Management of HPV(+) Oropharyngeal cancer another entity?

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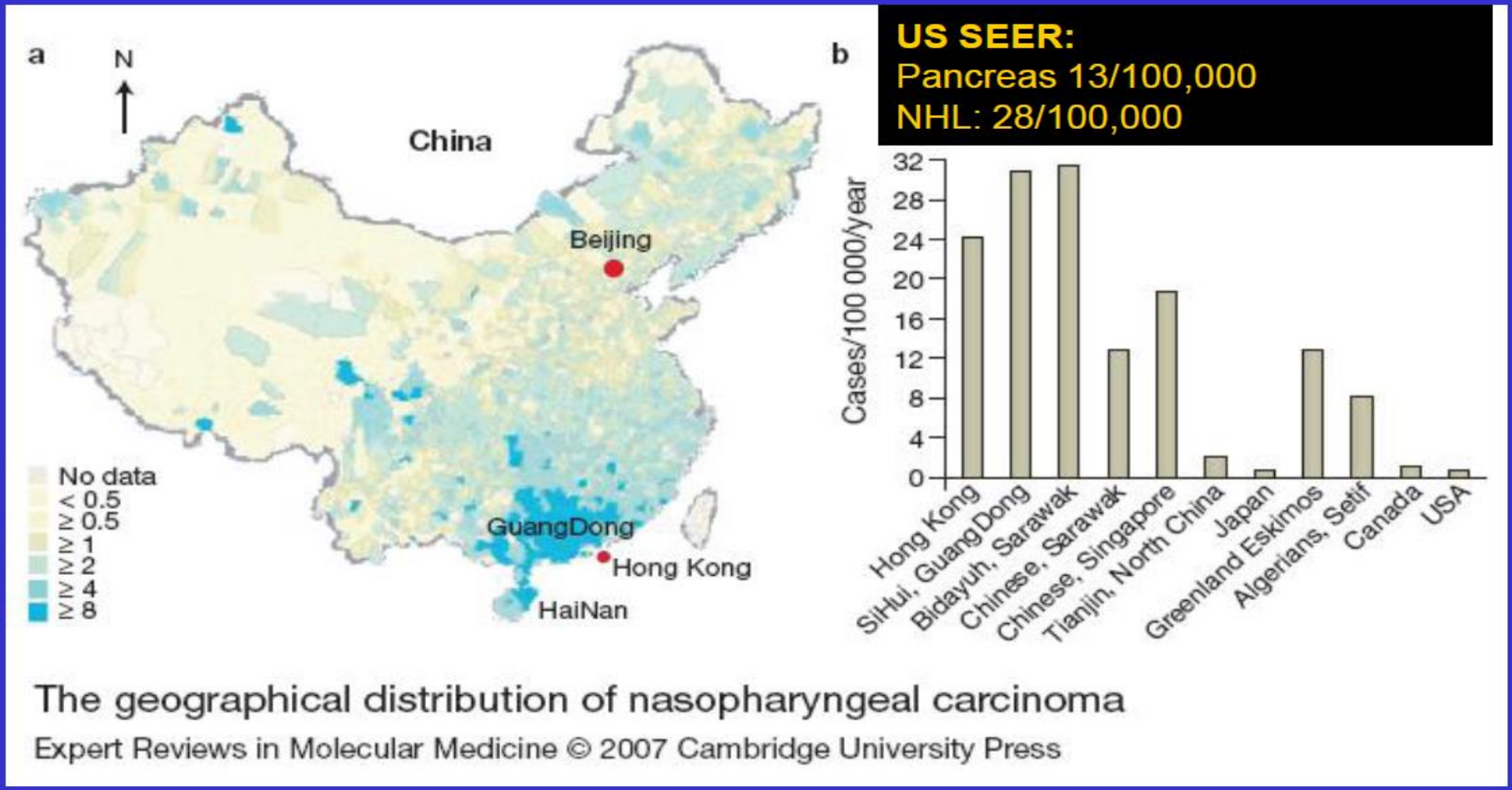
Conflicts of interest

- **No relevant conflicts of interest**

Head and neck cancer

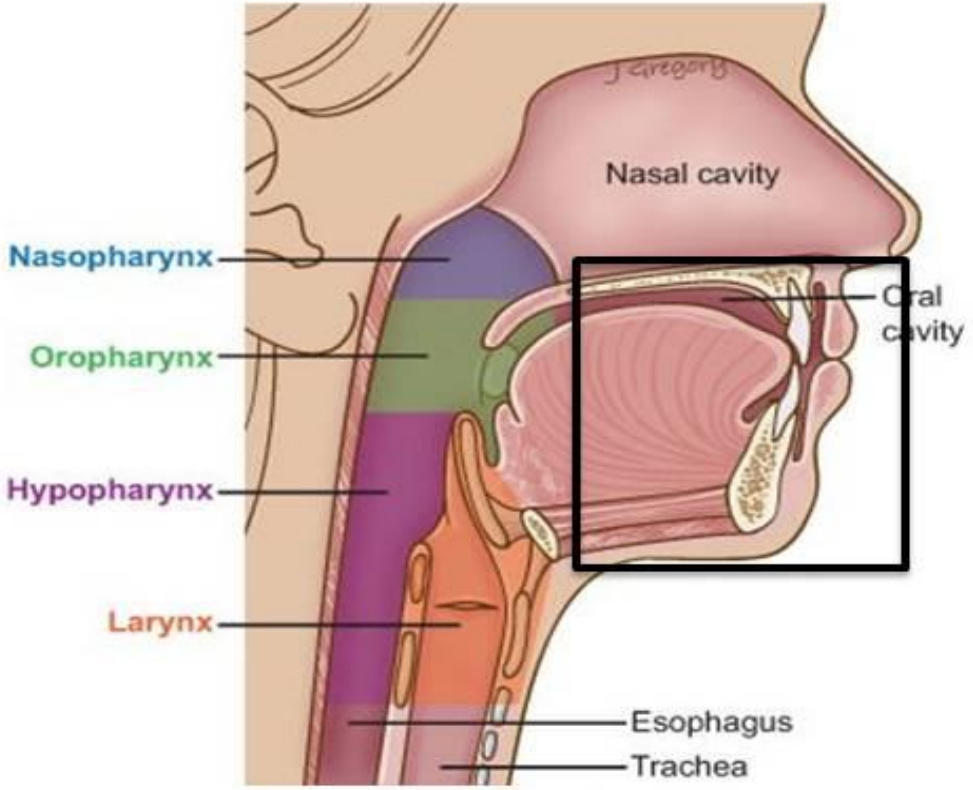
- **Multiple primary sites, but uniformity in biology, etiology and clinical course**
- **Mostly squamous cell histology**
- **Tobacco, ethanol and viruses (EBV, HPV), the main causative factors**

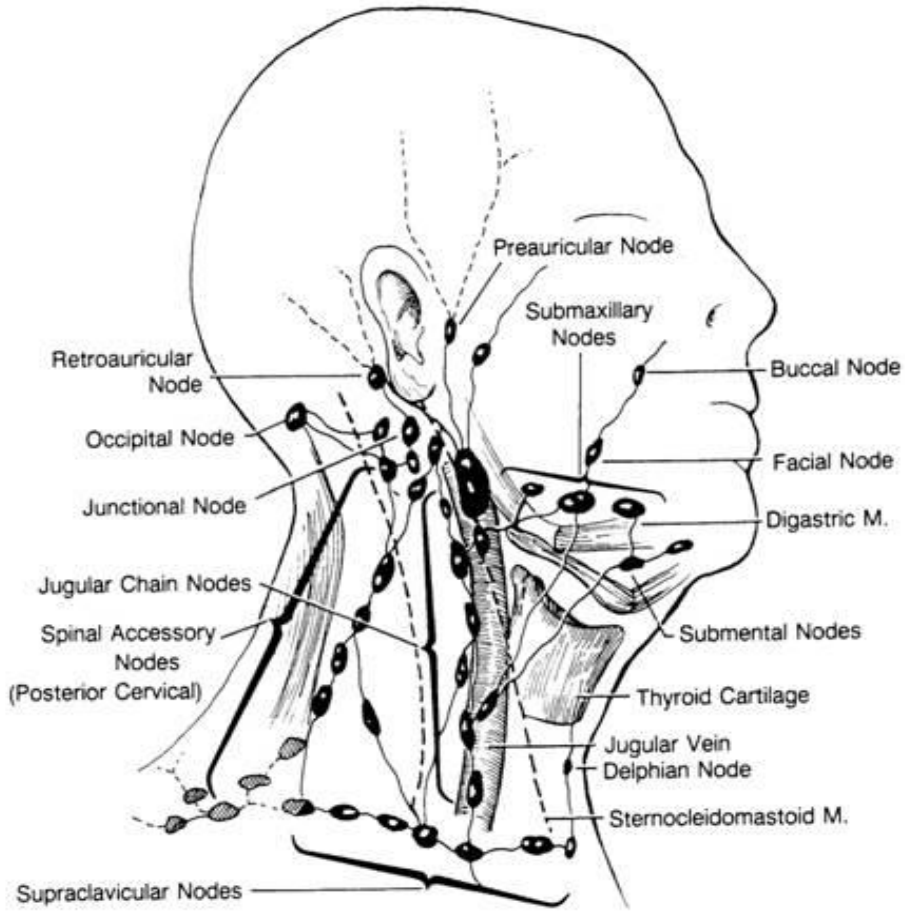
The global burden of endemic NPC



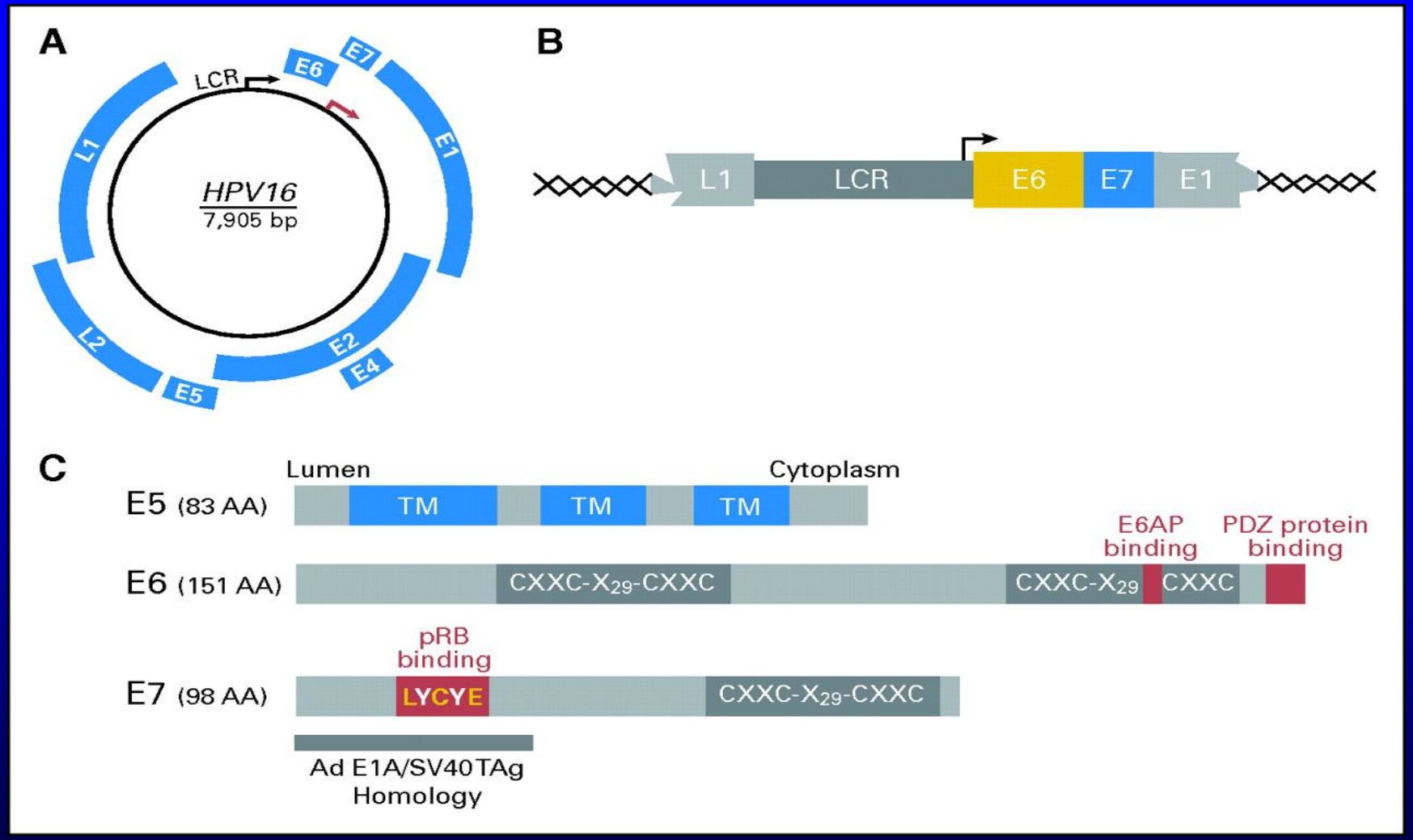
The geographical distribution of nasopharyngeal carcinoma

Q Tao, ATC Chan. Expert RW in Mole Med Vol. 9; Issue 12; May 2007



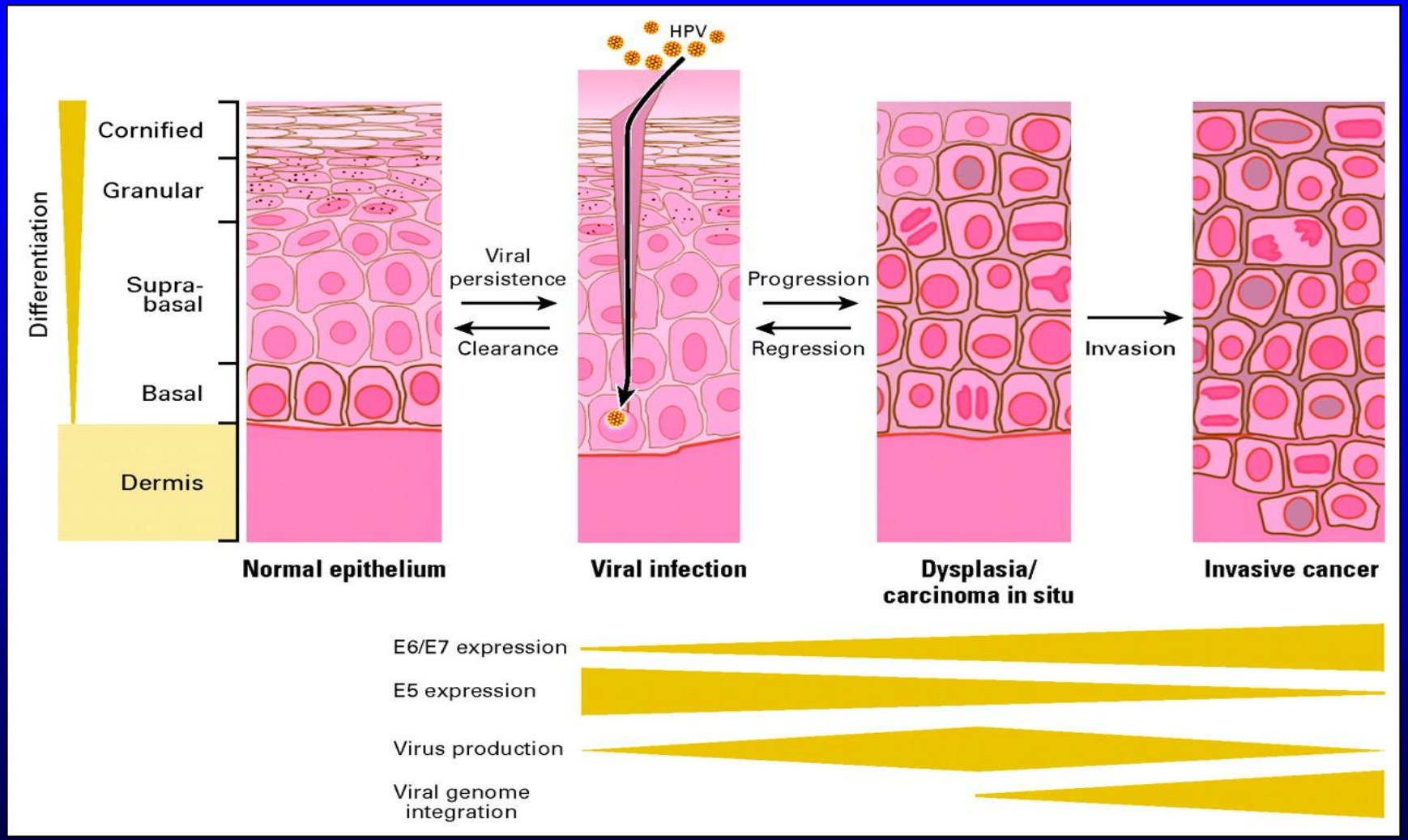


Human papillomavirus (HPV) genome organization.



Hellner K , Münger K JCO 2011;29:1785-1794

Human papillomavirus (HPV) infection of epithelial cells.



Hellner K , Münger K JCO 2011;29:1785-1794

JOURNAL OF CLINICAL ONCOLOGY

Changing epidemiology of head and neck cancers

- **Increasing incidence of HPV-related head and neck cancer sites**
  - **Canada (*Auluck et al. Cancer, 2010*)**
  - **Denmark (*Blomberg et al. IJC, 2010*)**
  - **Netherlands (*Braakhuis et al. Oral Oncol, 2009*)**
  - **Sweden (*Hammarstedt et al. IJC, 2006*)**
  - **USA (*Chaturvedi et al. JCO, 2008*)**
  - **UK (*Conway et al. Oral Oncol, 2006*)**

Abst# 6004: Human papillomavirus (HPV) as a risk factor for the increase in incidence of tonsillar cancer and its effect on survival

H. Dahlstrand, L. Hammarstedt, D. Lindquist, W. Ye, T. Dalianis, E. Munck-Wikland

SCCHN…

"Human papillomavirus (HPV) as a risk factor for the increase in incidence of tonsillar cancer and its effect on survival.

- In Stockholm, 2.8 fold increase incidence 1970 – 2002
- 99/203 (49%) HPV ⊕
- E6 / E7 mRNA expressed in 94% of HPV 16 positive samples

Dahlstrand et al
Abst 6004, ASCO 208

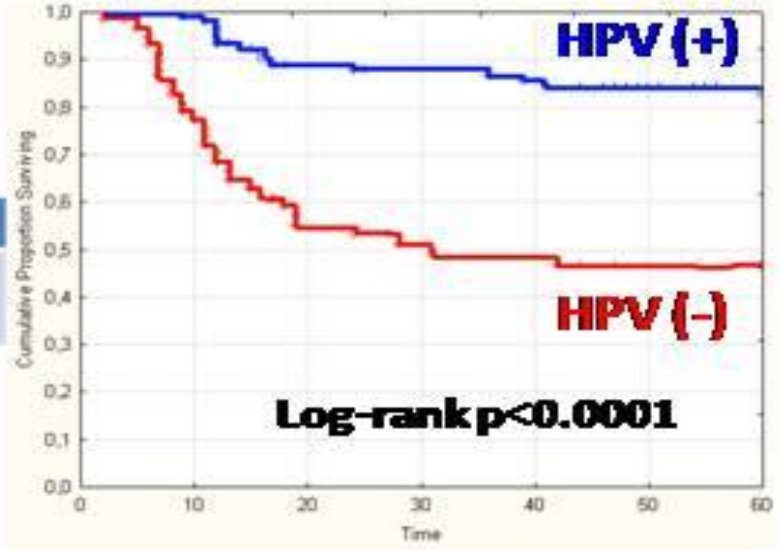
HPV and Tonsillar Cancer in Stockholm

- 99/203: 49% HPV positive (1970-2003)

HPV16	HPV33	HPV35	HPV45	HPVX
86 (87%)	3 (3%)	1 (1%)	1 (1%)	8 (5%)

- HPV-16 E6 and/or E7 mRNA was expressed in 94% of assessable HPV-16 positive tonsillar cancer samples

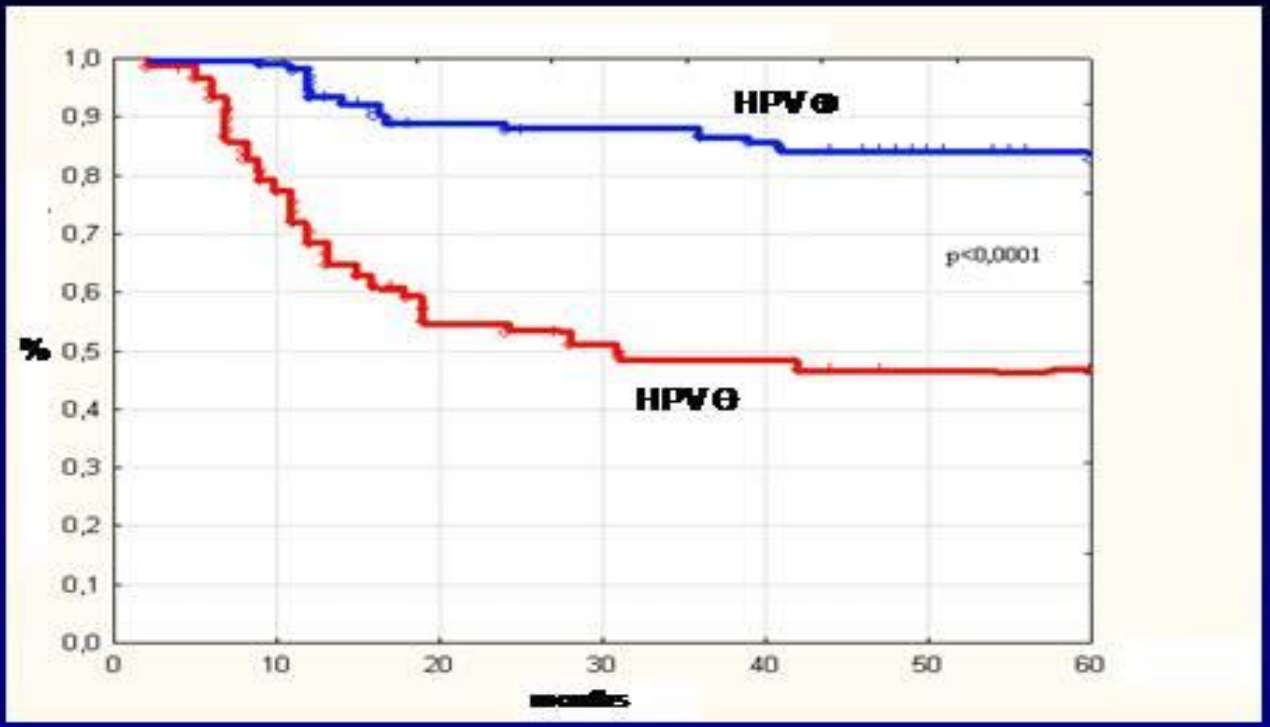
Disease-Specific Survival
Treated with radiation alone



Independent of age, gender and stage:
Cox multivariate HR 0.17 (95 % CI 0.09-0.32)

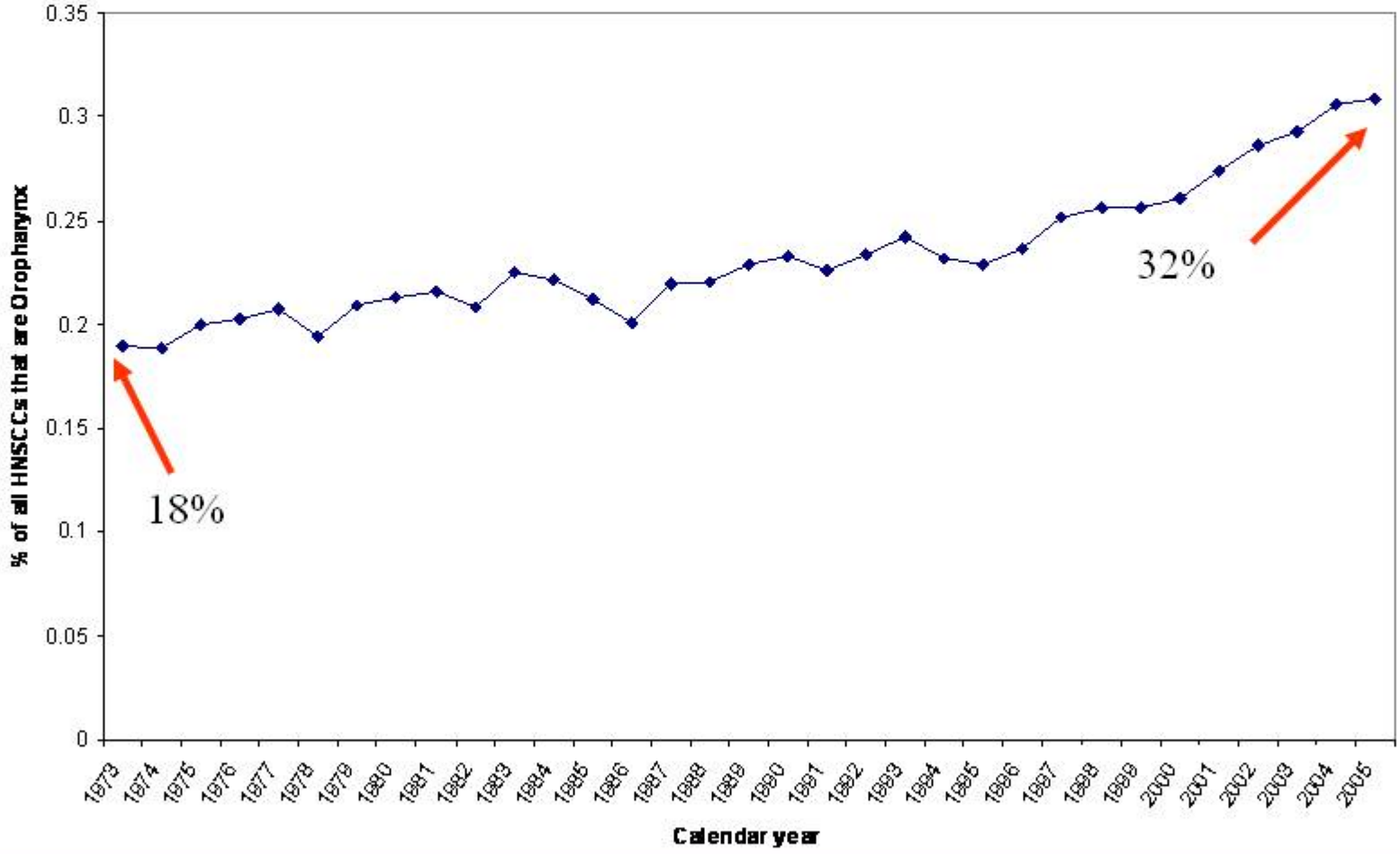
Dahlstrand, et al. ASCO 2008

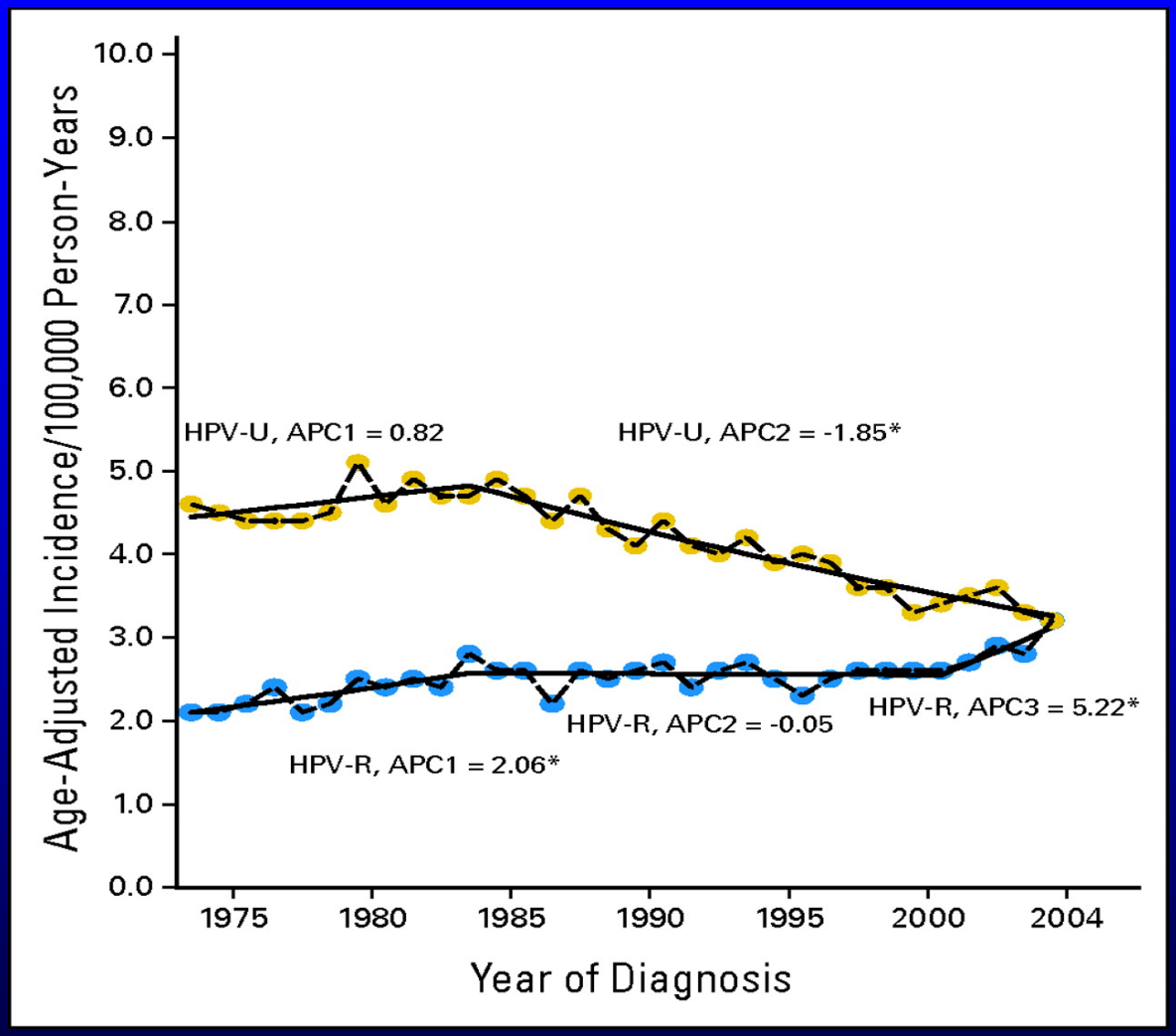
Higher survival rate in patients with HPV-positive tonsillar cancer in Stockholm



H Dahlstrand

Proportion of all HNSCC that are oropharynx, U.S. 1973-2005





Chaturvedi A K et al. JCO 2008;26:612-619

JOURNAL OF CLINICAL ONCOLOGY

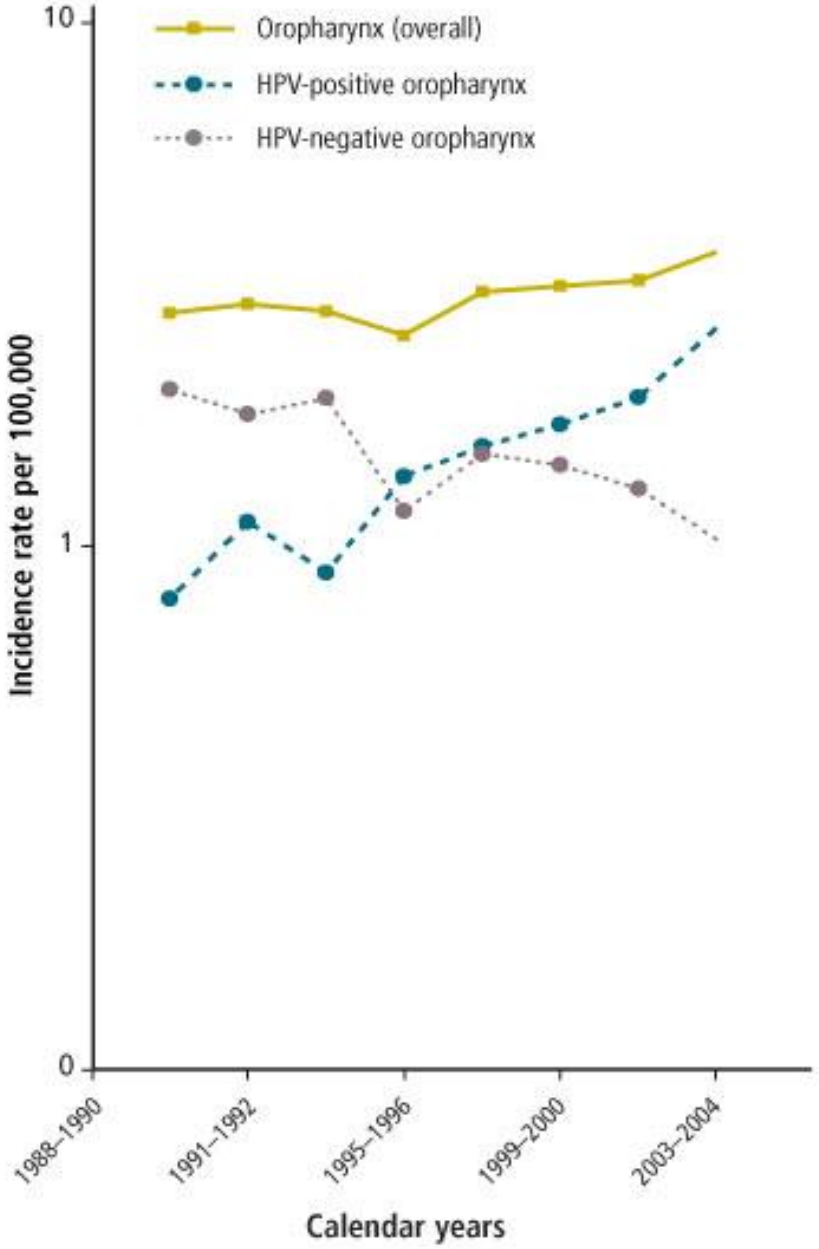
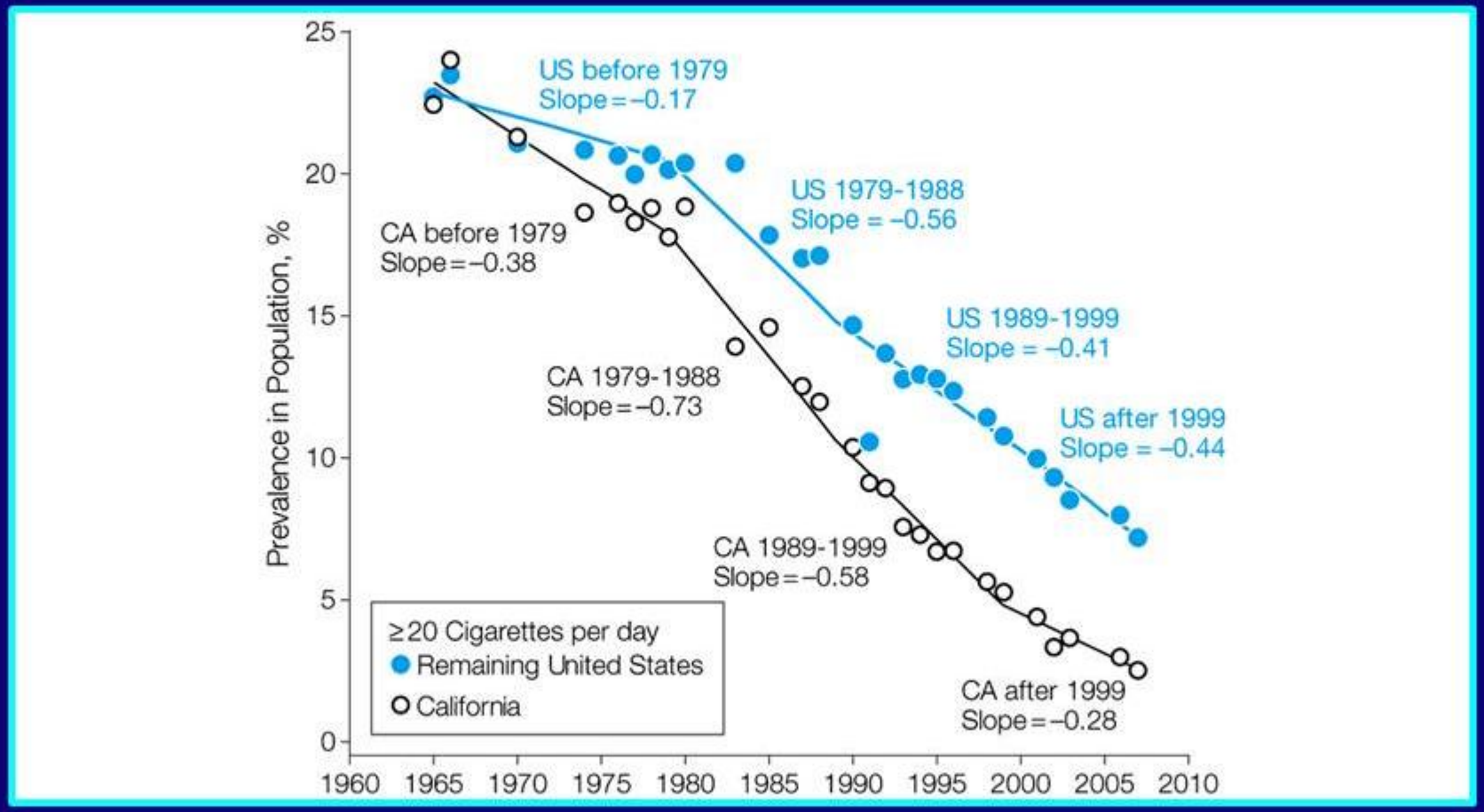


Figure 2. Incidence rates for overall oropharyngeal cancer, HPV-positive oropharyngeal cancer, and HPV-negative oropharyngeal cancer from 1988 to 2004 in Hawaii, Iowa, and Los Angeles. (Chaturvedi AK, et al. *J Clin Oncol* 2011)

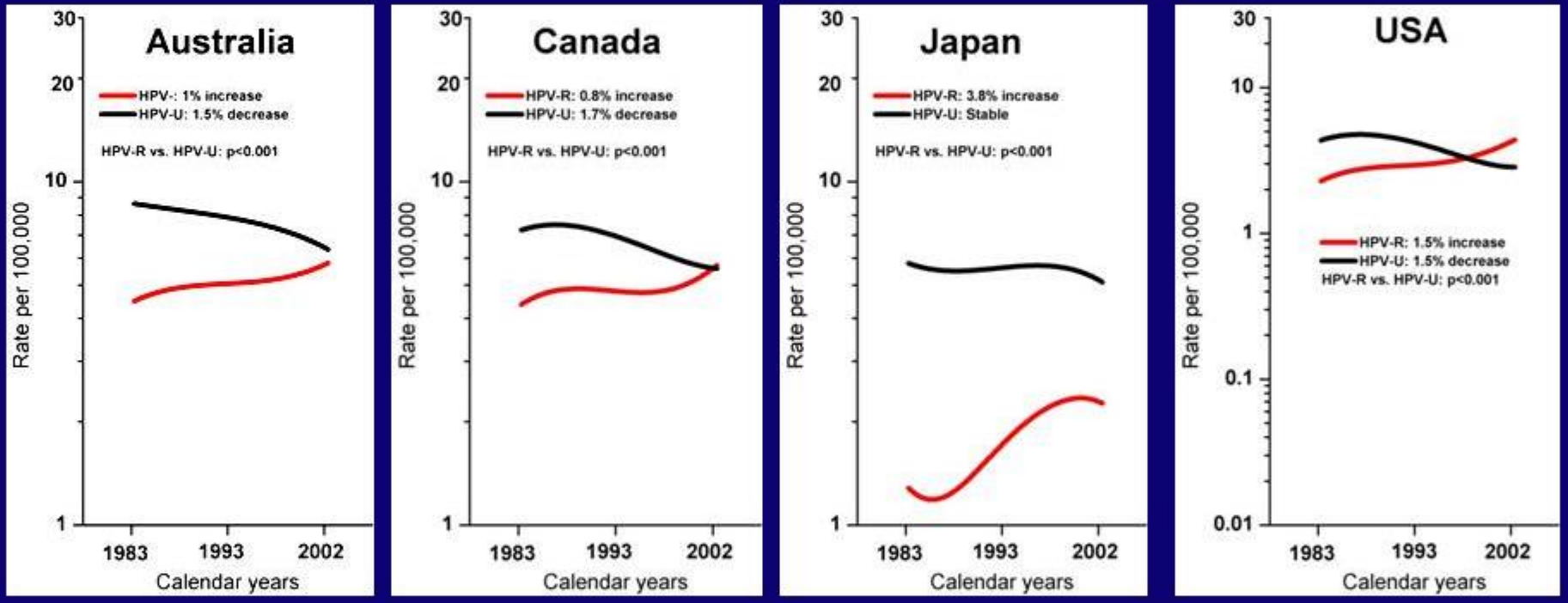
Prevalence of High-Intensity Smoking, 1965-2007



Pierce, J. P. et al. JAMA 2011;305:1106-1112

JAMA

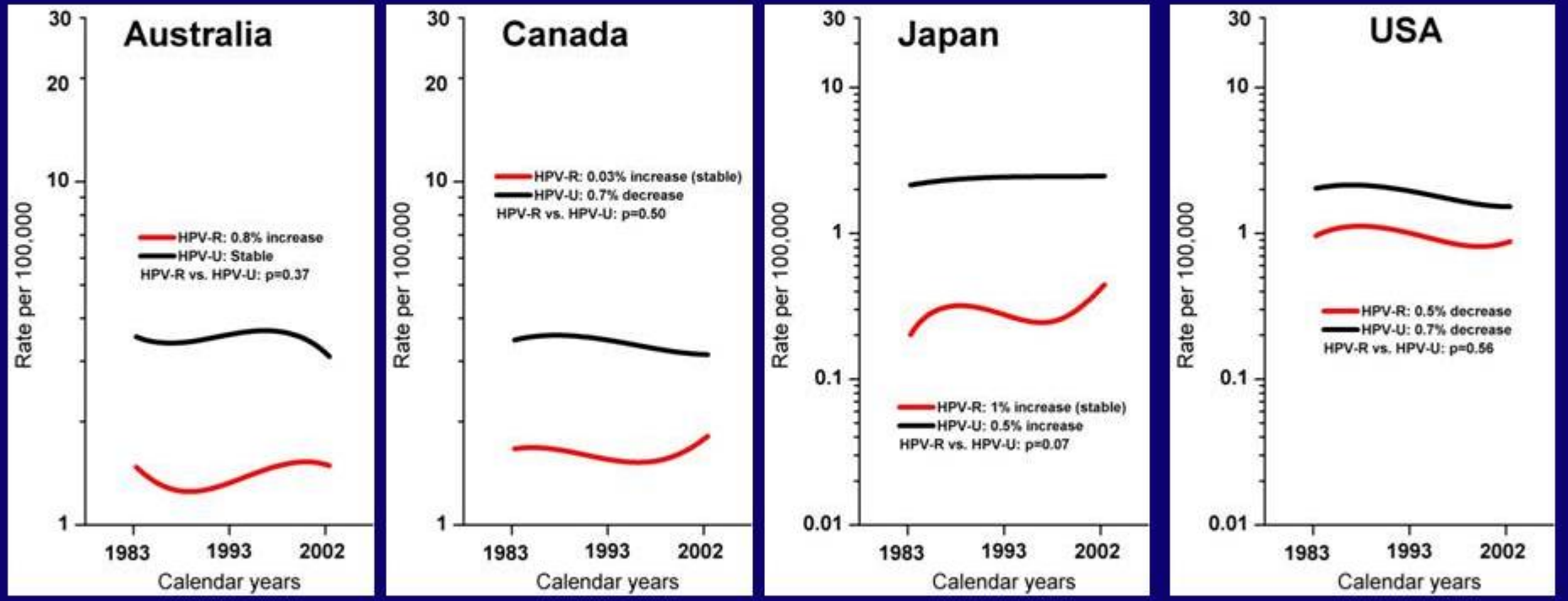
Rising incidence for HPV-R HNSCC 1983-2002 (men)



- **Increasing incidence for HPV-R and decreasing/stable incidence for HPV-U**

Chaturvedi AK et al. In preparation

A male phenomenon



- **No increases in incidence for HPV-R HNSCC sites among women**

Original Article

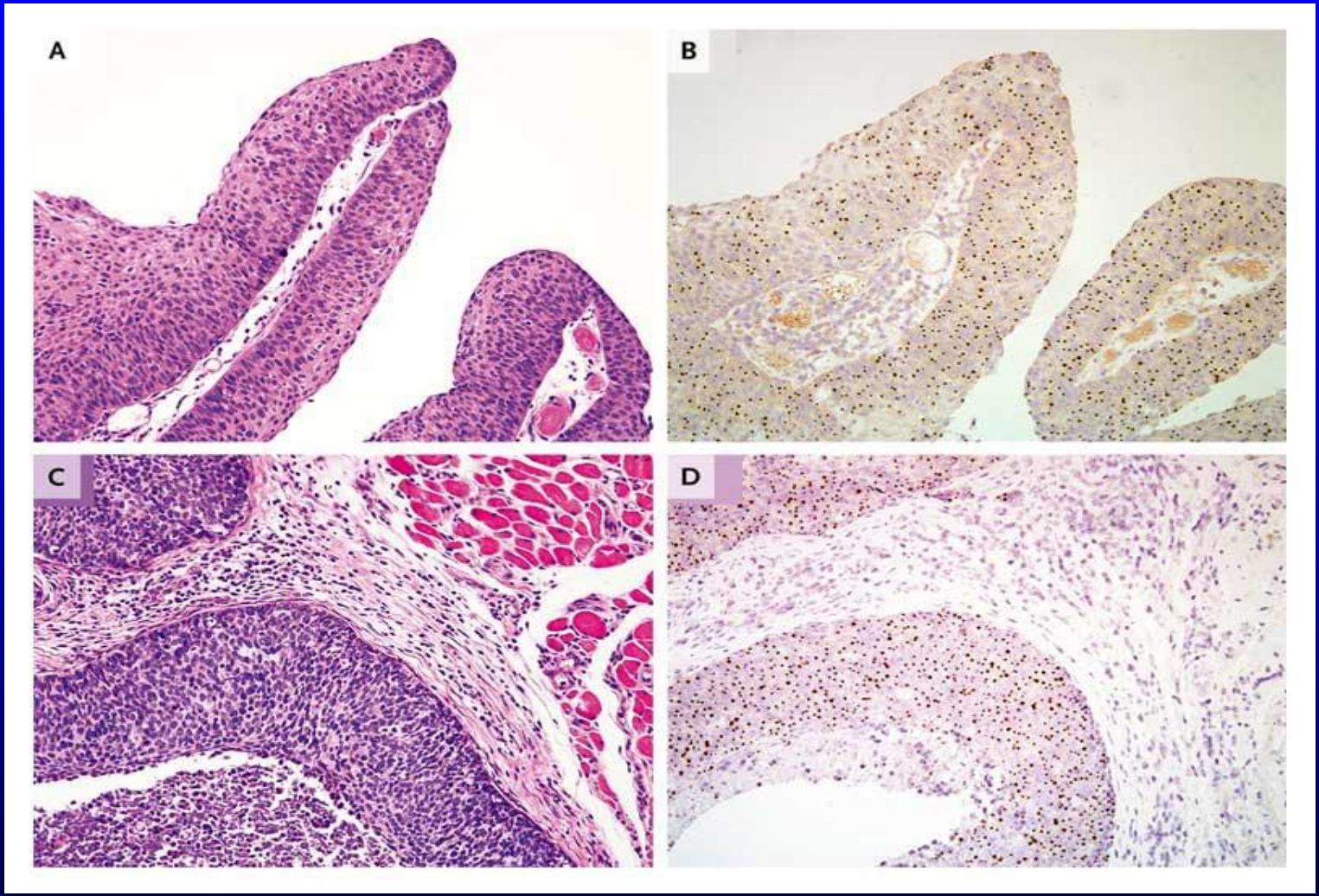
Case-Control Study of Human Papillomavirus and Oropharyngeal Cancer

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.

N Engl J Med
Volume 356(19):1944-1956
May 10, 2007

The NEW ENGLAND JOURNAL of MEDICINE

Representative Case of Oropharyngeal Squamous-Cell Carcinoma That Was Positive for HPV-16 on In Situ Hybridization



D'Souza G et al. N Engl J Med 2007;356:1944-1956

Association of Oropharyngeal Cancer with Exposure to HPV and with Biomarkers of Cancer Associated with HPV-16

Table 3. Association of Oropharyngeal Cancer with Exposure to HPV and with Biomarkers of Cancer Associated with HPV-16.

Measure of HPV Exposure or Disease	Prevalence		Odds Ratio (95% CI)	
	Case Patients (N=100)	Control Patients (N=200)	Unadjusted	Adjusted*
	number (percent)			
HPV-16 L1 serologic status				
Seronegative	43 (43)	186 (93)	1.00	1.00
Seropositive	57 (57)	14 (7)	17.6 (8.8–34.5)	32.2 (14.6–71.3)
Oral HPV-16 infection†				
Negative	68 (68)	192 (96)	1.00	1.00
Positive	32 (32)	8 (4)	11.3 (5.0–25.7)	14.6 (6.3–36.6)
Any oral HPV infection‡				
Negative	63 (63)	189 (94)	1.00	1.00
Positive	37 (37)	11 (6)	10.0 (4.8–20.7)	12.3 (5.4–26.4)
HPV-16 E6 or E7 serologic status				
Seronegative for E6 and E7	36 (36)	192 (96)	1.00	1.00
Seropositive for E6 or E7	64 (64)	8 (4)	33.3 (16.2–68.6)	58.4 (24.2–138.3)
HPV-16 DNA in tumor				
Absent	28 (28)	—	—	—
Present	72 (72)	—	—	—

* Odds ratios were adjusted for age, sex, tobacco use, alcohol use, dentition and toothbrushing, and presence or absence of a family history of head and neck cancer.

† Oral HPV-16 infection was detected with the use of a real-time PCR assay. The median number of cells analyzed for HPV DNA in case patients and control patients was similar (16,282 vs. 11,053 cells per 10-μl sample; P=0.11). The median HPV-16 viral load was 13.0 and 3.5 copies per 1000 cells among case patients and control patients who were positive for HPV-16, respectively.

‡ Infection of the oral cavity with any of 37 types of HPV was detected with the use of consensus-primer PCR. The HPV types detected, in order of prevalence, were 16 (23 patients), 72 (4 patients), 62 (3 patients), 58 (2 patients), 6 (2 patients), and 18, 31, 51, 55, 61, 66, 68, and 73 (1 patient each) among case patients and 58 (2 patients), 62 (2 patients), and 6, 42, 51, 56, 61, 66, 68, 73, and CP6108 (1 patient each) among control patients. Seven case patients and two control patients were infected with multiple types of HPV.

D'Souza G et al. N Engl J Med 2007;356:1944-1956

The NEW ENGLAND JOURNAL of MEDICINE

Conclusion

- Oral HPV infection is strongly associated with oropharyngeal cancer among subjects with or without the established risk factors of tobacco and alcohol use

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Two distinct head and neck cancers

	HPV-positive	HPV-negative
Anatomic site	Tonsil / BOT Paranasal sinus Larynx	All sites
Histology	Basaloid	Keratinized
Age	Younger	Older
Gender	3:1 men	3:1 men
SE status	High	Low
Risk factors	Sexual behavior	Alcohol / tobacco
Cofactors	Marijuana	Diet, hygiene
Survival	Improved	Worse
Incidence	Increasing	Decreasing

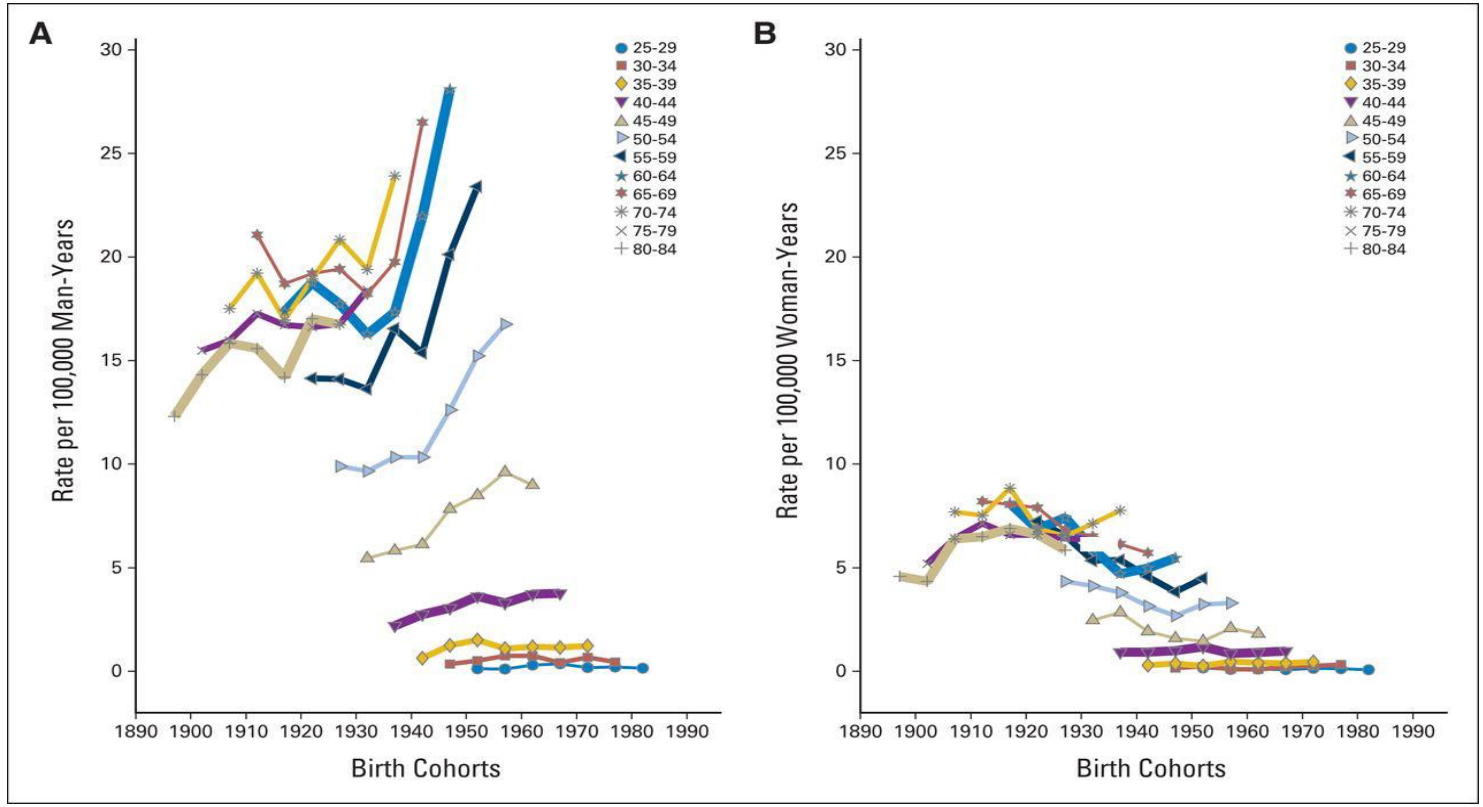

Fig 1. Shown are incidence rates for oropharyngeal cancers among (A) men and (B) women, stratified by cohort year of birth (in 10-year overlapping groups) and age (in 5-years groups). Data were derived from nine cancer registries covered by the National Cancer Institute's SEER program (1973 to 2011). Oropharyngeal cancers include the base of tongue, lingual tonsil, soft palate, uvula, tonsil, oropharynx, and Waldeyer's ring.

Published in: Maura L. Gillison; Anil K. Chaturvedi; William F. Anderson; Carole Fakhry; *JCO* **2015,** 33, 3235-3242.
DOI: 10.1200/JCO.2015.61.6995

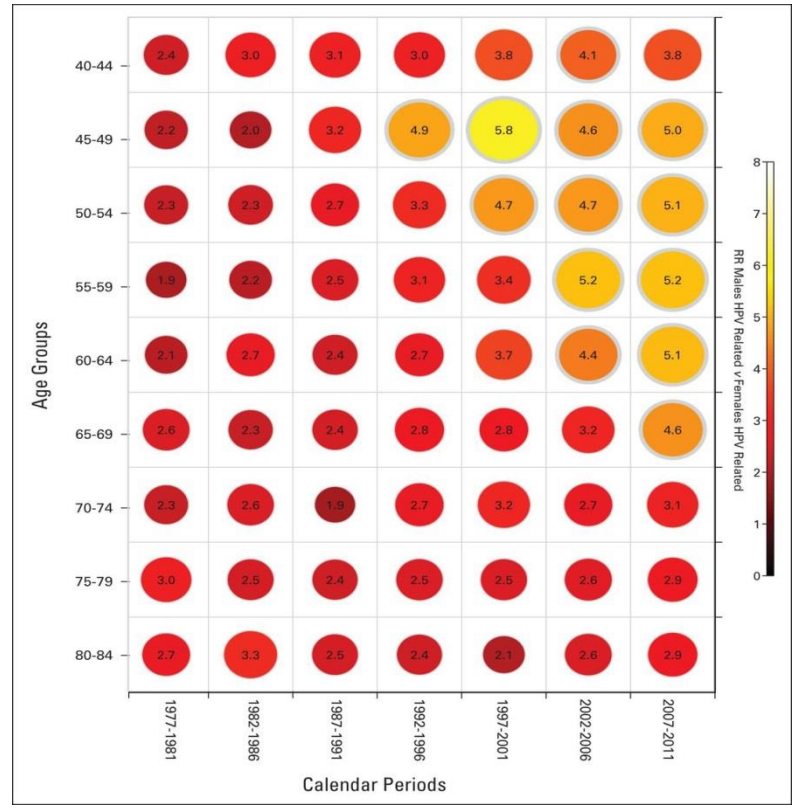

Fig 2. Shown are male-female incidence rate ratios (RRs) for oropharynx cancers, stratified by age in rows (5-year groups) and calendar periods in columns (5-year groups). The diagonals across the age groups and calendar years represent birth cohorts. The scale for the color-coded RRs is also shown on the right. Data were derived from nine cancer registries covered by the National Cancer Institute's SEER program (1973 to 2011). Oropharyngeal cancers include the base of tongue, lingual tonsil, soft palate, uvula, tonsil, oropharynx, and Waldeyer's ring. HPV, human papillomavirus.

Published in: Maura L. Gillison; Anil K. Chaturvedi; William F. Anderson; Carole Fakhry; *JCO* **2015,** 33, 3235-3242.
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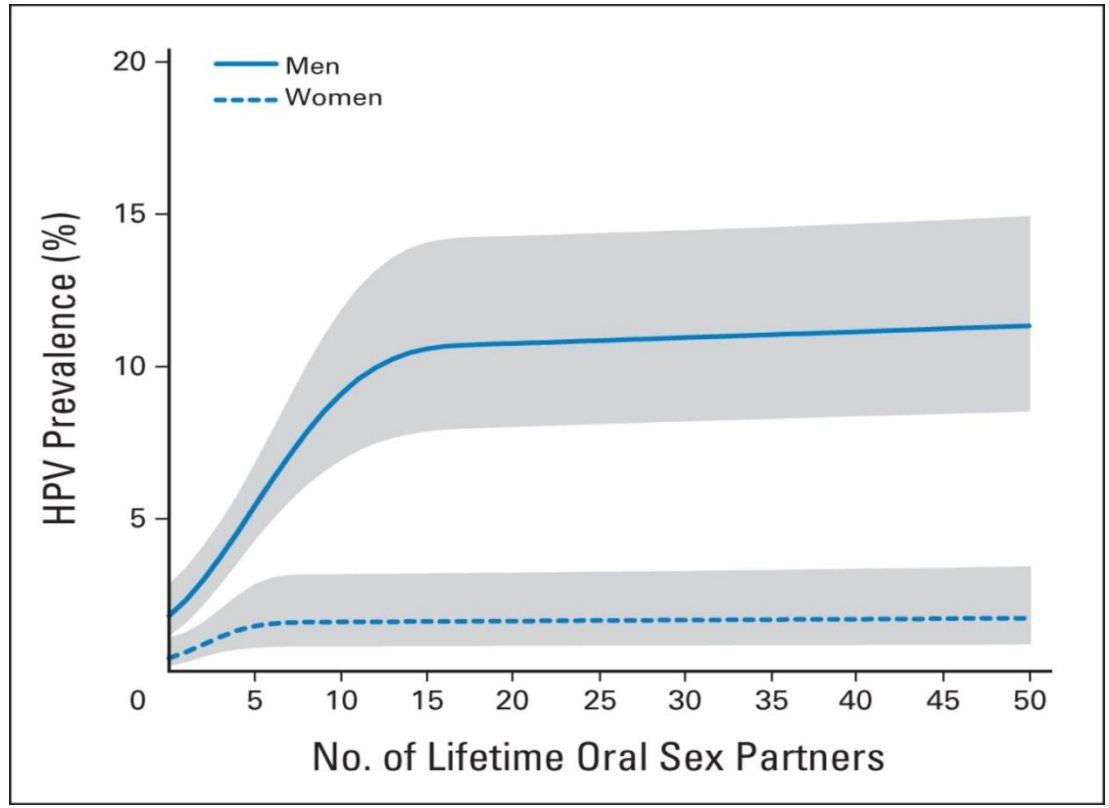


Fig 3. Shown are the associations of lifetime number of oral sex partners with oral human papillomavirus (HPV) prevalence among men (solid line) and women (dashed line) in the US population age 14 to 69 years. Data are based on the National Health and Nutrition Examination Survey (NHANES) 2009 to 2010 and 2011 to 2012 cycles. The shaded areas represent the 95% CIs. Reprinted by permission from the American Association for Cancer Research: Chaturvedi A, Graubard B, Broutian T, et al: NHANES 2009 to 2012 findings: Association of sexual behaviors with higher prevalence of oral oncogenic human papillomavirus infections in U.S. men. Cancer Res [epub ahead of print on April 14, 2015].

Published in: Maura L. Gillison; Anil K. Chaturvedi; William F. Anderson; Carole Fakhry; *JCO* **2015,** 33, 3235-3242.
DOI: 10.1200/JCO.2015.61.6995

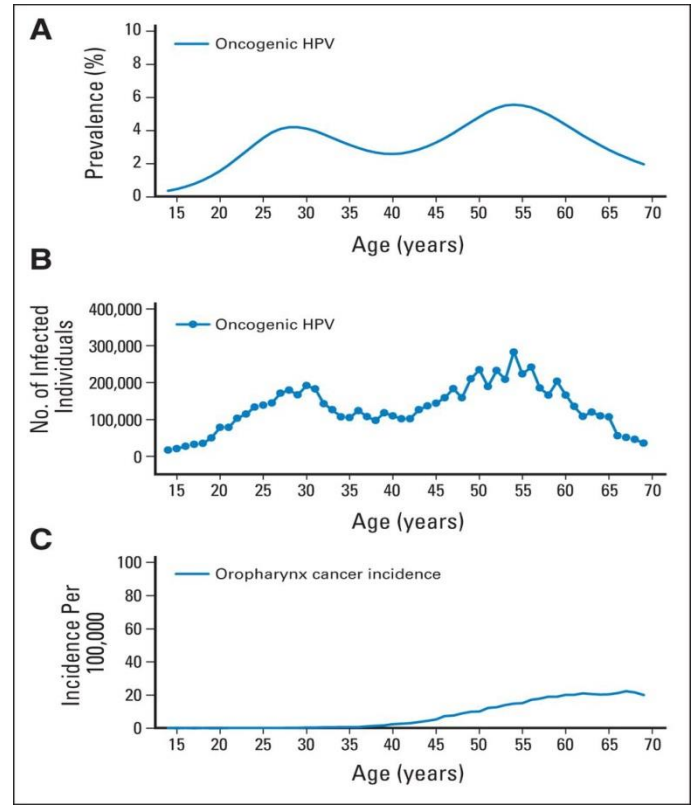
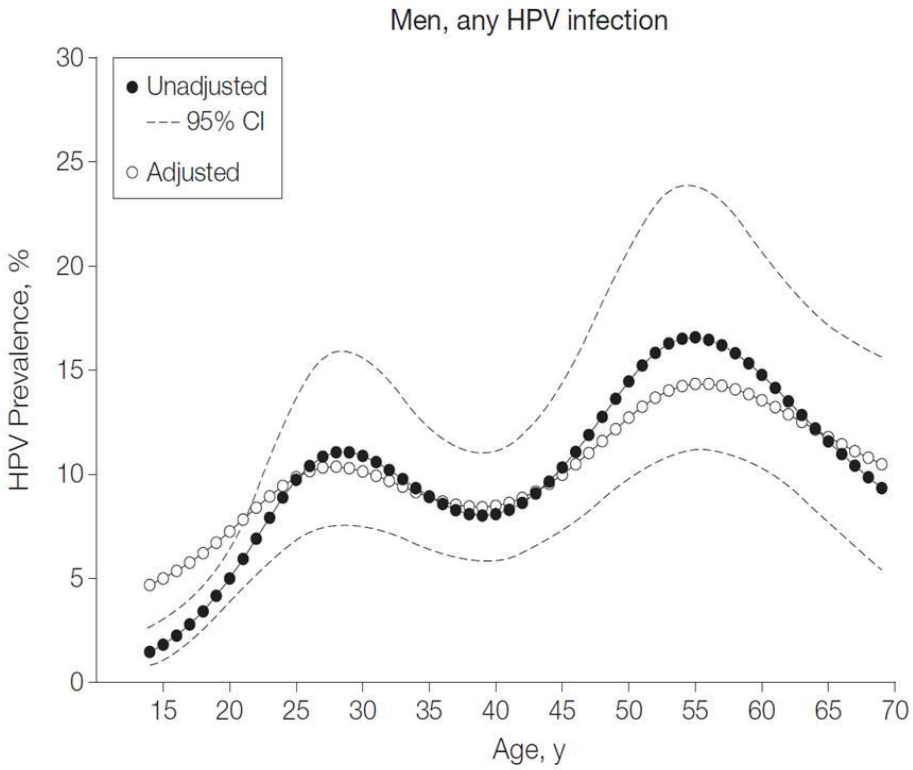


Fig 4. Shown are (A) the prevalence of 12 oral oncogenic human papillomavirus (HPV) types, (B) the number of individuals with prevalent infection with 12 oral oncogenic HPV types, and (C) the incidence rate per 100,000 of oropharyngeal cancer for ages 14 to 69 years in the US population. Oral HPV data are based on the National Health and Nutrition Examination Survey 2009 to 2010 and 2011 to 2012 cycles. Cancer incidence data are based on incidence rates in the year 2011 from nine cancer registries covered by the National Cancer Institute's SEER program (1973 to 2011). Oropharyngeal cancers include the base of tongue, lingual tonsil, soft palate, uvula, tonsil, oropharynx, and Waldeyer's ring.

Published in: Maura L. Gillison; Anil K. Chaturvedi; William F. Anderson; Carole Fakhry; *JCO* **2015,** 33, 3235-3242.
DOI: 10.1200/JCO.2015.61.6995

Oral HPV precedes oropharyngeal cancer



Gillison et al. JAMA 2012

Table 2. Associations of HPV-16, High-Risk Oncogenic HPVs, and Other α-HPV Types With Overall Risk of Incident HNSCC and Tumor Subtypes

	Participants, No. (%)		Adjusted Model[a]	
α-HPV Type	Cases	Controls	OR (95% CI)[a]	*P* Value
All HNSCCs	n = 132	n = 395[b]		
HPV-16	12 (9.1)	7 (1.8)	7.07 (2.22-22.55)	.001
High-risk HPVs excluding HPV-16[c]	6 (4.5)	20 (5.1)	0.82 (0.27-2.48)	.72
Non-high-risk HPV types	20 (15.2)	38 (9.6)	1.78 (0.90-3.50)	.10
Any α-HPV	32 (24.2)	55 (13.9)	2.25 (1.27-4.01)	.01
Oropharynx cancer	n = 25	n = 75		
HPV-16	5 (20.0)	1 (1.3)	22.41 (1.81-276.7)	.02
High-risk HPVs excluding HPV-16[c]	1 (4.0)	3 (4.0)	0.90 (0.07-11.17)	.93
Non-high-risk HPV types	5 (20.0)	11 (14.7)	1.61 (0.48-5.43)	.44
Any α-HPV	9 (36.0)	13 (17.3)	2.69 (0.91-7.94)	.07
Oral cavity cancer	n = 43	n = 127		
HPV-16	6 (14.0)	2 (1.6)	4.51 (0.59-34.73)	.15
High-risk HPVs excluding HPV-16[c]	1 (2.3)	9 (7.1)	0.51 (0.06-4.26)	.53
Non-high-risk HPV types	6 (14.0)	9 (7.1)	1.93 (0.54-6.85)	.31
Any α-HPV	12 (27.9)	18 (14.2)	1.93 (0.70-5.31)	.20
Larynx cancer[d]	n = 64	n = 193		
HPV-16	1 (1.6)	4 (2.1)	0.11 (0.01-834.8)	.63
High-risk HPVs excluding HPV-16[c]	4 (6.3)	8 (4.2)	0.91 (0.16-5.12)	.91
Non-high-risk HPV types	9 (14.1)	18 (9.3)	3.15 (0.95-10.43)	.06
Any α-HPV	11 (17.2)	24 (12.4)	2.46 (0.83-7.27)	.10

Agalliu et al. Jama Oncol 2016

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.

N Engl J Med
Volume 363(1):24-35
July 1, 2010

The NEW ENGLAND JOURNAL of MEDICINE

Study Overview

- Human papillomavirus (HPV)-associated oropharyngeal squamous-cell carcinoma differs from oropharyngeal cancers caused by tobacco and other factors
- In this study, patients with oropharyngeal cancer were treated with cisplatin plus radiation therapy; the 3-year rate of overall survival was 82.4% among patients with HPV-positive tumors and 57.1% among patients with HPV-negative tumors
- HPV status is an independent prognostic factor for survival among patients with oropharyngeal squamous-cell carcinoma

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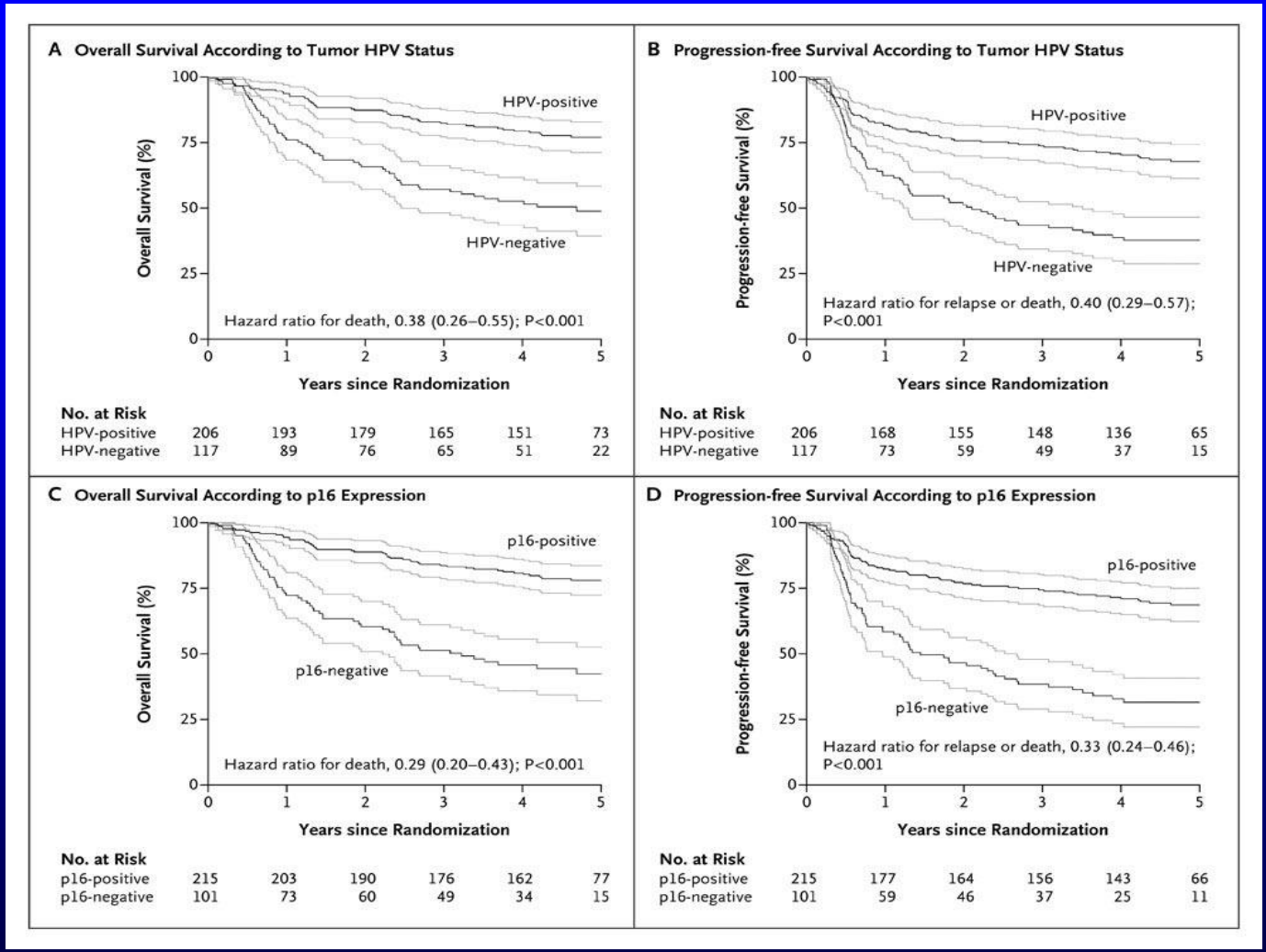
Kaplan-Meier Estimates of Survival among the Study Patients with Oropharyngeal Cancer, According to Tumor HPV Status or p16-Expression Status



Ang KK et al. N Engl J Med 2010;363:24-35

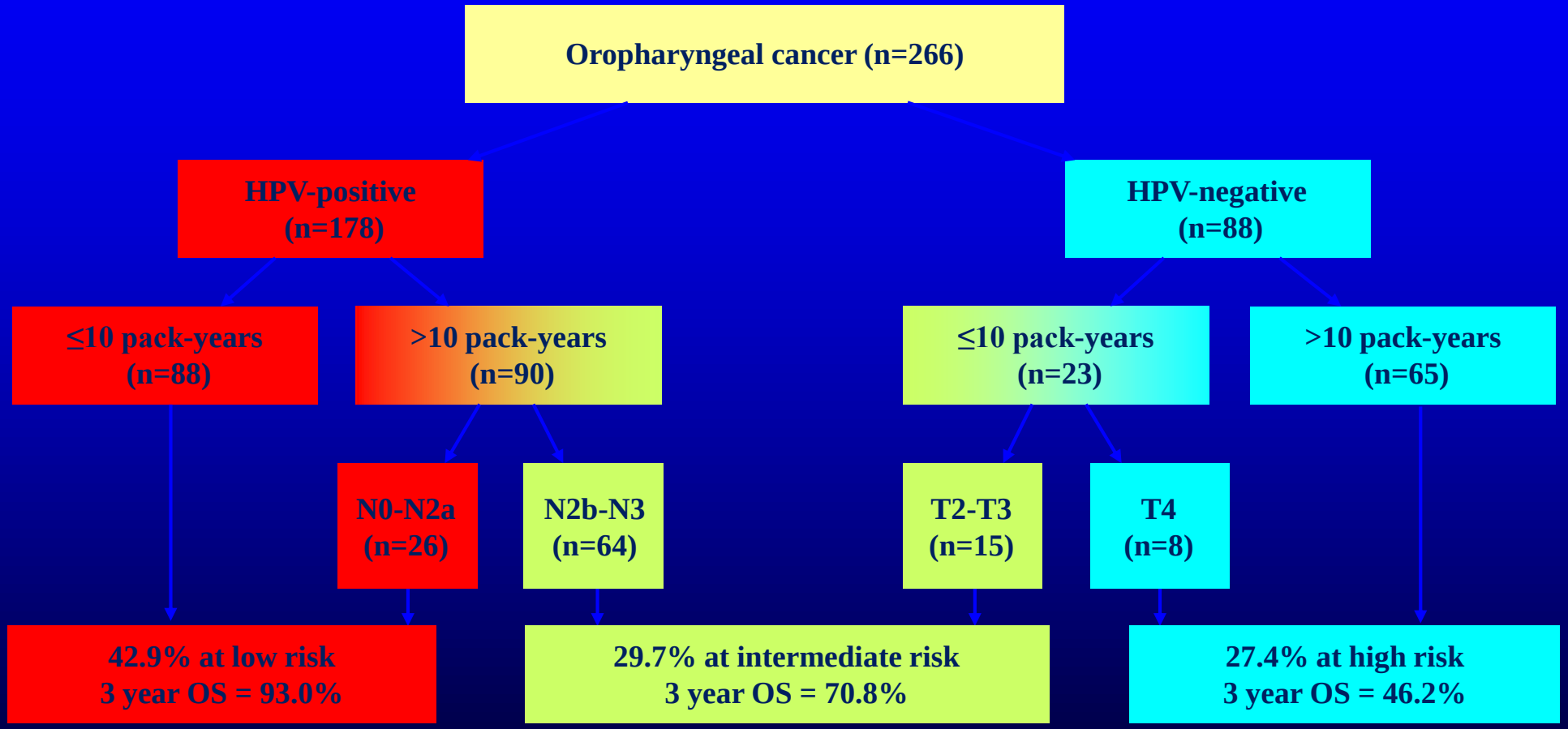
The NEW ENGLAND JOURNAL of MEDICINE

Conclusion

- **Tumor HPV status is a strong and independent prognostic factor for survival among patients with oropharyngeal cancer**

The NEW ENGLAND JOURNAL of MEDICINE

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



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

Ang KK, et al. NEJM

Effect of p16 and tobacco use on OS and PFS for oropharynx cancer in RTOG 9003

ML Gillison, Q Zhang, KK Ang, KK Fu, ME Hammond, R Jordan, A Trotti, S Spencer, M Rotman, CH Chung on behalf of the Radiation Therapy Oncology Group

The Ohio State University, RTOG Statistical Center, University of Texas M.D. Anderson Cancer Center, LDS Hospital, University of California San Francisco, H. Lee Moffitt Cancer Center & Research Institute, University of Alabama at Birmingham Medical Center, SUNY Health Science Center Brooklyn, Vanderbilt University Medical Center.

Radiation Therapy Oncology Group 9003

STRATIFY

Tumor Site
1. Oral Cavity
2. Oropharynx
3. Hypopharynx/larynx

Nodal Stage
1. N0
2. N1-N3

Karnofsky PS
1. 90-100
2. 60-80

RANDOMIZE

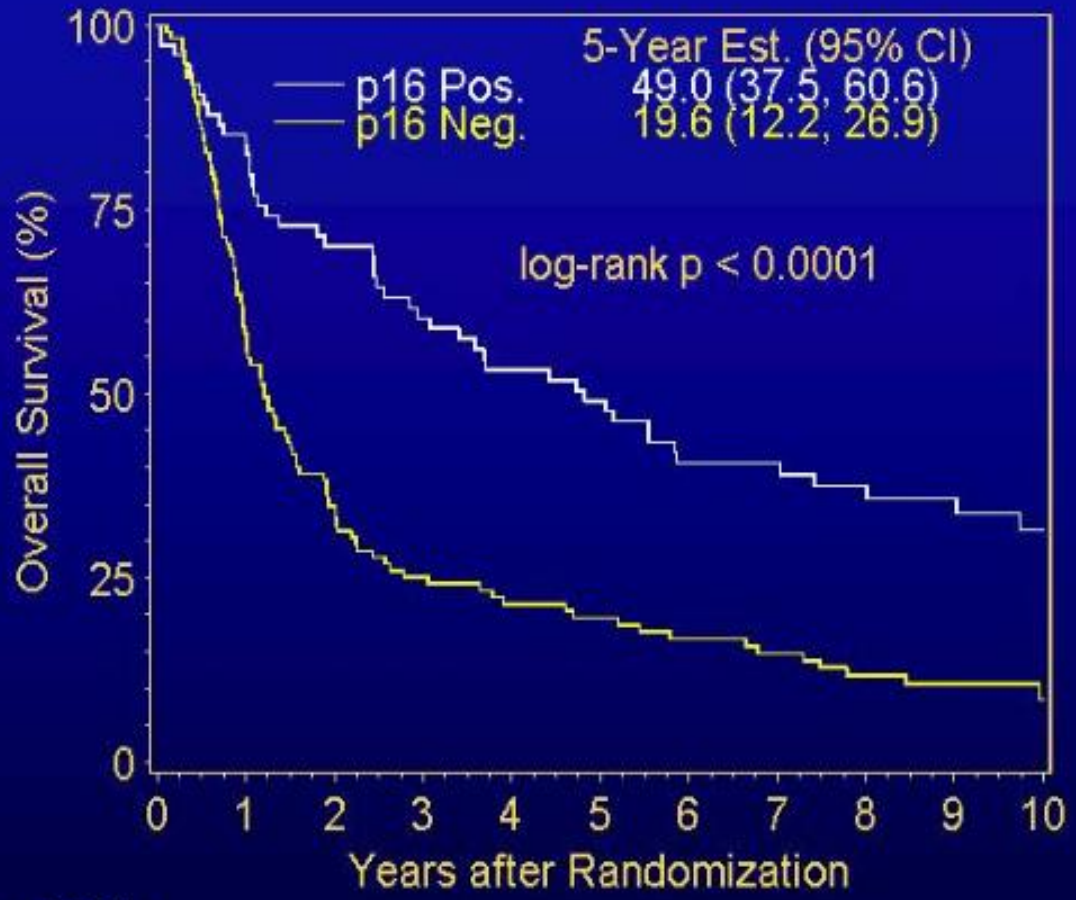
Arm 1:
Standard Fractionation

Arm 2:
Hyperfractionation

Arm 3:
Accelerated
Fractionation with split

Arm 4:
Accelerated
Fractionation by
Concomitant Boost

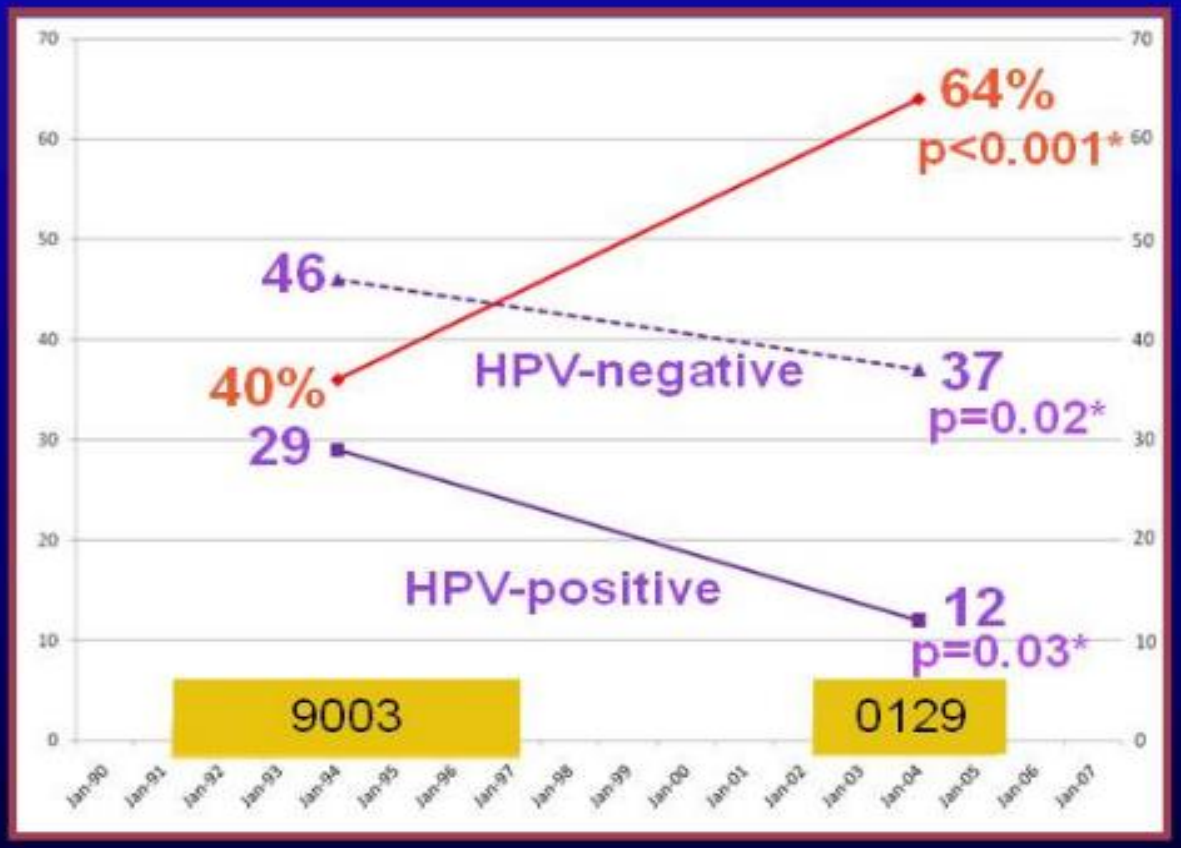
Overall Survival by p16 status



Patients at Risk

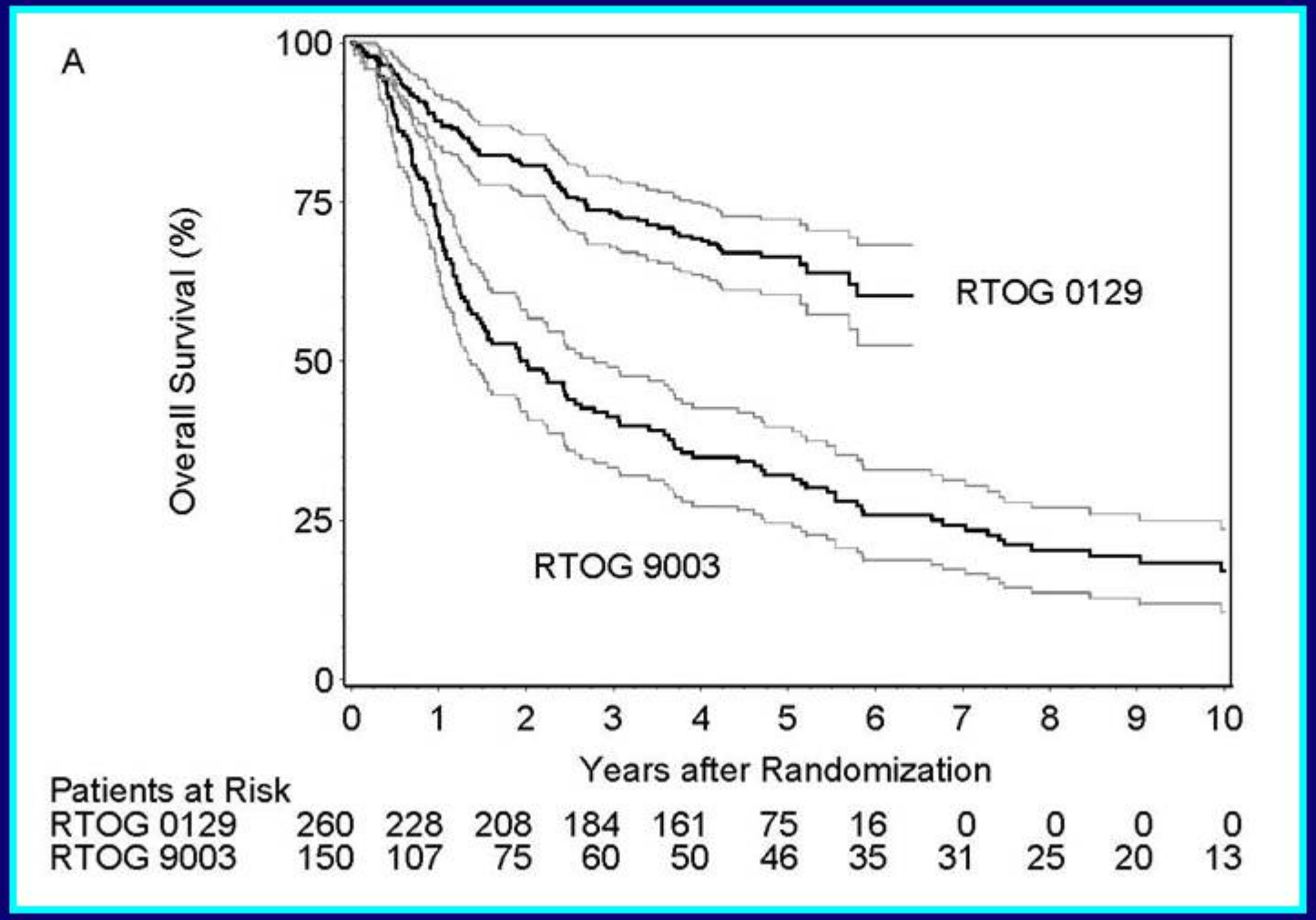
p16 Pos.	75	61	51	43	38	35	27	26	22	18	12
p16 Neg.	115	67	40	28	23	21	18	15	12	8	4

HPV status and tobacco use in 9003 and 0129



*test of proportions
*median test

A decade makes a huge difference
Overall survival, RTOG 0129 vs. 9003



Guideline statements

- NCCN guidelines: “HPV testing recommended for all oropharynx tumors”
- National Cancer Institute US, CTEP: “HPV status must be included as stratification factor for trials including oropharynx cancer patients”
- U.S Cooperative Groups and European Organization for Research and Treatment of Cancer: “HPV-positive oropharynx cancer is a distinct disease entity”

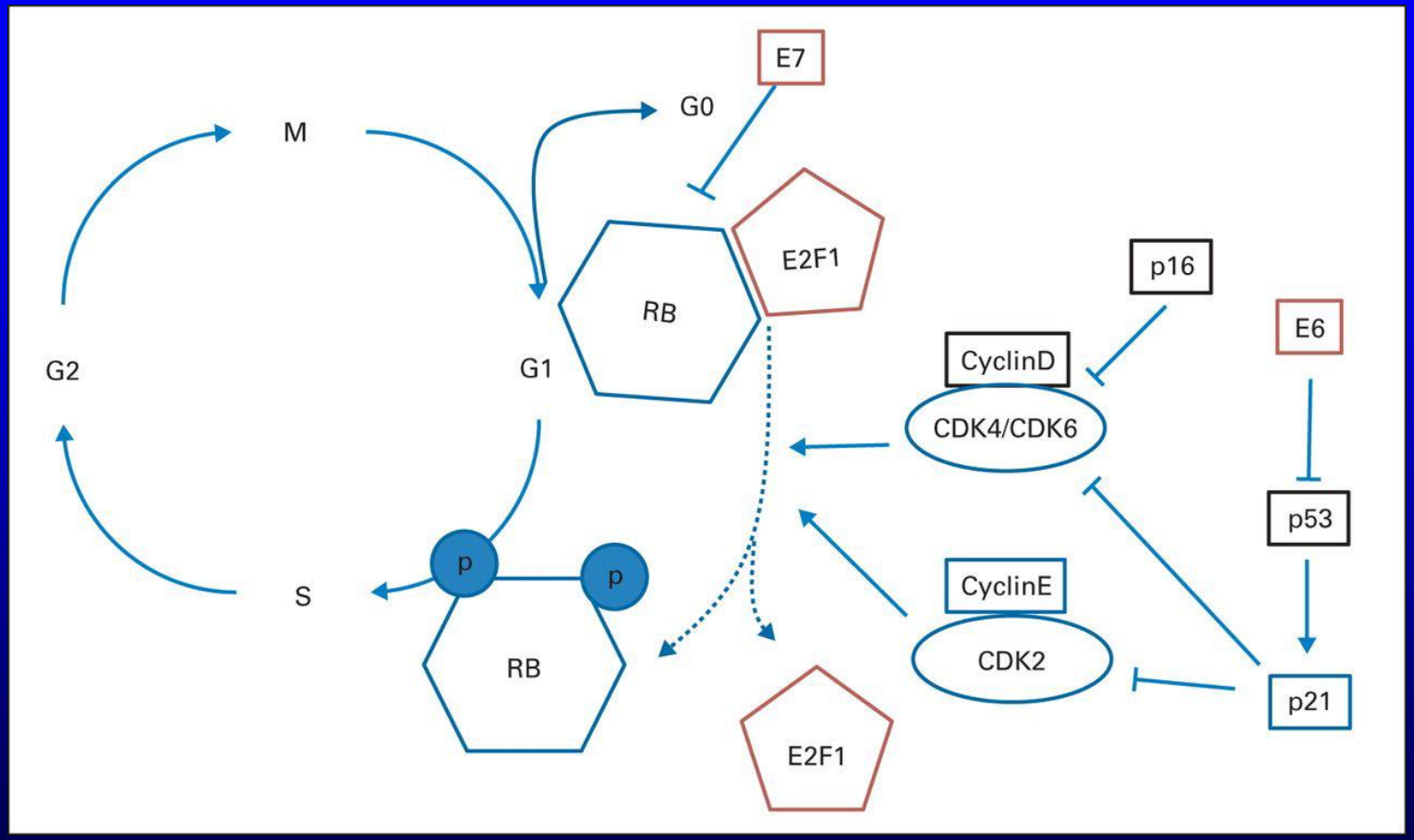
Implications for treatment of HPV-associated HNSCC

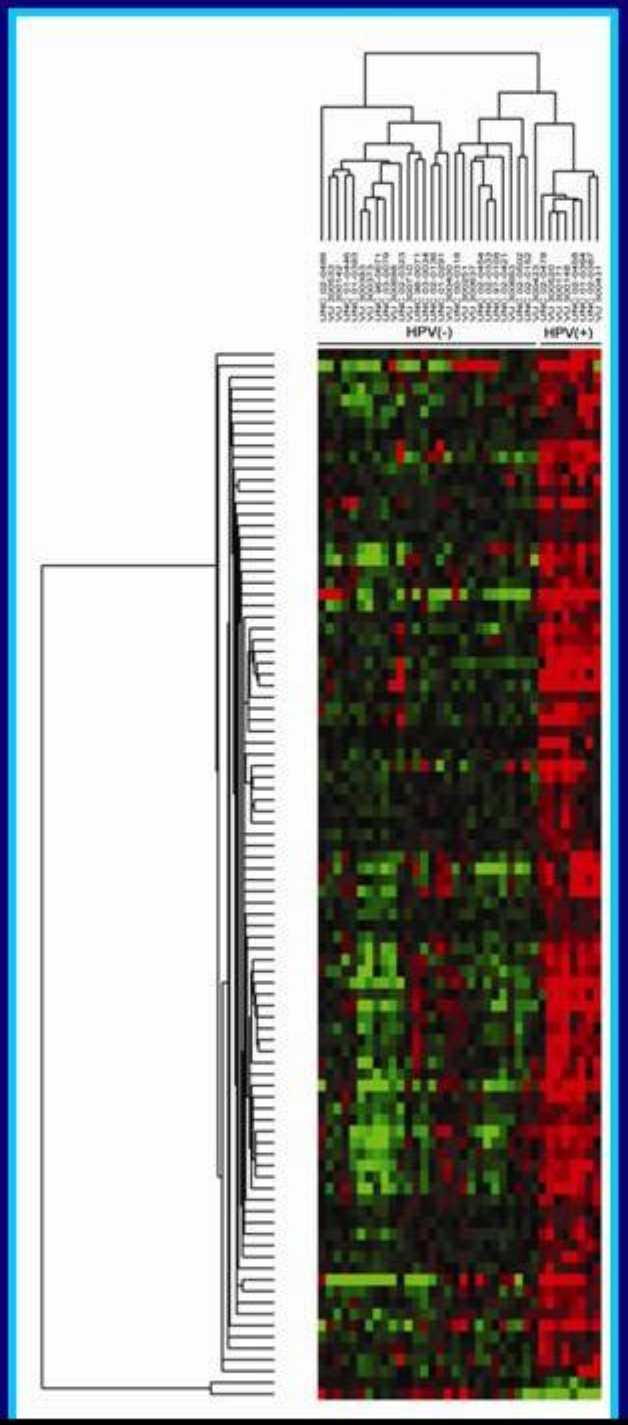
- Guidelines do not currently recommend using HPV status to direct treatment
- However, strategies to treat HPV+ LA-SCCHN have been proposed that take advantage of its tendency to respond to treatment, and are being investigated

HPV-associated HNSCC is a distinct molecular-genetic entity

	HPV-positive	HPV-negative
p53	WT	MU
pRb	↓	↑
p16	↑	↓
Cyclin D	↓	↑
EGFR	↓	↑
Survivin	↓	↑

Wilczynski, *AM J Pathol* 1998; Andl, *Cancer Research* 1998; Klussman, *AM J Pathol* 2003; Balz, *Cancer Research* 2003; Wiest, *Oncogene* 2002


E7
G0
M
E2F1
RB
p16
E6
CyclinD
G2
G1
CDK4/CDK6
p53
p
p
CyclinE
S
RB
CDK2
p21
E2F1

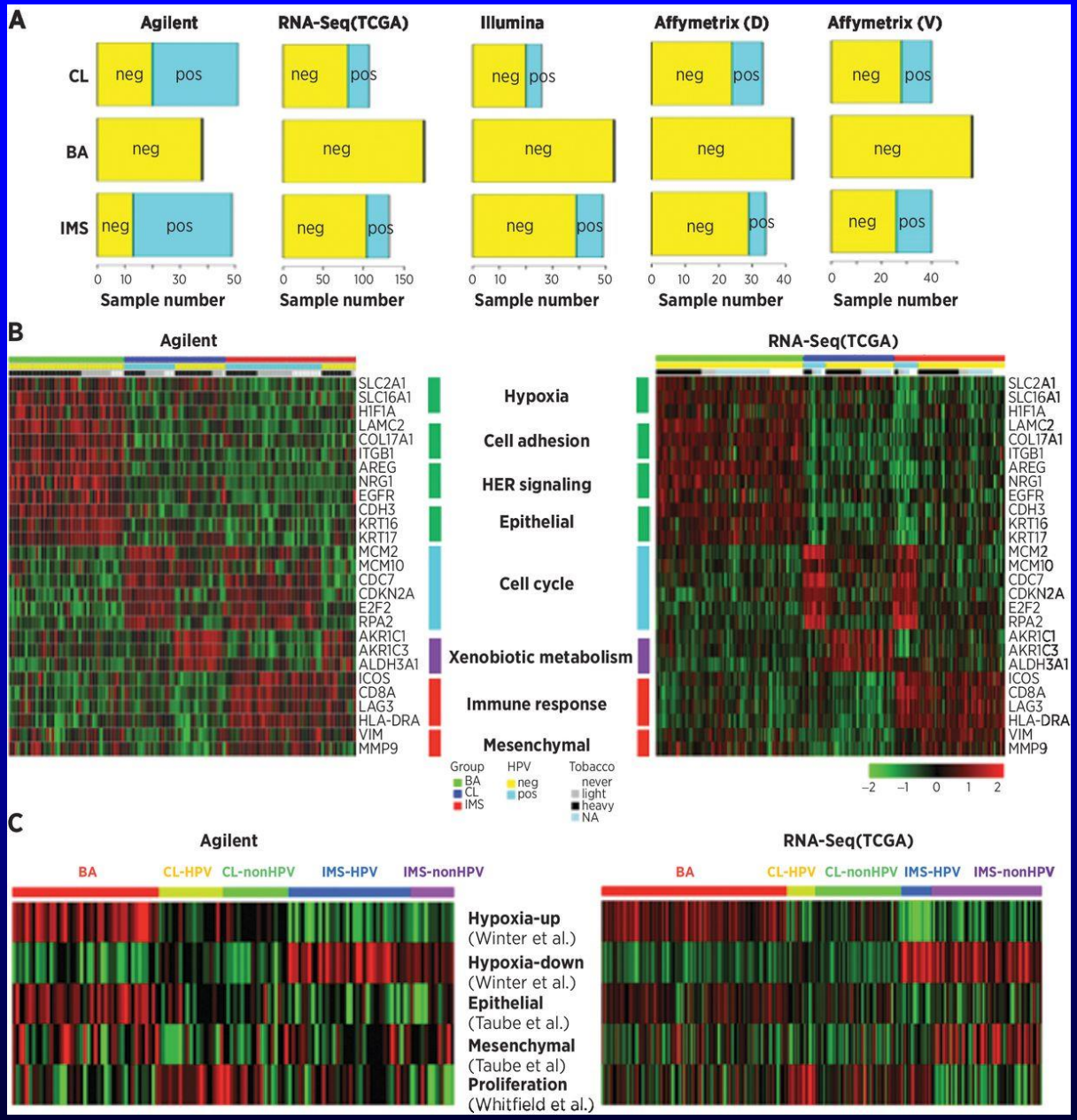


Gene expression profiles: HPV-positive vs. HPV-negative tumors

89 genes with higher expression

2 genes with lower expression

Slebos R, et al. *Clin Cancer Res*, 2006


A
Agilent
RNA-Seq(TCGA)
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Affymetrix (D)
Affymetrix (V)
CL
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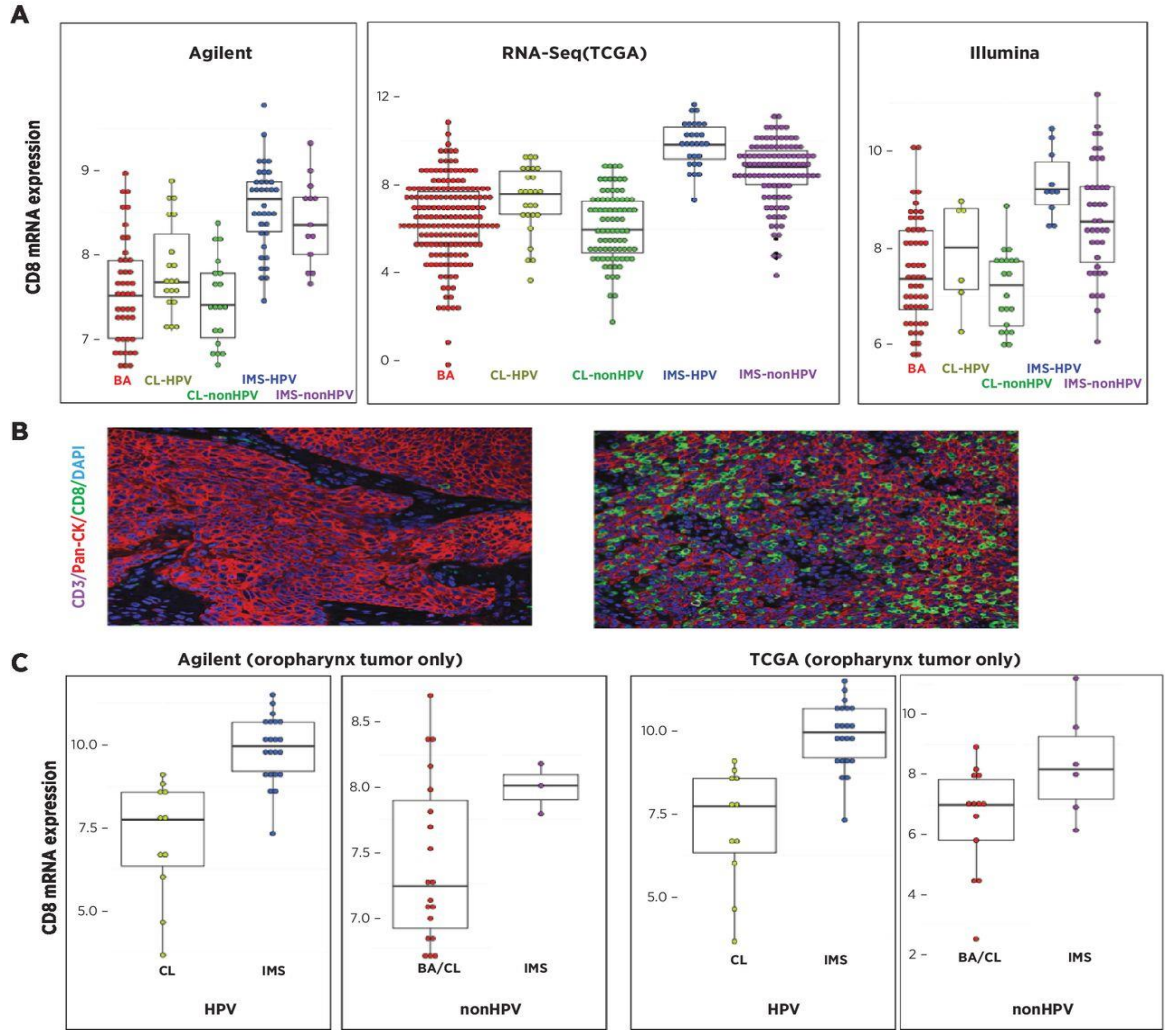
Sample number
B
Agilent
RNA-Seq(TCGA)
SLC2A1
SLC16A1
H1F1A
LAMC2
COL17A1
ITGB1
AREG
NRG1
EGFR
CDH3
KRT16
KRT17
MCM2
MCM10
CDC7
CDKN2A
E2F2
RPA2
AKR1C1
AKR1C3
ALDH3A1
ICOS
CD8A
LAG3
HLA-DRA
VIM
MMP9
Hypoxia
Cell adhesion
HER signaling
Epithelial
Cell cycle
Xenobiotic metabolism
Immune response
Mesenchymal
Group
BA
CL
IMS
HPV
neg
pos
Tobacco
never
light
heavy
NA
−2 −1 0 1 2
C
Agilent
RNA-Seq(TCGA)
BA
CL-HPV
CL-nonHPV
IMS-HPV
IMS-nonHPV
Hypoxia-up
(Winter et al.)
Hypoxia-down
(Winter et al.)
Epithelial
(Taube et al.)
Mesenchymal
(Taube et al)
Proliferation
(Whitfield et al.)

CD8 T cell infiltration differs between HNC subtypes.



Michaela K. Keck et al. Clin Cancer Res 2015;21:870-881

Clinical Cancer Research
AACR American Association for Cancer Research

Session: Changes in Head and Neck Cancer Staging: It's personal

"HPV Associated Oropharynx Cancer: New Staging for a New Disease"

Brian O'Sullivan
Professor, Department of Radiation Oncology
The Princess Margaret / University of Toronto

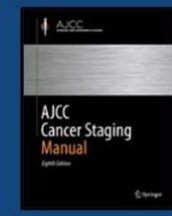
Chair, UICC Prognostic Factors Classification Committee
UICC Liaison to the AJCC Head and Neck Expert Committee

Presented By Brian O''Sullivan at 2018 ASCO Annual Meeting

8th edition TNM:
Recognition of a new disease
Introduction of a new classification
(*HPV+ OPC & HPV+ CUP*)

HPV-Mediated (p16+) Oropharyngeal Cancer **10**

Brian O'Sullivan, William M. Lydiatt, Bruce H. Haughey, Margaret Brandwein-Gensler, Christine M. Glastonbury, and Jatin P. Shah



Cervical Lymph Nodes and Unknown Primary Tumors of the Head and Neck **6**

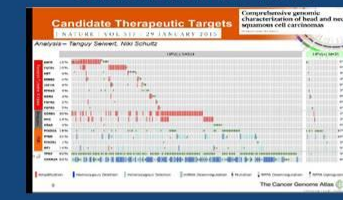
Snehal G. Patel, William M. Lydiatt, John A. Ridge, Christine M. Glastonbury, Suresh K. Mukherji, Ronald A. Ghossein, Margaret Brandwein-Gensler, Raja R. Seethala, A. Dimitrios Colevas, Bruce H. Haughey, Brian O'Sullivan, and Jatin P. Shah

Presented By Brian O''Sullivan at 2018 ASCO Annual Meeting

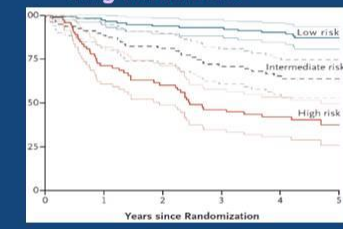
Why Do We Need a New TNM for HPV+ OPC

- HPV+ and HPV– OPCs are two different diseases with different:
  - Etiology and biology[1-2]
  - Clinical behavior[3]
  - Radiology appearances[4-5]
  - Pathology features[1]
  - Treatment response[6-7] and outcomes[8-9]
- Up to TNM 7th edition, we used the same stage classification for both diseases

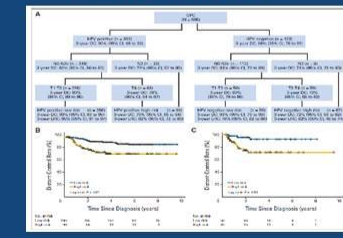
[1]Seiwert Nature 2015



[7]Ang NEJM 2010



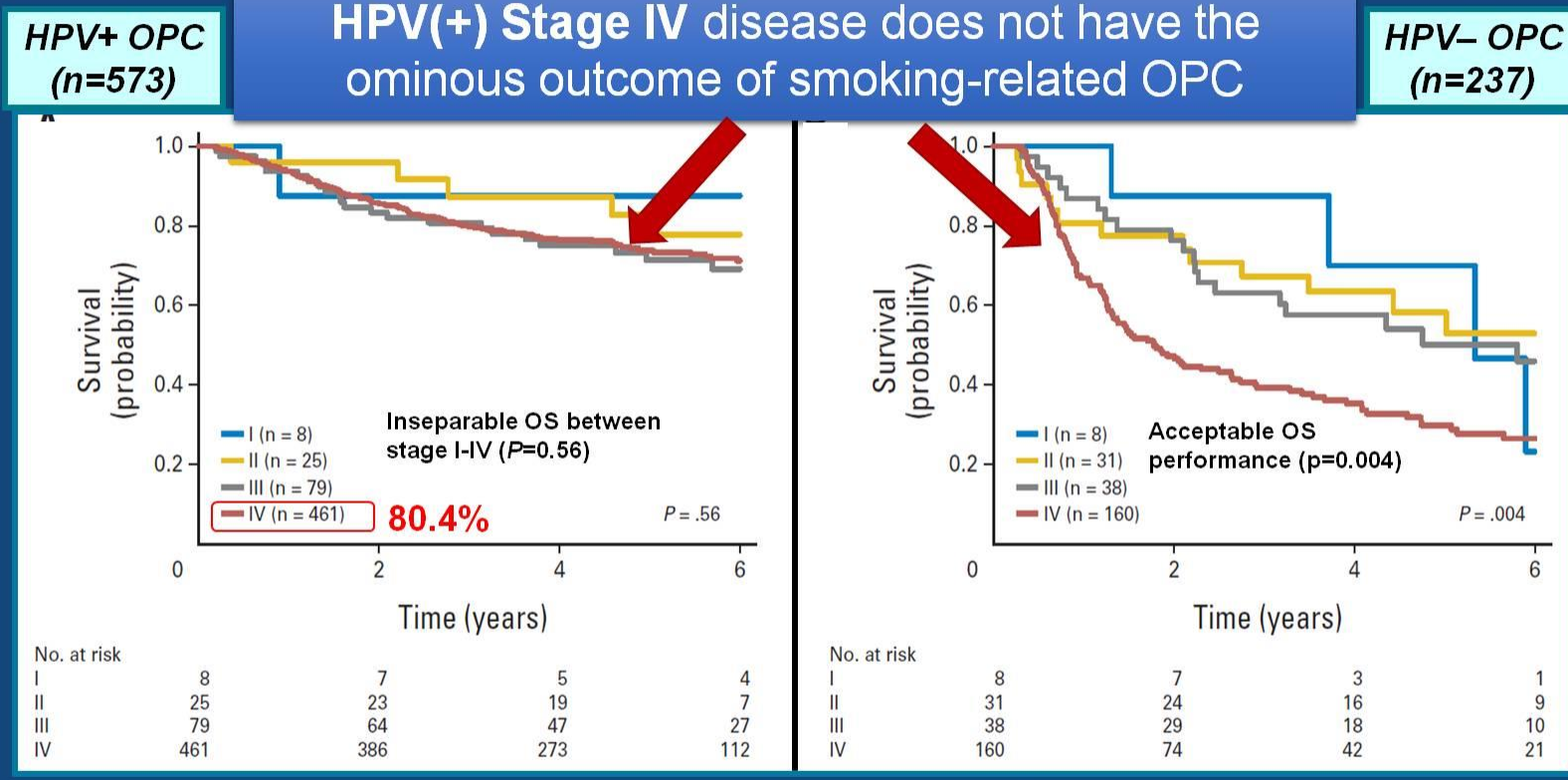
[8]O'Sullivan JCO 2013



[1]Gillison, JNCI, 2000; [2]Seiwert Nature 2015; [3]Huang IJROBP 2012; [4]Goldenberg, HN 2008; [5]Cantrell, AJNR Am J Neuroradiol 2013; [6]Chen Laryngoscope 2013; [7]Huang IJROBP 2013; [8]Ang NEJM 2010; [9]O'Sullivan JCO 2013

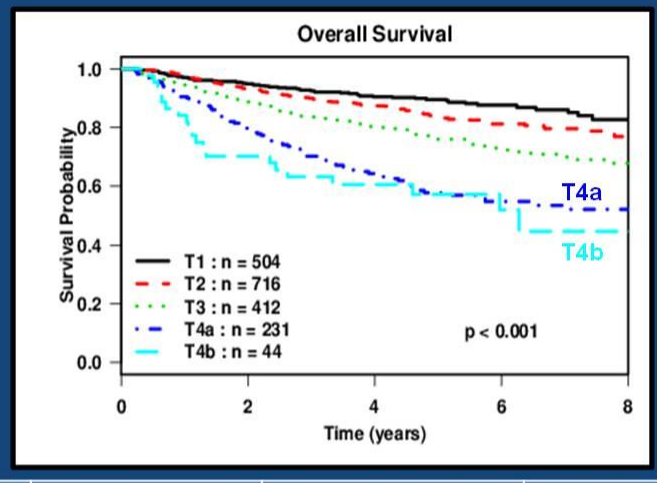
OS by 7th edition TNM Stage Groups [PMH Data 2000-2010]

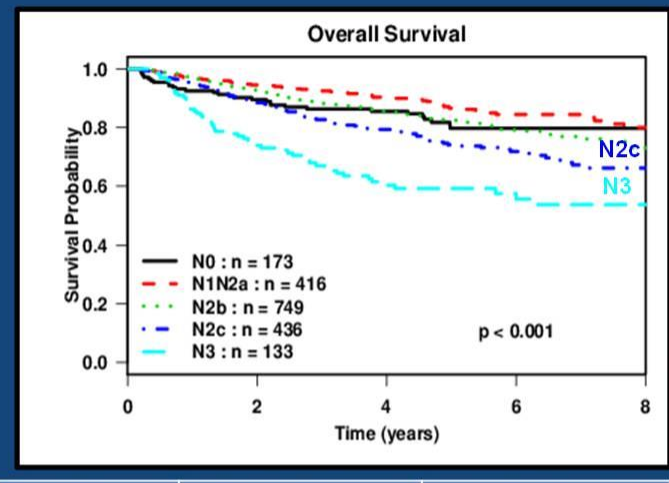
HPV(+) Stage IV disease does not have the ominous outcome of smoking-related OPC



Huang, Xu, Siu, Waldron, O'Sullivan, et al. JCO, March, 2015

HPV+ OS by 7th T- & N-category [multi-institutional dataset] (n=1907)





O'Sullivan, Huang et al 2016

T	Events/Total	5-year OS	P value
Total	395 / 1907	80% (78-82)	<0.001
T1	60 / 504	89% (87-92)	
T2	116 / 716	83% (80-87)	
T3	106 / 412	76% (72-81)	
T4a	93 / 231	58% (51-65)	
T4b	20 / 44	57% (44-75)	

N	Events/Total	5-year OS	P value
Total	395 / 1907	80% (78-82)	<0.001
N0	32 / 173	80% (73-87)	
N1-N2a	59 / 416	87% (83-90)	Unilateral Neck LNs
N2b	136 / 749	83% (80-86)	
N2c	112 / 436	74% (70-79)	Bi-/contra-lat Neck LNs
N3	56 / 133	59% (51-69)	

- T: T1, T2, T3, and T4 separate well; T4a and T4b behave similarly
- N: inferior OS in N2c and N3; Similar OS between N0 / N1-N2a and N2b

THE LANCET Oncology

8th Edition cTNM and pTNM for HPV+ OPC / CUP

Huang, O'Sullivan Curr Treat Options in Oncol. 2017

HPV+ OPC	Clinical stage			Pathologic stage		
Category	T	N	M	T	N	M
Stage I	T1, T2	N0: no regional LNs N1: ipsilateral LNs	M0	T1, T2	N0: no regional LNs N1: 1–4 LNs	M0
Stage II	T1, T2	N2: bilateral or contralateral LNs	M0	T1, T2	N2: ≥ 5 LNs	M0
	T3	N0: no regional LNs N1: ipsilateral LNs N2: bilateral or contralateral LNs	M0	T3, T4	N0: no regional LNs N1: 1–4 LNs	M0
Stage III	T4	Any N	M0	T3, T4	N2: ≥ 5 LNs	M0
	Any T	N3: >6.0 cm LN(s)	M0			M0
Stage IV	Any T	Any N	M1	Any T	Any N	M1

Lydiatt, Patel, O'Sullivan et al, CA Cancer J Clin. 2017

[a]Any M1 is stage IV.

CUP →

cTNM	cN0	cN1 Unilat	cN2 Bilat	cN3
T0	NA	I	II	III
T1	I	I	II	III
T2	I	I	II	III
T3	II	II	II	III
T4	III	III	III	III

CUP →

pTNM	pN0	pN1 1-4 LNs	pN2 ≥5 LNs
T0	NA	I	II
T1	I	I	II
T2	I	I	II
T3	II	II	III
T4	II	II	III

Uniqueness of HPV+ OPC / CUP TNM (8th edition) - the 1st time in HNC:

- *T4* or *N3* M0 is no longer *Stage IV*
- Different cN and pN classification, and stage groupings

Comments About HPV+ cTNM

- The 8th edition HPV+ cTNM reflects prognosis under current treatment paradigms
  - But many had received intensified treatment
- Stage I disease fares very well
  - Unknown if all stage I is suitable for less intensified treatment
  - Uncertainty also about the optimal deintensification strategies
- Stage I can be considered candidates for de-intensification trials
  - Pre-mature to change treatment without trial data

Impact of prophylactic HPV vaccination on oral HPV infections among young adults in US

Maura L Gillison, Barry I. Graubard, Tatevik Broutian, Robert K.L. Pickard, Zen-Yue Tong, Weihong Xiao, Lisa Kahle, Anil K. Chaturvedi

ASCO
June, 2017

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Background

- HPV-positive oropharyngeal cancer
  - Fastest rising cancer in young white US men
  - >90% caused by HPV16
- HPV vaccination recommended
  - Since 2006: Ages 9-26 in women
  - Since 2011: Ages 9-21 years in men (26 for MSM)
- Oral HPV infection and precancer/cancer not an indication

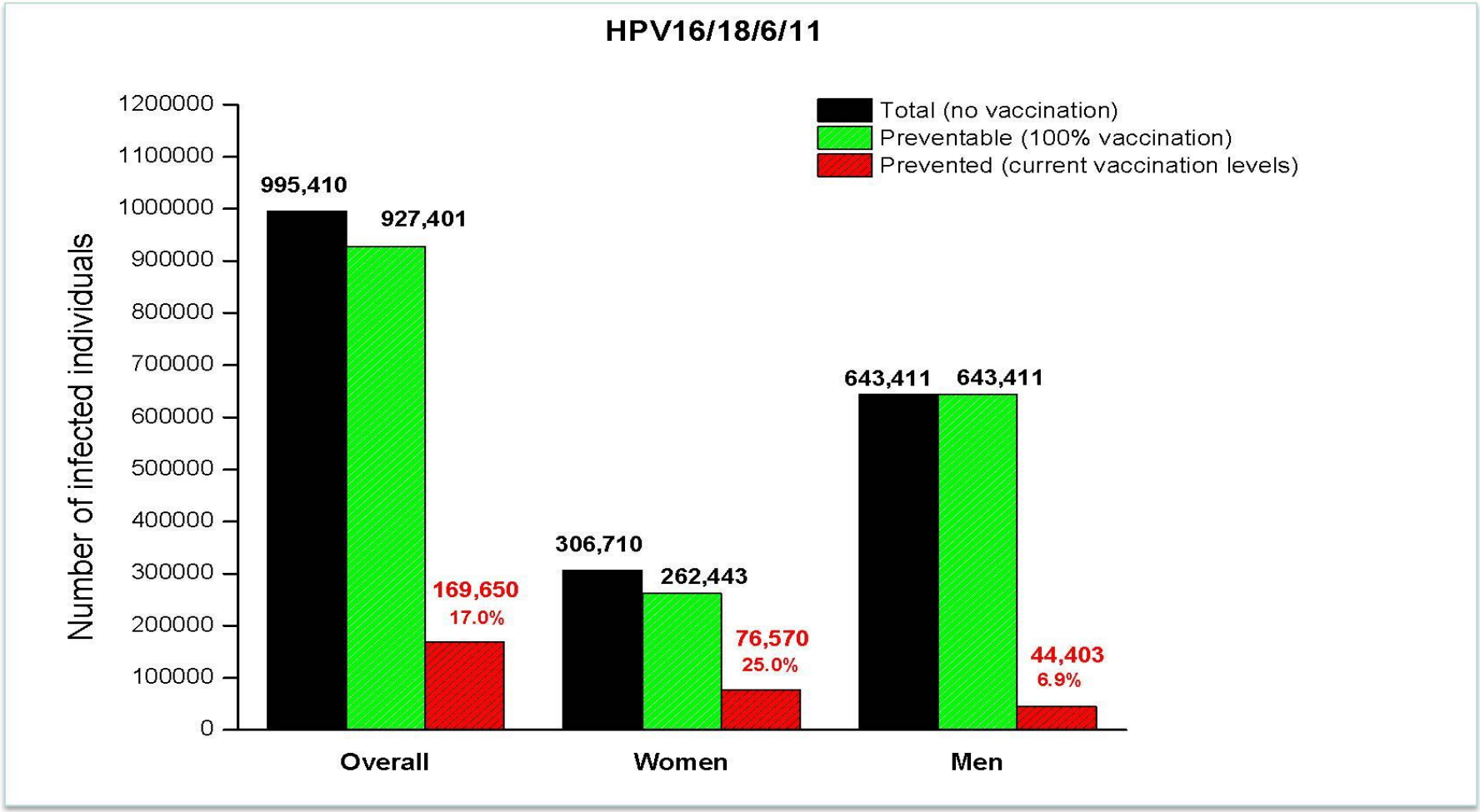
Impact of HPV vaccination, US 2011-14, 18-33 years

Outcome	Vaccinated N=496 / 11,310,006	Unvaccinated N=2,131 / 50,516,709	P Value	% Reduction
HPV16/18/6/11				
Infections	1	32	0.008	88
Prevalence	0.11%	1.61%		
Men only				
Infections	0	23	0.007	100
Prevalence	0.00%	2.13%		
Men only, HPV16				
Infections	0	13	0.07	100
Prevelance	0.00%	1.12%		

Binary logistic regression models adjusted for age, gender and race

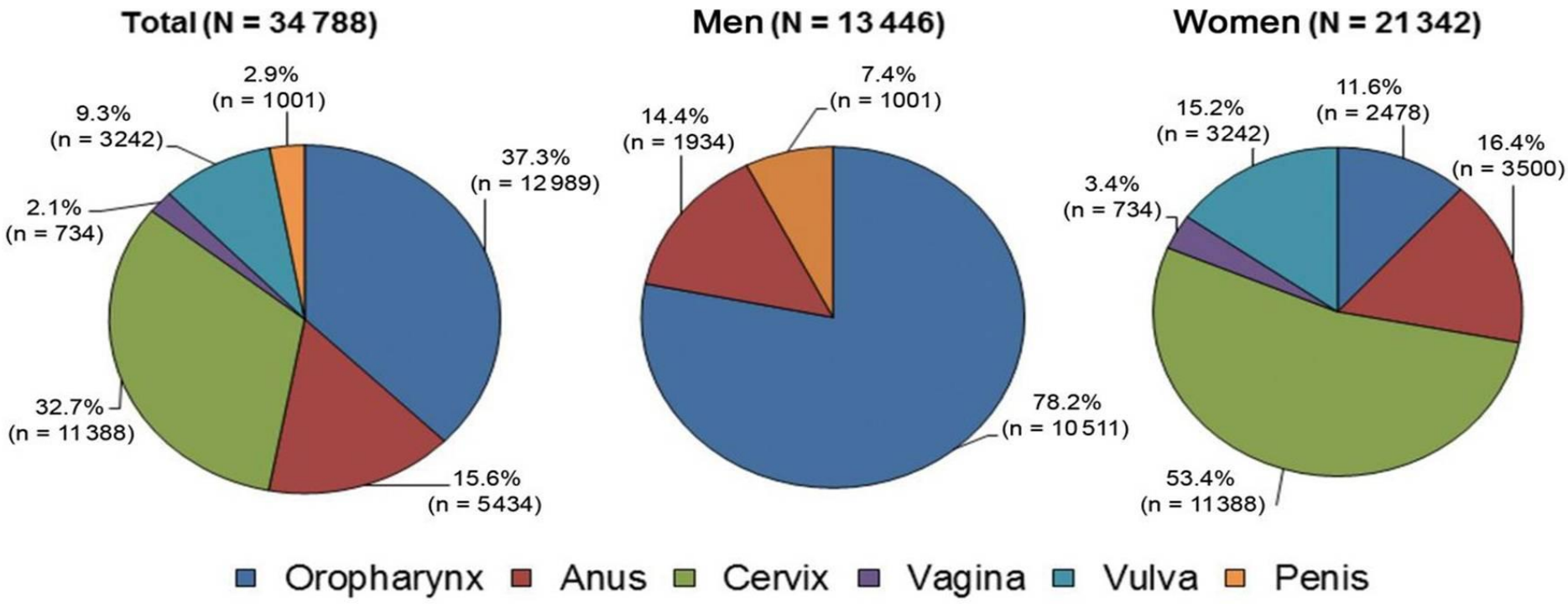
Chaturvedi and Gillison, submitted

Opportunity to reduce oral HPV infections; low vaccination for men



Chaturvedi and Gillison, ASCO 2017

Largest burden of HPV-related malignancy for men in oropharynx cancer in US



Jemal, JNCI 2013

If You Could Prevent Cancer, Would You?

ASCO
AMERICAN SOCIETY OF CLINICAL ONCOLOGY

HPV is preventable

HPV or human papillomavirus is passed from person to person during direct skin-to-skin contact, particularly during sexual activity.

6+ HPV IS LINKED WITH MORE THAN 6 TYPES OF CANCER

GARDASIL 9

This vaccine protects against strains 16 and 18, which are most likely to cause cancer, and 5 additional strains linked with cancer.*

*Other vaccines may be used outside the US.

The Centers for Disease Control (CDC) recommends HPV vaccination for:

- ALL BOYS AND GIRLS AGES 11 OR 12
- ALL MEN THROUGH AGE 21
- ALL WOMEN, GAY OR BISEXUAL MEN, AND PEOPLE WITH LOWERED IMMUNE SYSTEMS THROUGH AGE 26

VACCINATED
UNVACCINATED

Only 36% of girls and 14% of boys ages 11-13 are fully vaccinated.

Getting the HPV vaccine could save:

- 7 OUT OF 10 WOMEN FROM CERVICAL CANCER
- 6 OUT OF 10 MEN AND WOMEN FROM OROPHARYNGEAL CANCER
- 9 OUT OF 10 MEN AND WOMEN FROM ANAL CANCER
- 8 OUT OF 10 WOMEN FROM VAGINAL CANCER
- 7 OUT OF 10 WOMEN FROM VULVAR CANCER
- 6 OUT OF 10 MEN FROM PENILE CANCER

Men don't need to worry about HPV, right?

Wrong.

HPV affects men and women. In fact, oropharyngeal cancer from HPV is 3 to 5 times more common in men.

The HPV vaccine is a series of 2 or 3 shots.

Nivolumab and ISA101 Vaccine in Patients with Incurable HPV-16+ Cancer

Bonnie Glisson[1], Erminia Massarelli[2], William William[1], Faye Johnson[1], Merrill Kies, Renata Ferrarotto[1], Ming Guo[1], S. Andrew Peng[1], J. Jack Lee[1], Hai Tran[1], Young U. Kim[1], Cara Haymaker[1], Chantale Bernatchez, Michael Curran[1], Beatriz Sanchez Espiridion[1], Jaime Rodriguez Canales[1], Ignacio Wistuba,[1r]Sjoerd van der Burg[3], Jing Wang[1], Cornelis J. Melief[3]. [1]

UT MD Anderson Cancer CTR, Houston, TX; [2]City of Hope, Duarte, CA; [3]Leiden University Medical Center, Leiden, Netherlands

Abstract 11360

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
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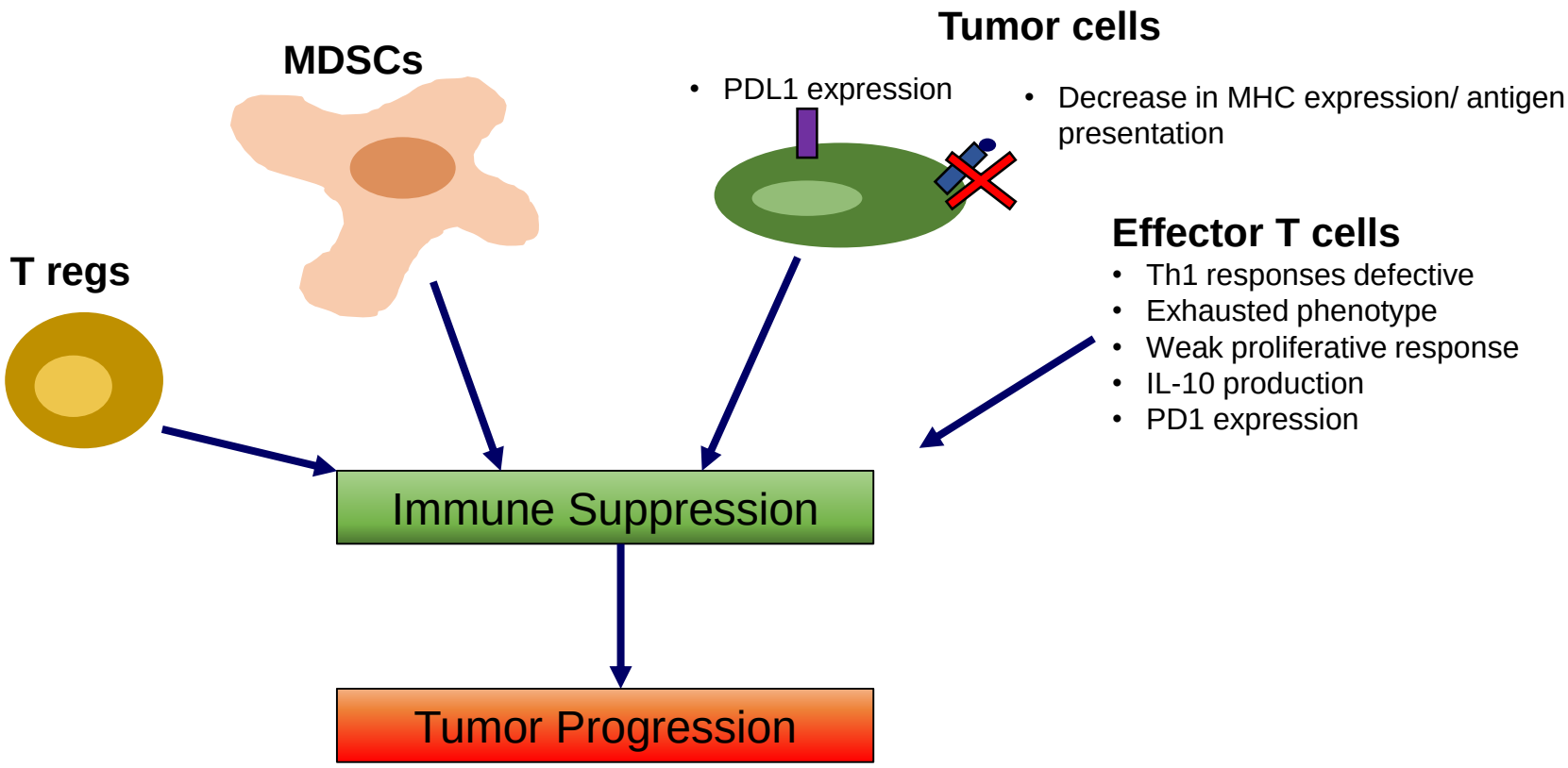
Rationale

HPV+ tumor microenvironment is immunosuppressive



Presented by Bonnie Glisson at 2017 ESMO Congress

Original Article

Vaccination against HPV-16 Oncoproteins for Vulvar Intraepithelial Neoplasia

Gemma G. Kenter, M.D., Ph.D., Marij J.P. Welters, Ph.D., A. Rob P.M. Valentijn, Ph.D., Margriet J.G. Lowik, Dorien M.A. Berends-van der Meer, Annelies P.G. Vloon, Farah Essahsah, Lorraine M. Fathers, Rienk Offringa, Ph.D., Jan Wouter Drijfhout, Ph.D., Amon R. Wafelman, Ph.D., Jaap Oostendorp, Ph.D., Gert Jan Fleuren, M.D., Ph.D., Sjoerd H. van der Burg, Ph.D., and Cornelis J.M. Melief, M.D., Ph.D.

N Engl J Med
Volume 361(19):1838-1847
November 5, 2009

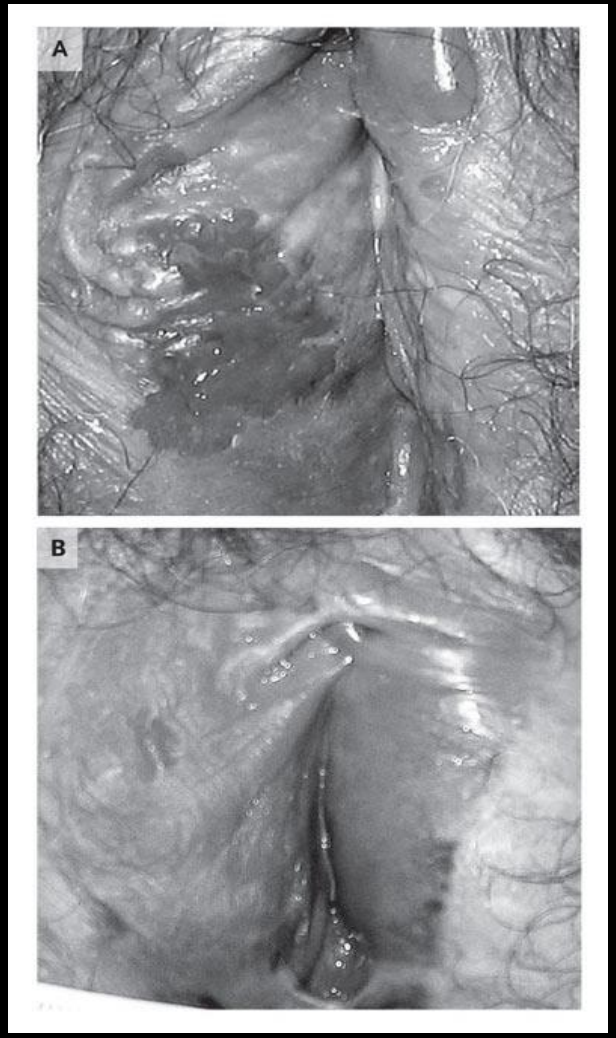
The NEW ENGLAND JOURNAL of MEDICINE

Study Overview

- In this single-group study involving women with grade 3 vulvar intraepithelial neoplasia associated with human papillomavirus type 16 (HPV-16), vaccination against HPV-16 infection with a peptide vaccine was related to a clinical response in 15 of 19 patients (79%) at 1 year
- This clinical response was associated with induction of HPV-16-specific T cells

The NEW ENGLAND JOURNAL of MEDICINE

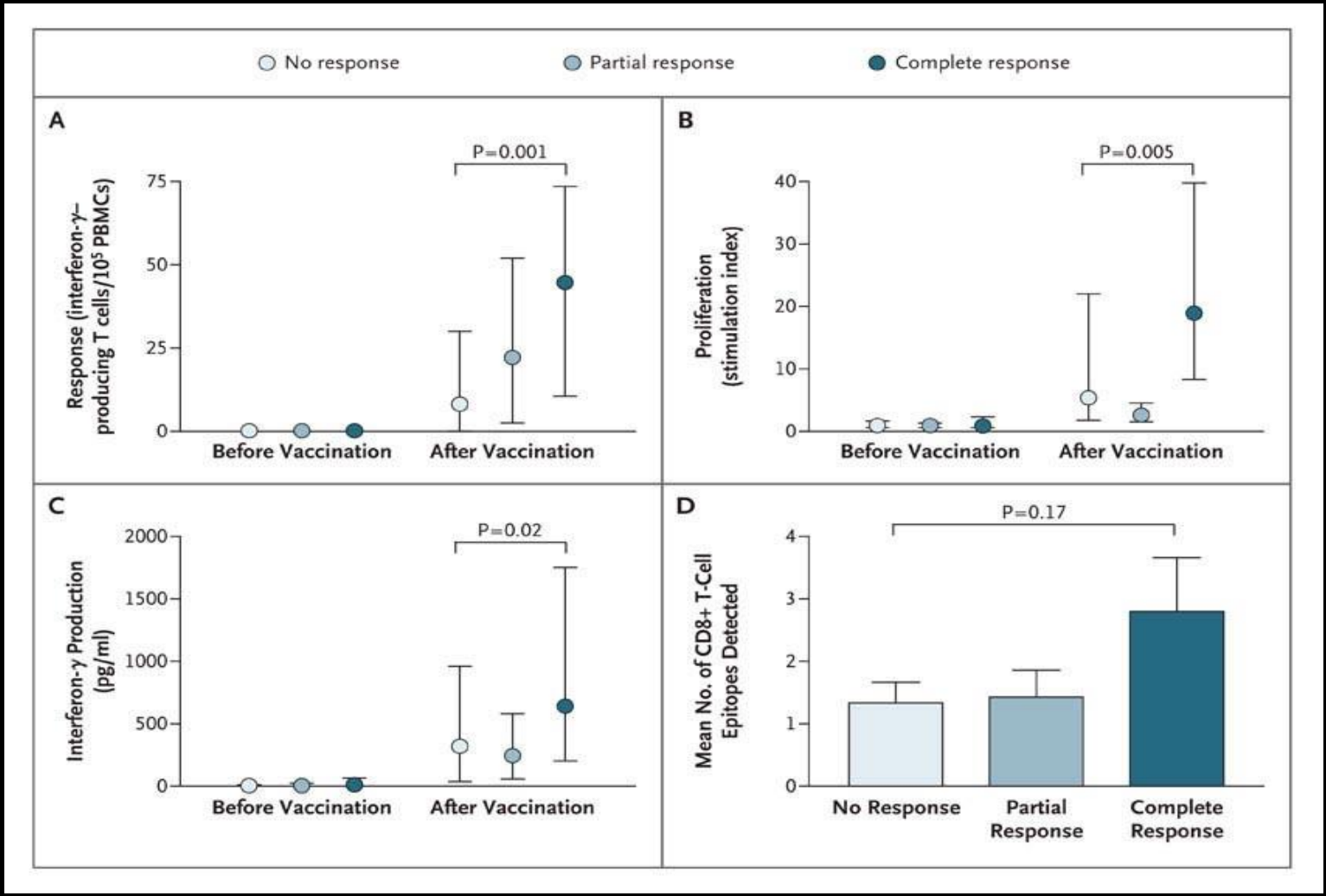
Complete Clinical Response to Vaccination in a Patient with Grade 3 Vulvar Intraepithelial Neoplasia



Kenter GG et al. N Engl J Med 2009;361:1838-1847

The NEW ENGLAND JOURNAL of MEDICINE

Immune Response before and after Vaccination



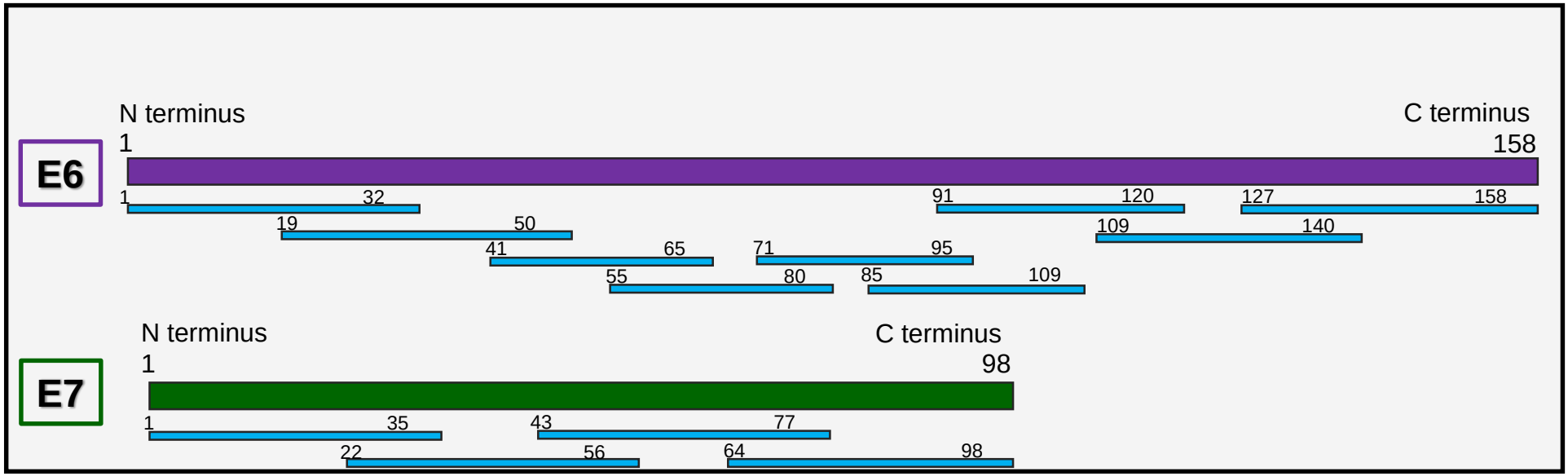
Kenter GG et al. N Engl J Med 2009;361:1838-1847

The NEW ENGLAND JOURNAL of MEDICINE

Rationale

Phase II Nivolumab + ISA101

ISA 101 synthetic long peptide (SLP) HPV E6/E7 vaccine

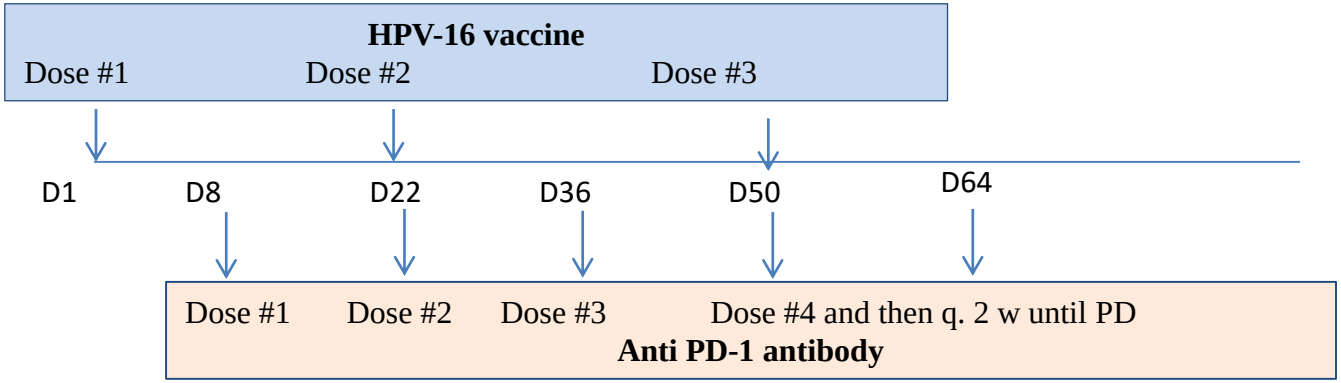


- Regression of high-grade premalignant vulvar lesions in 15/19 patients at 12 months; 9/19 no evidence of disease at 24 months
  - Strong IFNγ, HPV16-specific immunity in complete responders (*Kenter et al NEJM 2009)*
- ISA101 induces strong and durable HPV-specific T cell responses , but does not cause regression of invasive HPV-associated cancer *(Van Polgeest CCR 2016, Welters et al STM 2016, Gerritsen et al ASCO abstract 5525, 2017)*
- <u>Combination with immune checkpoint inhibition could overcome limitations imposed by immunosuppressive tumor microenvironment</u>

Presented by Bonnie Glisson at 2017 ESMO Congress

Study Schema and Assessments

Phase II Nivolumab and ISA101



W=week; PD=disease progression

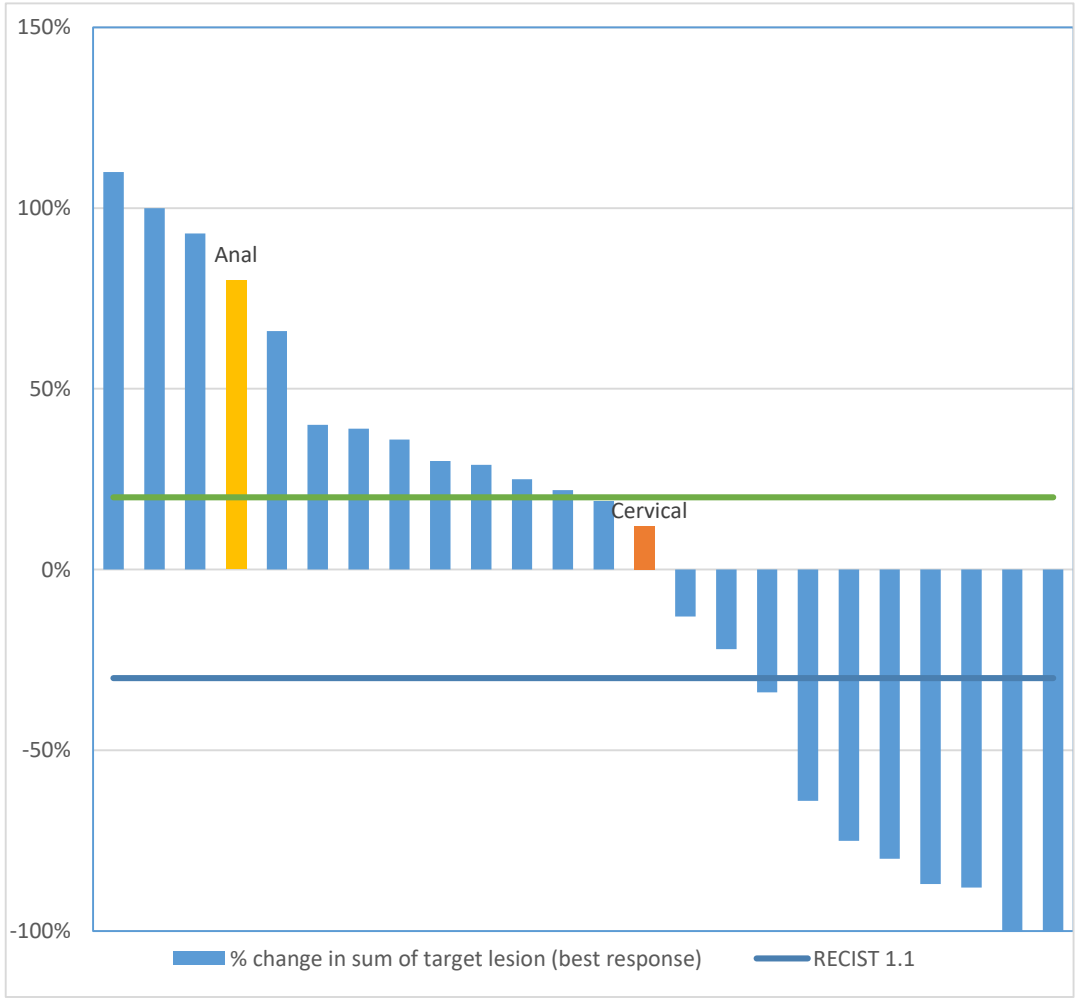
- ISA101 administered s.q. at 100 mcg/peptide for 3 doses, q 3 -4 wks
- Nivolumab administered i.v. 3 mg/kg every 2 weeks beginning on day 8 until PD, toxicity, or 1 yr tx

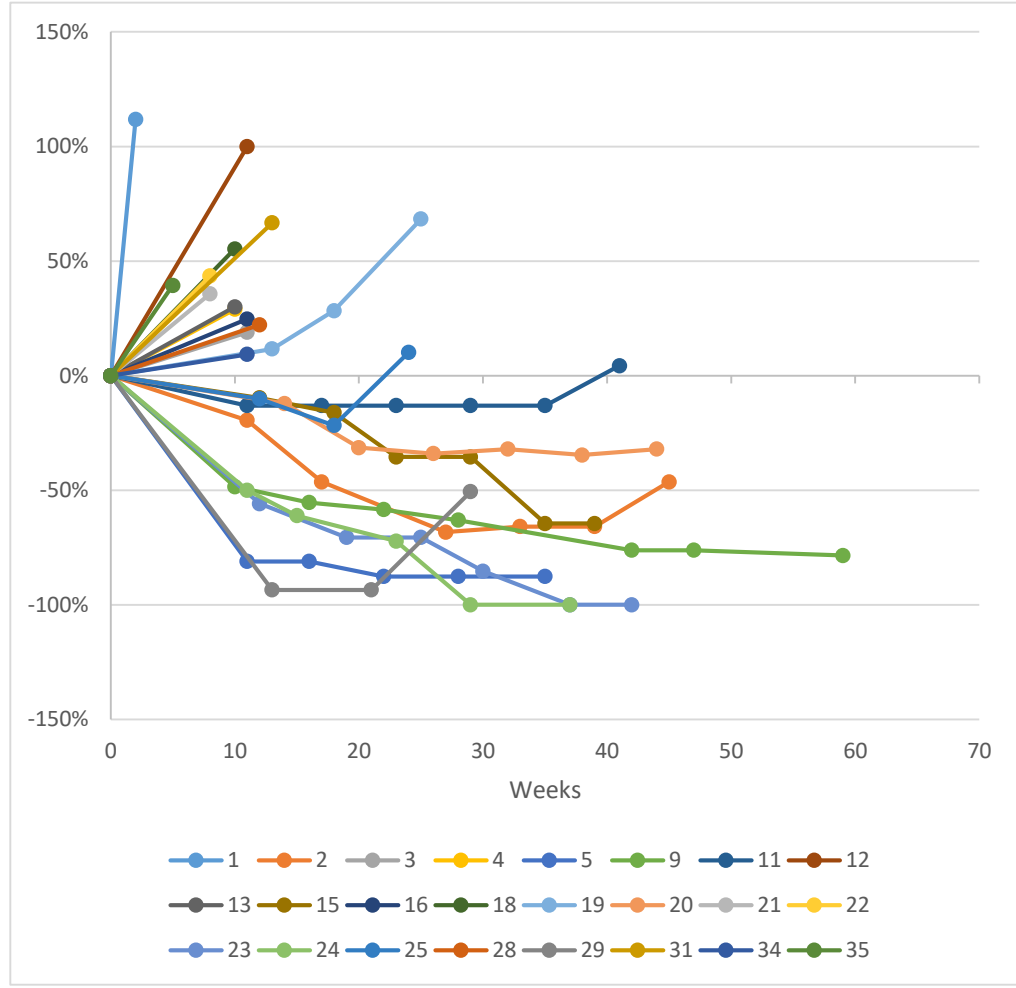
- Imaging: baseline, prior to cycle 6 nivolumab, q 6 wks thereafter
- Biopsies: baseline, restaging
- Blood: baseline, pre-vaccine doses 2 and 3, prior to nivolumab C5 and C6, then q 3 mos.

Presented by Bonnie Glisson at 2017 ESMO Congress

Percentage Change in Target Lesions

Phase II Nivolumab and ISA101

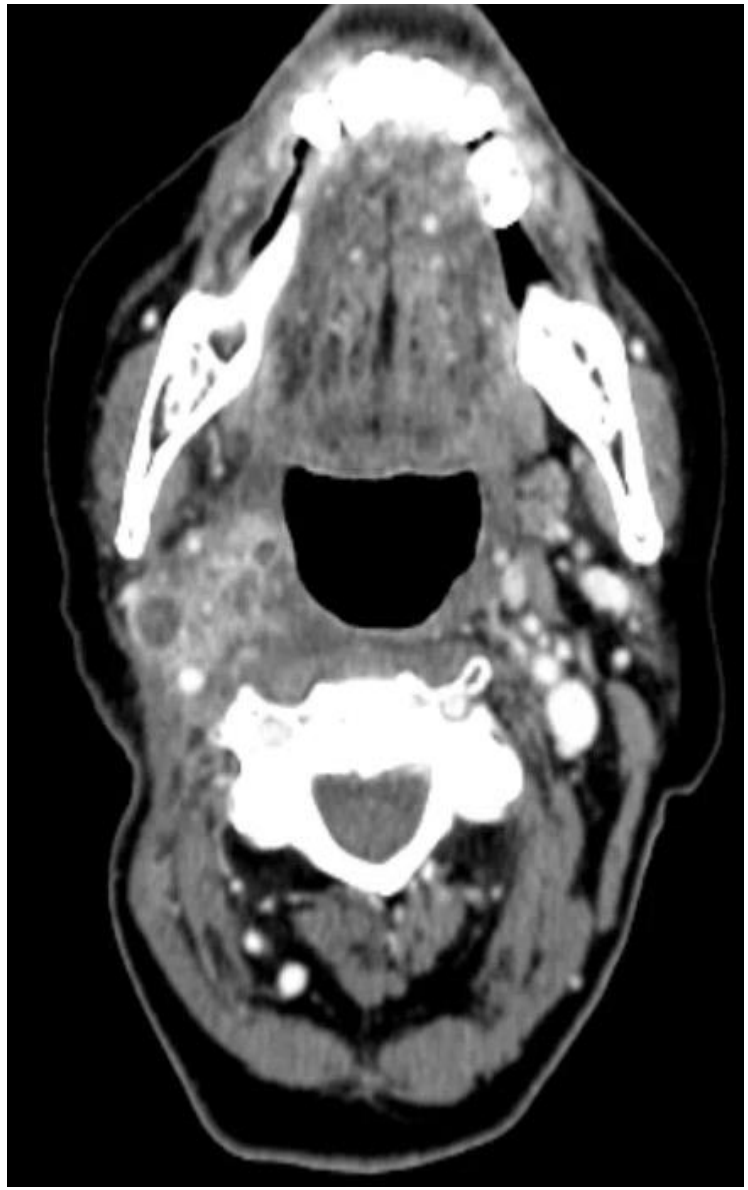




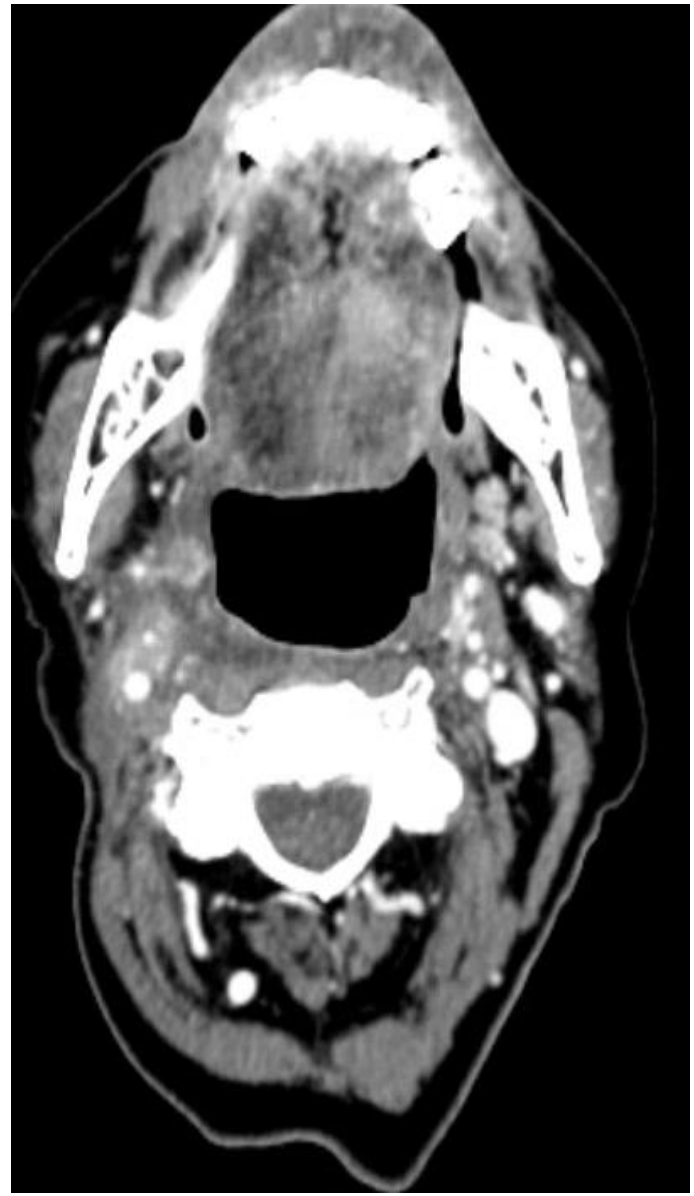
Presented by Bonnie Glisson at 2017 ESMO Congress

Acc. 2

Baseline

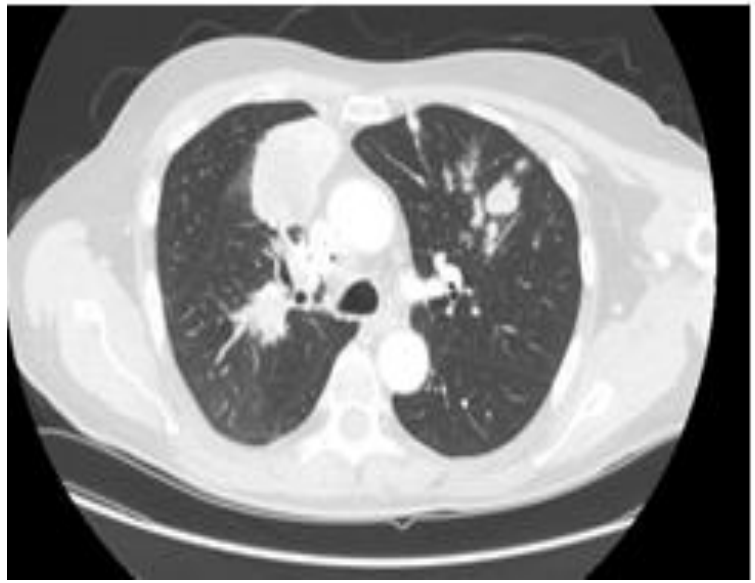


s/p 11 mos tx

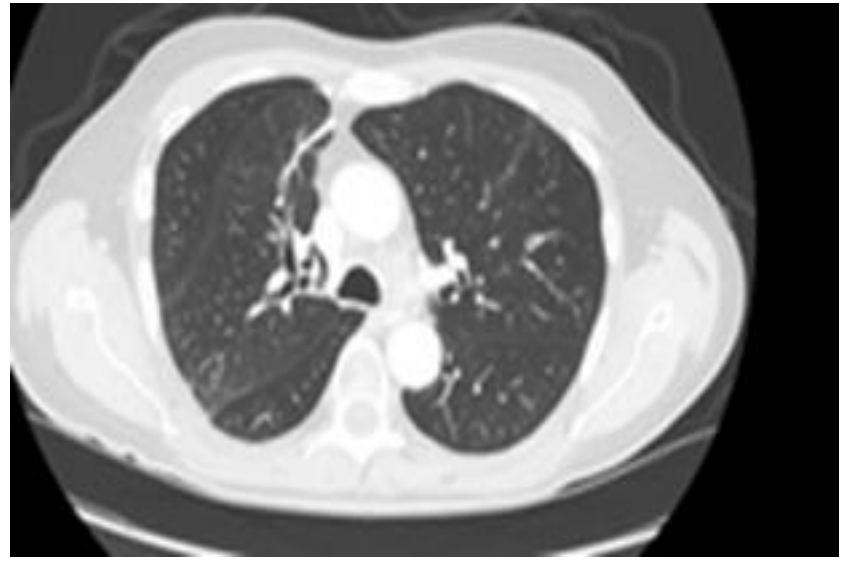


Acc. 5

Baseline

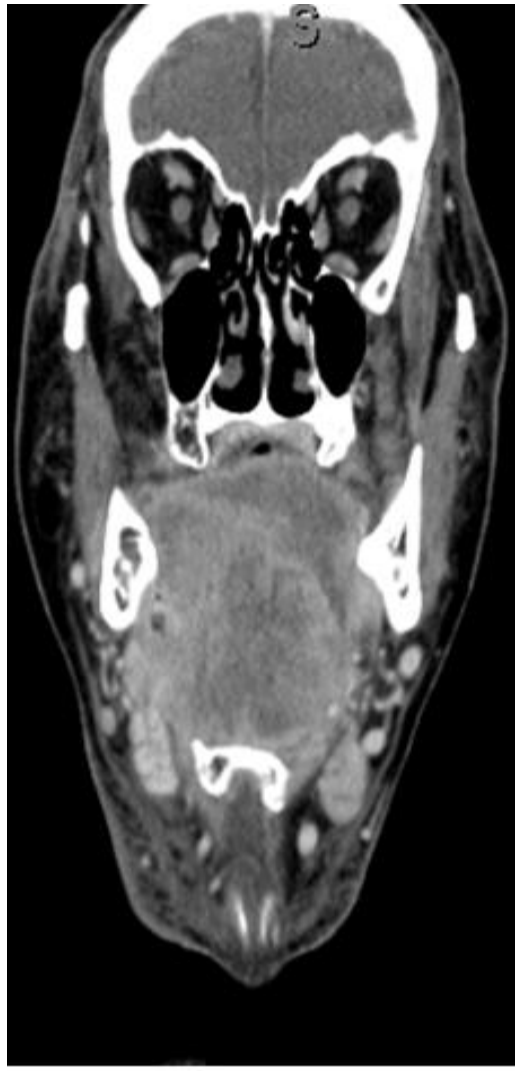


s/p 8 mos tx

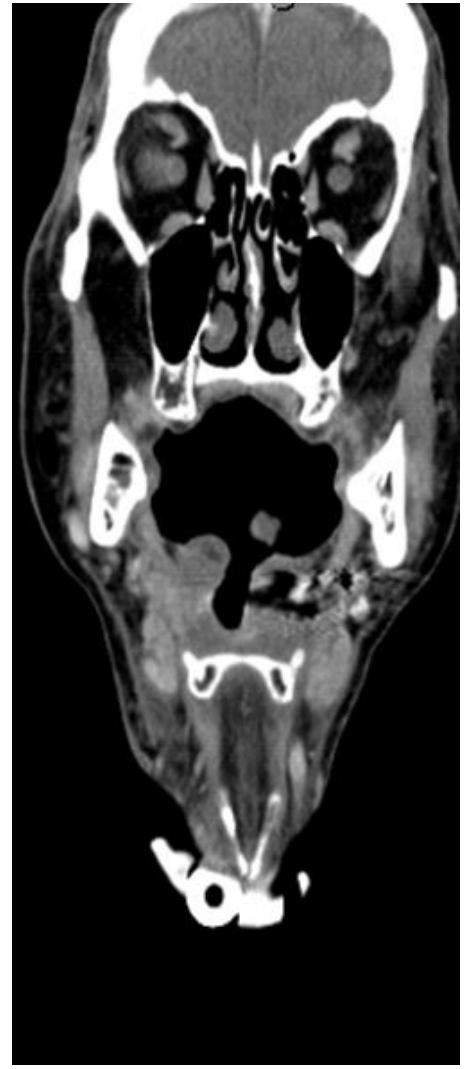


Acc. 9

Baseline



s/p 5 mos tx



Conclusion

- **HPV infection is a causative factor in head and neck cancer carcinogenesis**
- **An epidemic of sexually transmitted HPV oral infection has shifted the epidemiology of oropharyngeal cancer in a major way**
- **Identification of specific biologic characteristics of HPV related oropharyngeal cancer creates opportunities for individualzed therapy in HNC**
- **Prevention of HPV infection by vaccination could prevent many HPV related cancers and represents a challenge for Preventive Medicine**

8th Edition cTNM and pTNM for HPV+ OPC / CUP

Huang, O'Sullivan Curr Treat Options in Oncol. 2017

HPV+ OPC	Clinical stage			Pathologic stage		
Category	T	N	M	T	N	M
Stage I	T1, T2	N0: no regional LNs N1: ipsilateral LNs	M0	T1, T2	N0: no regional LNs N1: 1–4 LNs	M0
Stage II	T1, T2	N2: bilateral or contralateral LNs	M0	T1, T2	N2: ≥ 5 LNs	M0
	T3	N0: no regional LNs N1: ipsilateral LNs N2: bilateral or contralateral LNs	M0	T3, T4	N0: no regional LNs N1: 1–4 LNs	M0
Stage III	T4	Any N	M0	T3, T4	N2: ≥ 5 LNs	M0
	Any T	N3: >6.0 cm LN(s)	M0			M0
Stage IV	Any T	Any N	M1	Any T	Any N	M1

Lydiatt, Patel, O'Sullivan et al, CA Cancer J Clin. 2017

[a]Any M1 is stage IV.

CUP →

cTNM	cN0	cN1 (Unilat)	cN2 (Bilat)	cN3
T0	NA	I	II	III
T1	I	I	II	III
T2	I	I	II	III
T3	II	II	II	III
T4	III	III	III	III

CUP →

pTNM	pN0	pN1 (1-4 LNs)	pN2 (≥5 LNs)
T0	NA	I	II
T1	I	I	II
T2	I	I	II
T3	II	II	III
T4	II	II	III

Uniqueness of HPV+ OPC / CUP TNM (8th edition) - the 1st time in HNC:

- *T4* or *N3* M0 is no longer *Stage IV*
- Different cN and pN classification, and stage groupings

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, ≤ 3 cm in greatest dimension and ENE−
N2	Metastasis in a single ipsilateral lymph node > 3 cm but not > 6 cm in greatest dimension and ENE−; or metastases in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension and ENE−; or in bilateral or contralateral lymph nodes, none > 6 cm in greatest dimension, ENE−
N2a	Metastasis in single ipsilateral node > 3 cm but not > 6 cm in greatest dimension and ENE−
N2b	Metastasis in multiple ipsilateral nodes, none > 6 cm in greatest dimension and ENE−
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension and ENE-
N3	Metastasis in a lymph node more than 6 cm in greatest dimension and ENE-; or metastasis in a single ipsilateral node ENE+; or multiple ipsilateral, contralateral, or bilateral nodes any with ENE+
N3a	Metastasis in a lymph node > 6 cm in greatest dimension and ENE−
N3b	Metastasis in a single ipsilateral node ENE+ or multiple ipsilateral, contralateral or bilateral nodes any with ENE+

Abbreviations: ENE, extranodal extension; HPV, human papillomavirus; OPC, oropharyngeal cancer.

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TABLE 2. Regional Lymph Nodes Clinical Category Criteria (cN) Except Nasopharyngeal and High-Risk HPV+ OPC

Published in: William Lydiatt; Brian O'Sullivan; Snehal Patel; *American Society of Clinical Oncology Educational Book* 38, 505-514.
DOI: 10.1200/EDBK_199697

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N2a	Metastasis in single ipsilateral node > 3 cm but not > 6 cm in greatest dimension and ENE−
N2b	Metastasis in multiple ipsilateral nodes, none > 6 cm in greatest dimension and ENE−
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension and ENE-
N3	Metastasis in a lymph node more than 6 cm in greatest dimension and ENE-; or metastasis in a single ipsilateral node ENE+; or multiple ipsilateral, contralateral, or bilateral nodes any with ENE+
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