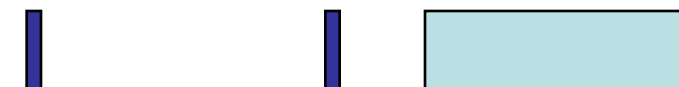
**R
A
N
D
O
M
I
Z
E**

P - 100 mg/M²

XRT

C225 400/250 mg

XRT



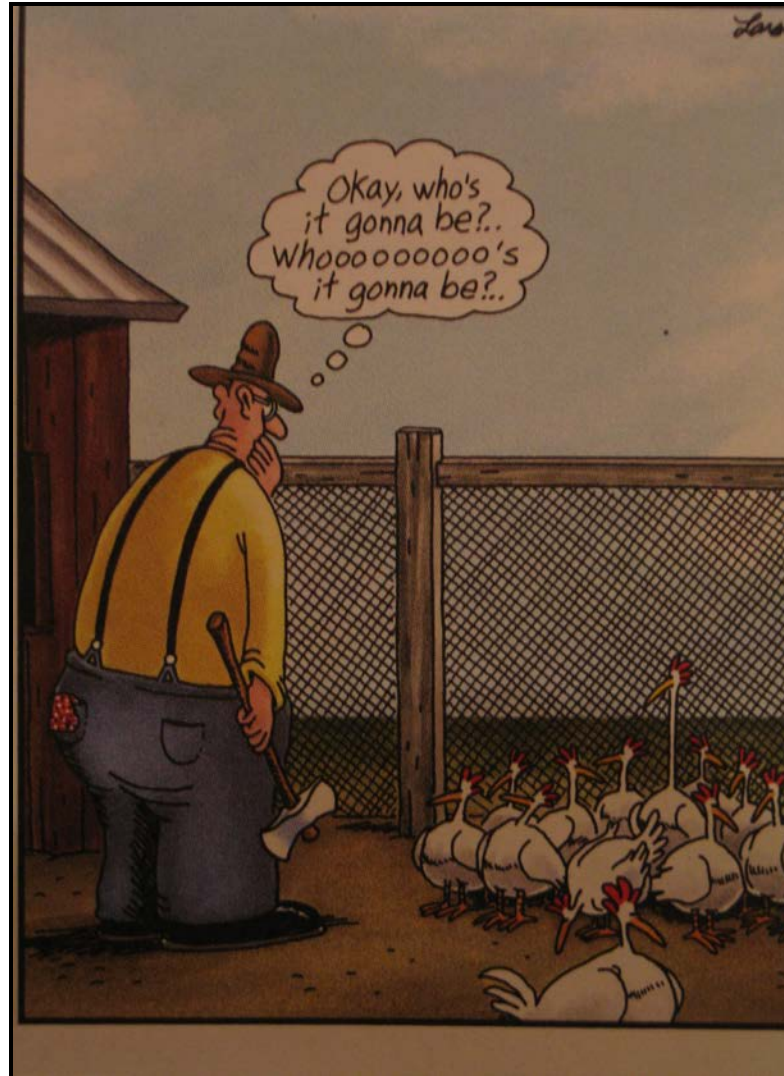
70 Gy in 35 Fxs

**LOW and INT RISK
OPC**

CI: Trotti, Gillison

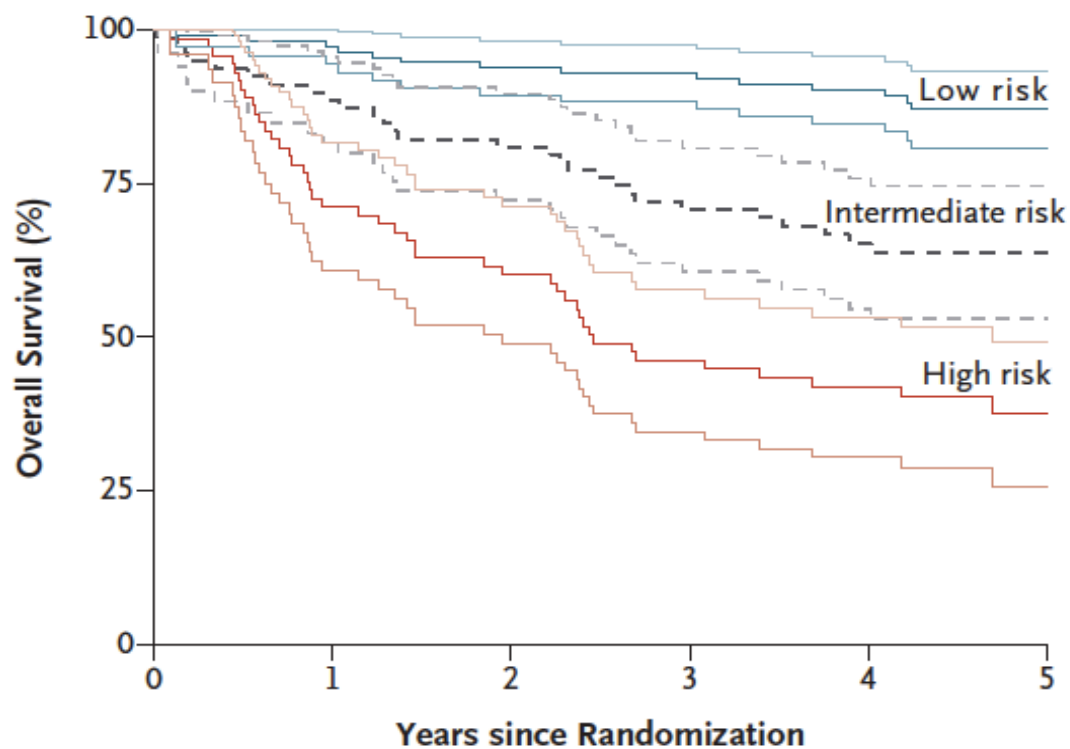
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Personalised treatment selection



Risk factors in the new age

3 risk categories:

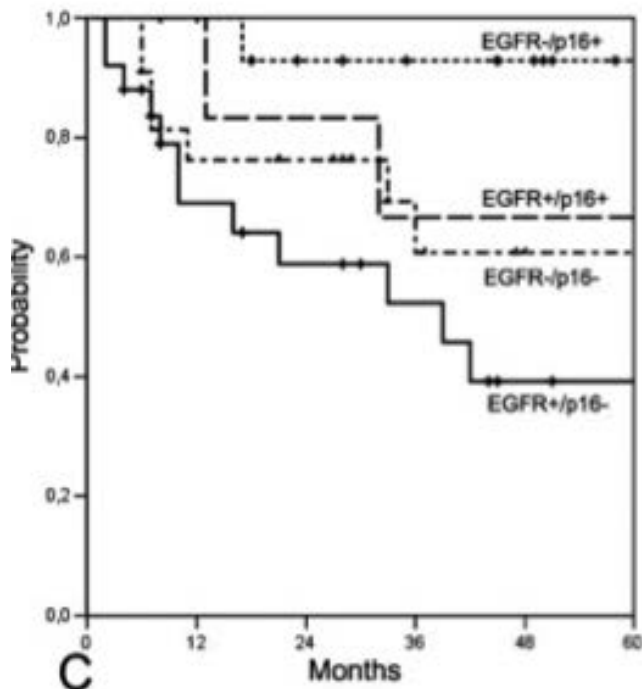


No. at Risk

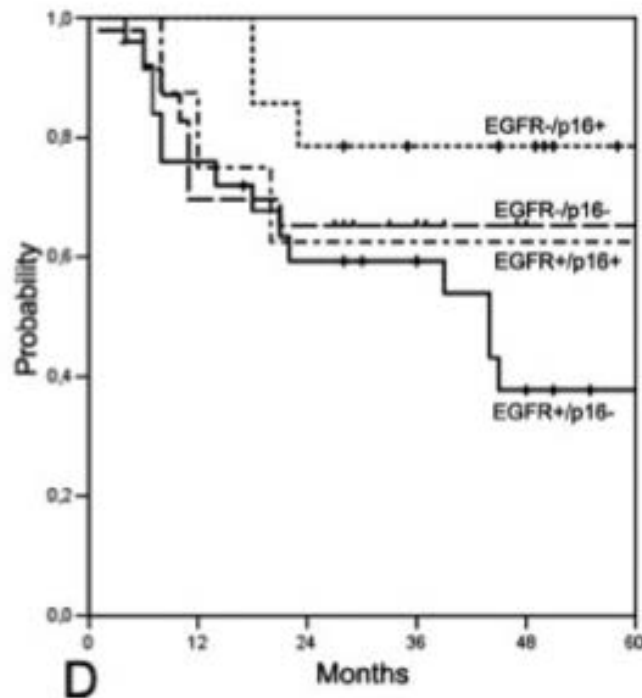
Low risk	114	111	106	102	95	46
Intermediate risk	79	70	64	54	44	24
High risk	73	52	43	33	28	8

EGFR inhibitors – biological rationale

- 40% of p16+ are high EGFR expressors Kumar, *JCO*, 2008
- p16+, EGFR+ worse outcome than p16+, EGFR-
Reimar. *Int J Cancer*. 2007



DSS



OS

Biomarkers with prognostic effect

CLINICAL REVIEW

David W. Eisele, MD, *Section Editor*

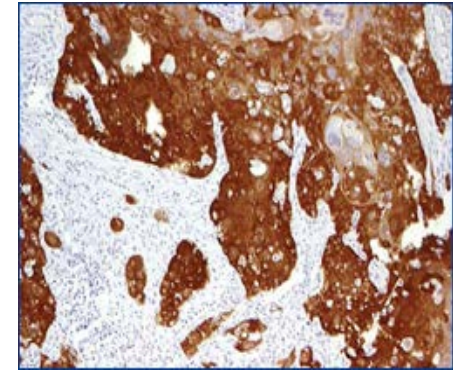
Prognostic biomarkers of survival in oropharyngeal squamous cell carcinoma: systematic review and meta-analysis

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Biomarkers with prognostic effect

Biomarker	No of cases	Distribution (% cohort that is positive)	Relative Risk (95% CI)
Bcl2	97	8.2	0.40 (0.22-0.71)
HPV *	538	37.9	0.44 (0.44-0.58)
p16 *	291	37.5	0.43 (0.31-0.60)
EGFR*	128	32	1.20 (0.94-1.53)
COX2	82	45.1	1.36 (1.00-1.83)
FHIT	34	42.4	1.62 (1.13-2.34)
MVP	78	26.9	1.88 (1.13-3.14)
CD31 microvessel density*	132	53.0	1.96 (1.5-2.55)
HIF1 α *	178	36.7	2.35 (1.42-3.90)
Cyclin D1 (nuclear)	32	50.8	3.61 (1.79-7.73)
c-met	97	4.1	3.72 (1.77-7.86)
PLK	157	50.3	4.30 (2.13-8.70)
Survivin (nuclear)	94	19.1	5.66 (1.57-20.33)
EGFR copy number	75	58	4.0 (1.4-11.6)



Biomarker classifiers to predict prognosis following treatment of oropharyngeal carcinoma

PredicTr-OPC

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

PredicTr-OPC team

- Buffa (Oxford)
- Harris (Oxford)
- Helliwell (Liverpool)
- Homer (Manchester)
- Jones (Liverpool)
- McCabe (Birmingham)
- Mehanna (Coventry)
- Nankivell (Coventry)
- Robinson (Newcastle)
- Snead (Coventry)
- Sloan (Newcastle)
- West (Manchester)

Economic cost of HPV

- HPV-related non-cervical disease, in USA, in 2003 = approx \$418 million (range, \$160 million - \$1.6 billion)

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Cover note





Do not change management of OPSCC patients without evidence

Enroll your patients into appropriate clinical trials

My ancestors were right....



"These guys were more health conscious
than we previously thought!"

InHANSE team

Clinical trials

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Michelle Faupel
Gemma Jones
Nyra Nyamayaro
Linda Wagstaff
Lucy Winterbottom

Translational

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