Minimally Invasive Office ENT
Sarasota, Florida
February 27th – March 3rd, 2013

Management of HPV Related Oropharyngeal Cancer

Dennis H. Kraus, MD

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New York Head & Neck Institute

North Shore – LIJ Cancer Institute

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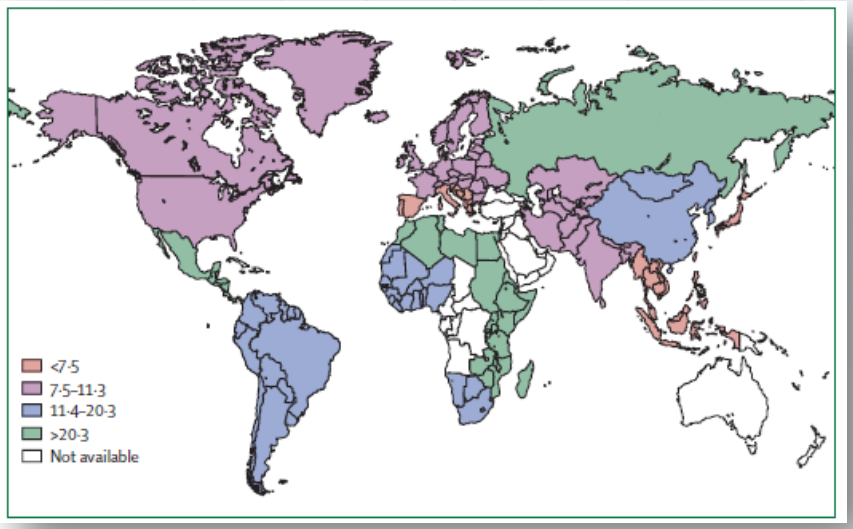
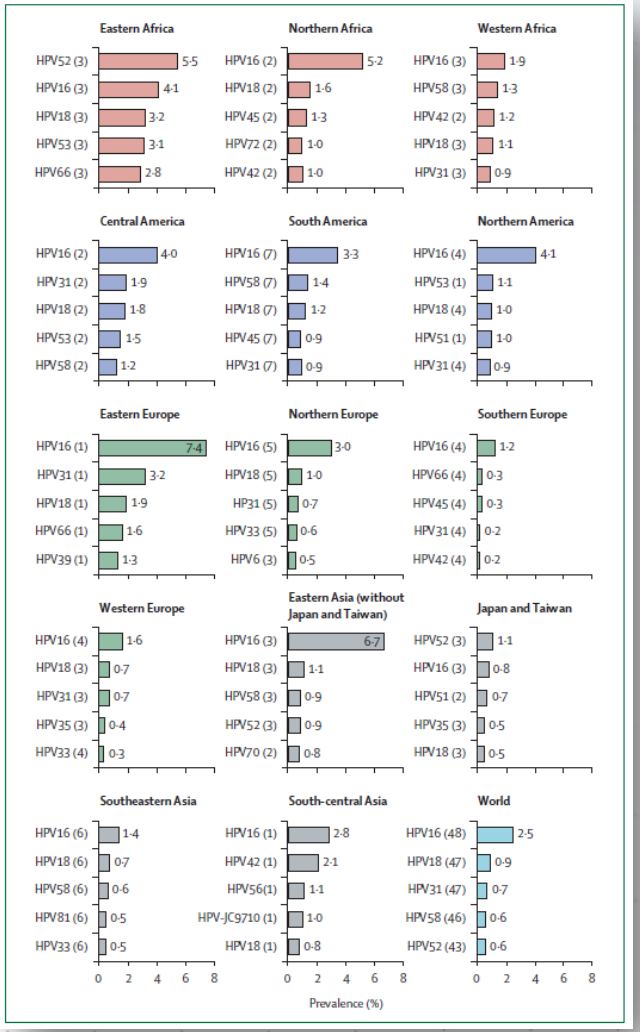
Objectives

- Epidemiology
- Pathogenesis and genetics
- Risk factors
- Survival and outcome
- Racial differences
- Role of smoking
- Treatment options Current trials

Prevalence





Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis.

de Sanjose S - Lancet Infect Dis - 01-JUL-2007; 7(7): 453-9

15879 women with normal cervical cytology

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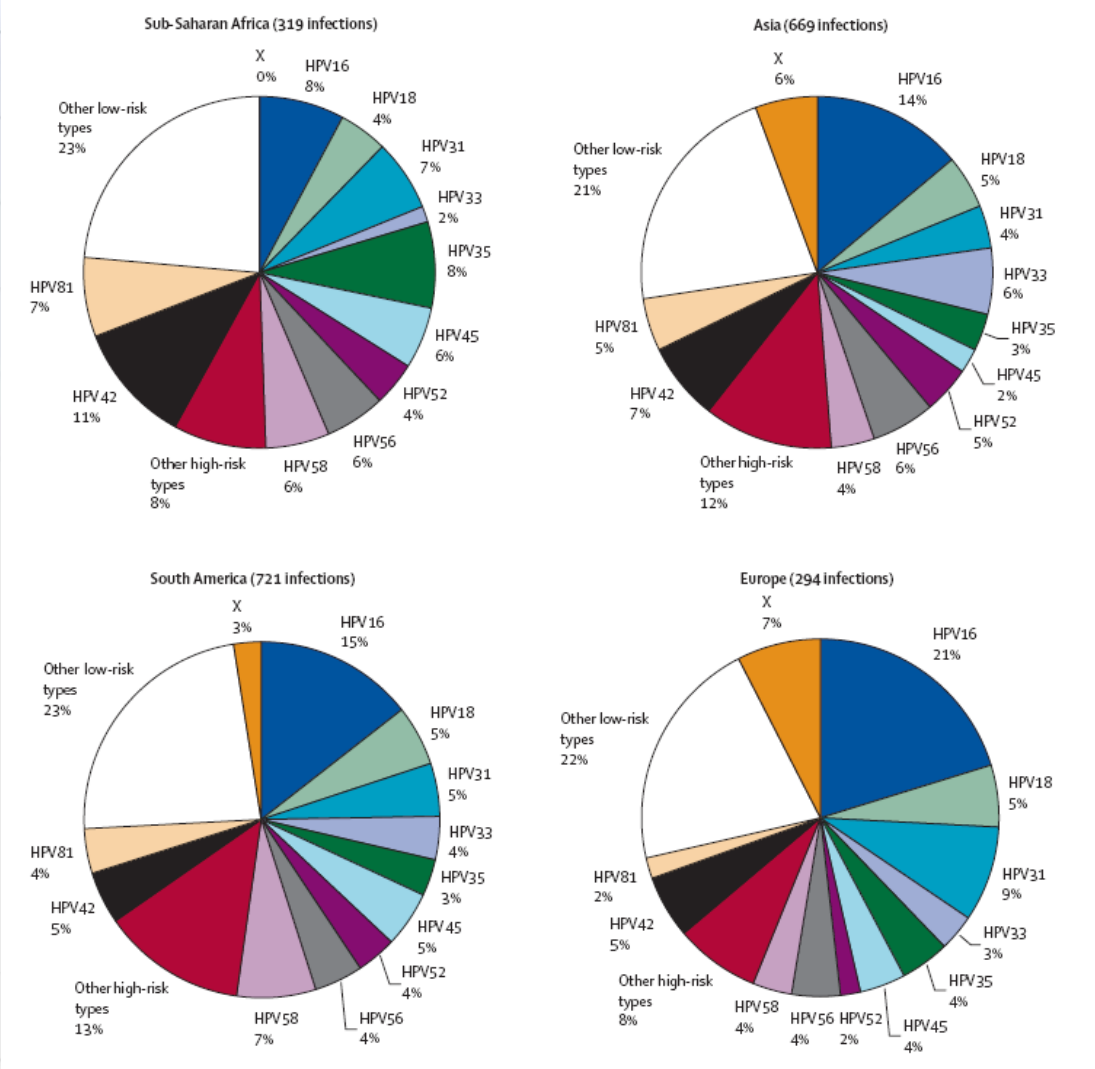
- 15,613 women aged 15-74 years without cytological abnormalities were included in a pooled analysis
- Age standardized HPV prevalence varied nearly 20 times between populations, from 14% (95%CI 0.5-2.2) in Spain to 25.6% (22.4-28.8) in Nigeria
- 66.8% of all HPV+ women had high risk HPV strains of which 19.7% was HPV 16



Worldwide distribution of human papillomavirus types in cytologically normal women in the International Agency for Research on Cancer HPV prevalence surveys: a pooled analysis

Lancet 2005; 366: 991–98

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Human Papillomavirus Types in Head and Neck Squamous Cell Carcinomas Worldwide: A Systematic Review

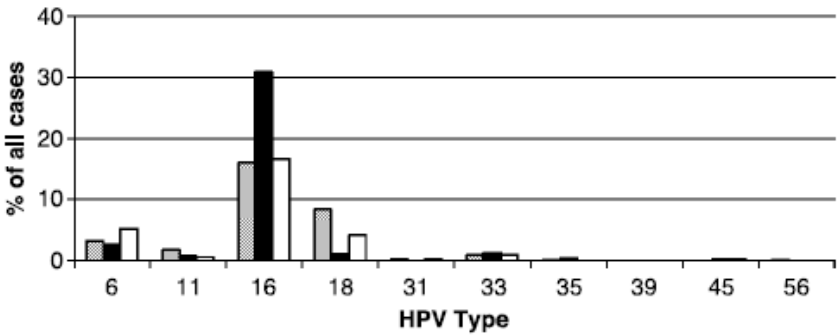
Aimee R. Kreimer,[1,2] Gary M. Clifford,[1] Peter Boyle,[1] and Silvia Franceschi[1]

[1]International Agency for Research on Cancer (IARC), Lyon, France and [2]Cancer Prevention Fellowship Program, Division of Cancer Prevention, National Cancer Institute, NIH, Bethesda, Maryland

Cancer Epidemiology biomarkers and Prevention 14 (2), pp. 467-475

Site	Geographic Location	No. Studies	No. Cases	Overall HPV Prevalence (95% CI)
Oropharynx	Australia, Canada, Cuba, Finland, France, Germany, India, Ireland, Italy, Japan, Netherlands, Norway, Poland, Spain, Slovenia, Sudan, Sweden, Switzerland, United States	27	969	35.6 (32.6-38.7)

	No. studies	No. cases	Overall HPV prevalence (95% CI)	HPV16 prevalence (95% CI)
Oropharynx				
Europe	17	529	28.2 (24.4-32.2)	23.8 (20.2-27.7)
North America	7	285	47.0 (41.1-53.0)	42.1 (36.3-48.1)
Asia	4	54	46.3 (32.6-60.4)	35.2 (22.7-49.4)
Other*	2	101	36.6 (27.3-46.8)	33.7 (24.6-43.8)



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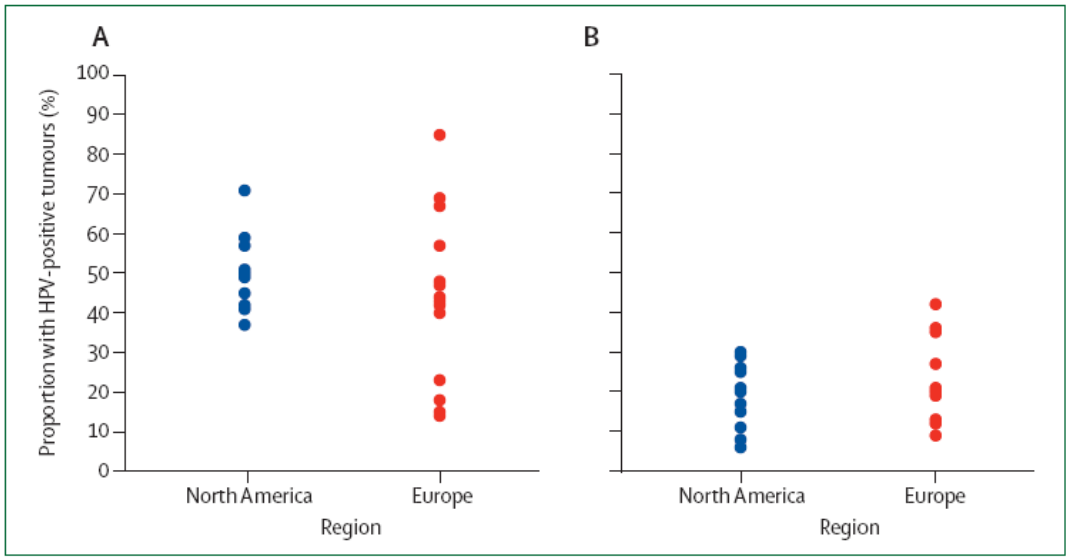
HPV-Associated Head and Neck Cancer: A Virus-Related Cancer Epidemic

Shanthi Marur, Gypsyamber D'Souza, William H Wwestra, Arlene A Forastiere
Lancet Oncol 2010; 11:781-89

Proportion of Oropharyngeal (A) and head and neck (B) squamous cell carcinomas caused by HPV in North America and Europe



Only studies with more than 25 oropharyngeal cancers (n=27) or 50 head and neck tumours (n=30) were included.

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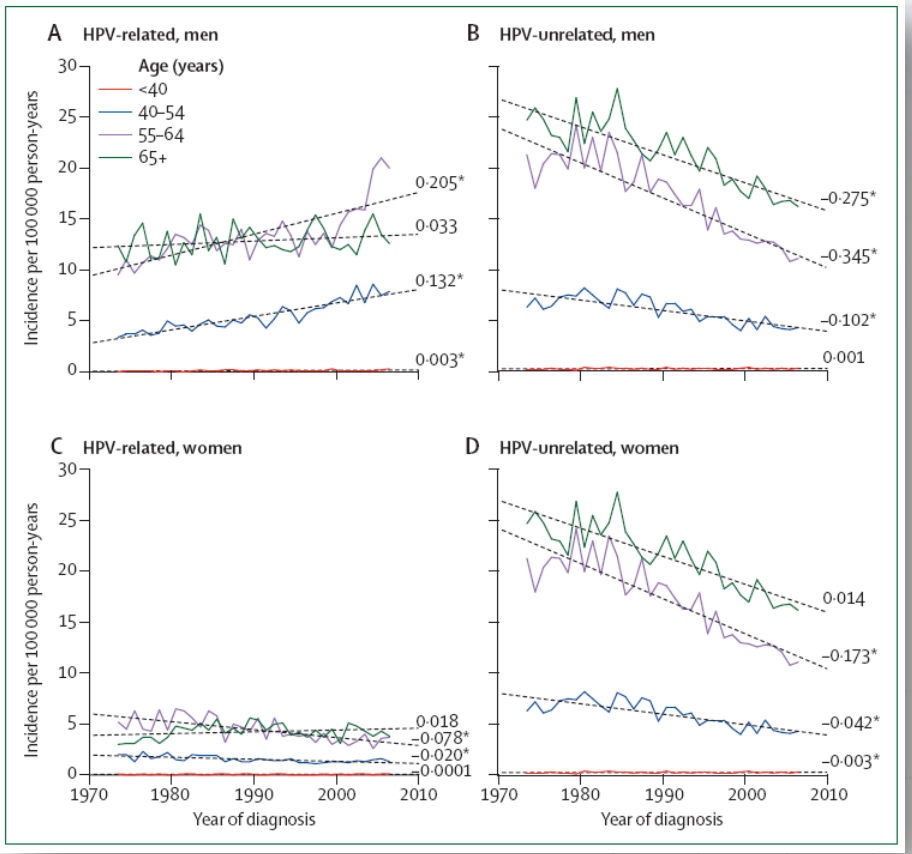
Incidence in HPV Related HNSCC

Journal of Clinical Oncology, Vol 26, No 4 (February 1), 2008: pp. 612-619
The Lancet Oncology, Vol 11, Issue 4, August 2010, Pages 781-789



Age-adjusted incidence of head and neck squamous cell cancers between 1973 and 2006, stratified by age at diagnosis.

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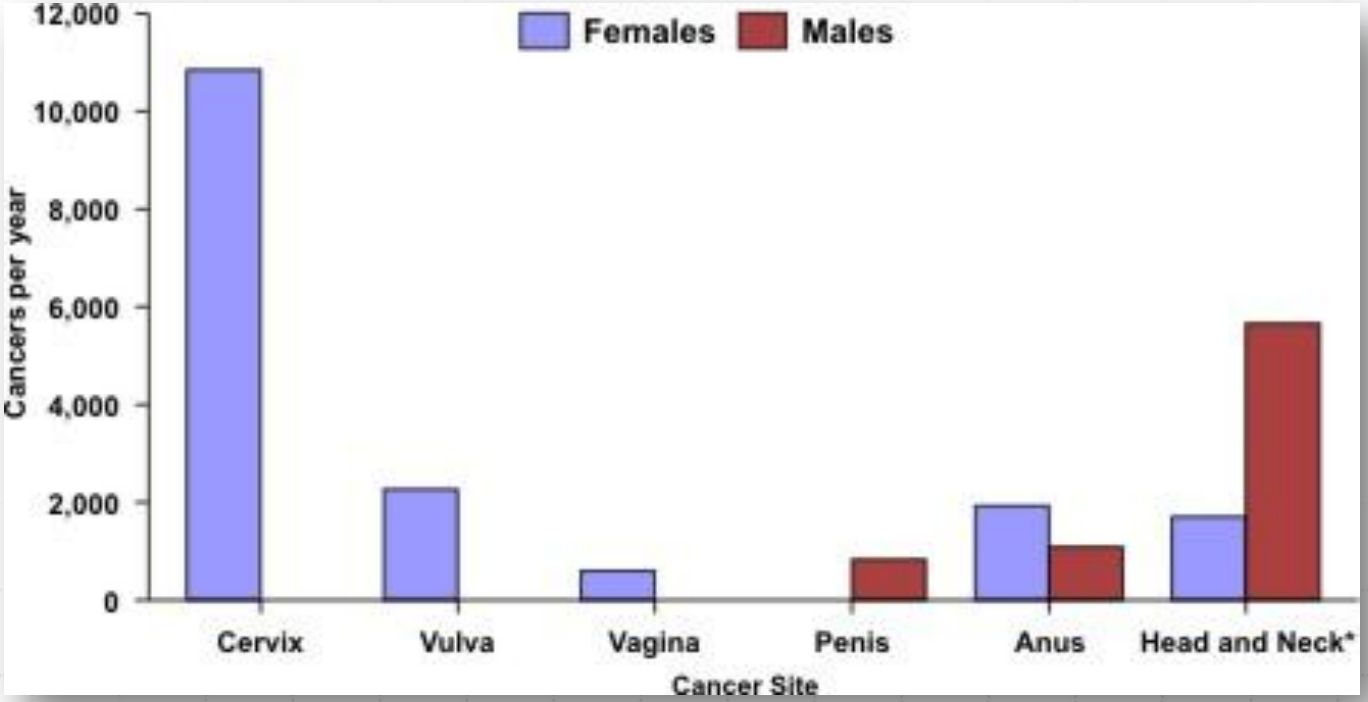
Yearly Counts of HPV-Associated Cancers in the United States, 1998-2003

1,700 HPV-Associated HNSCC in Women and 5,700 in Men



http://www.cdc.gov/cancer/hpv/statistics/cases.htm

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Tongue and Tonsil Carcinoma

Increasing Trends in the U.S. Population Ages 20–44 Years

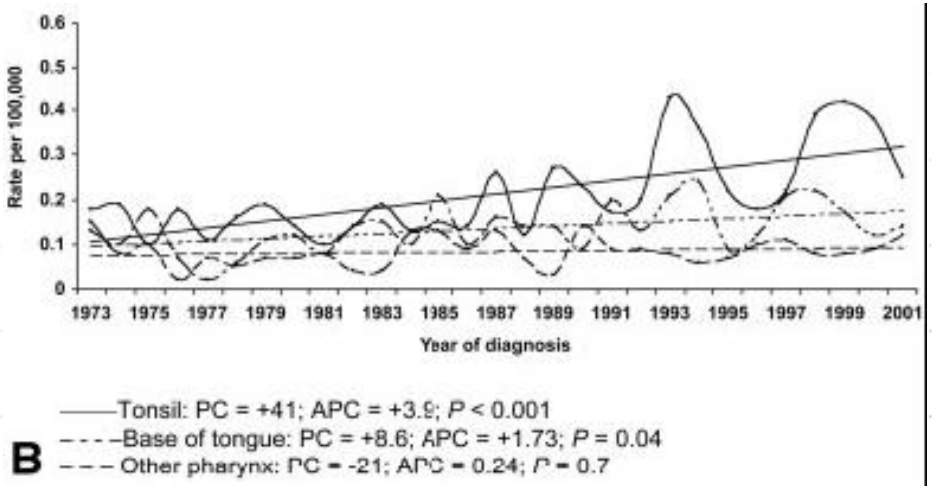
Caroline H. Shiboski, D.D.S., M.P.H., Ph.D.[1,2]
Brian L. Schmidt, D.D.S., M.D., Ph.D.[2,3]
Richard C. K. Jordan, D.D.S., Ph.D.[1,2,4]

CANCER May 1, 2005 / Volume 103 / Number 9

- 33,864 cases of SCC affecting the oral cavity and 23,460 cases of SCC affecting the pharynx reported to the SEER program between 1973 and 2001
- The incidence of tonsil SCC increased, from 0.18 per 100,000 to 0.38 per 100,000 in 2000and 0.25 per 100,000 in 2001 (APC 3.9; P 0.001), as did the incidence of SCC
- The incidence of all other pharyngeal sites remained constant over time

Site	Stage at diagnosis: Localized No. (%)[b]	Spread[a] No. (%)[b]	Unstaged No. (%)[b]
Oral tongue			
20–44 yrs	537 (62)	275 (32)	59 (7)
≥ 45 yrs	4047 (56)	2618 (36)	551 (8)
Base of tongue			
20–44 yrs	67 (18)	296 (77)	19 (5)
≥ 45 yrs	1062 (19)	4296 (76)	299 (5)
Tonsil			
20–44 yrs	75 (14)	462 (83)	17 (3)
≥ 45 yrs	1194 (18)	4961 (76)	407 (6)

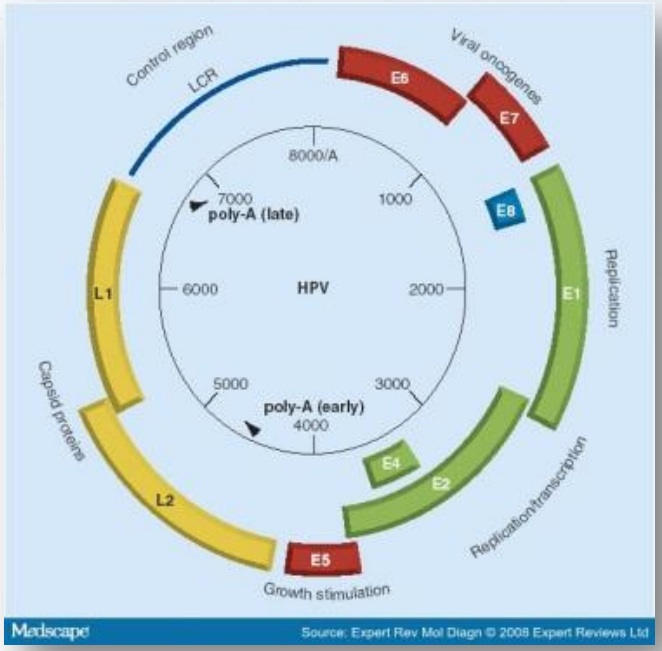
SCC: squamous cell carcinoma; SEER: Surveillance, Epidemiology and End Results program.
[a] Metastasis to regional lymph nodes or to a distant site.
[b] Row percentage (may not add to 100% because of rounding).

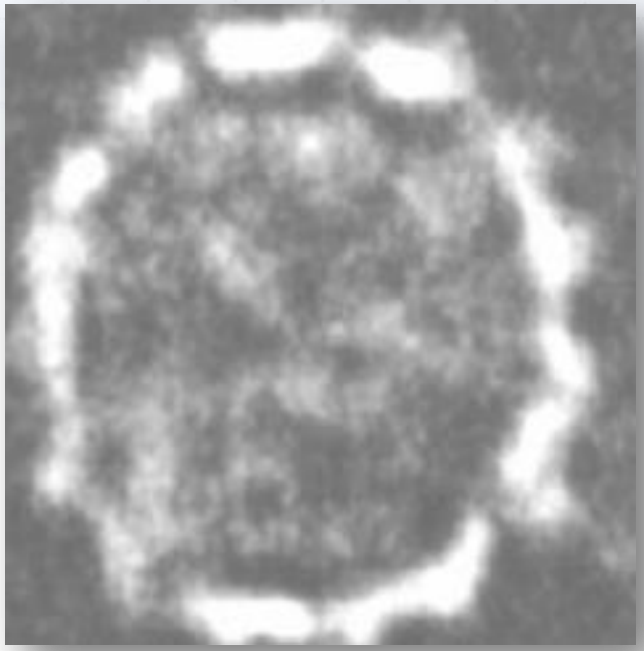


Questions Need to be Answered

- What is the natural history of oral HPV?
- What is the median time from oral HPV infection to cancer?
- Which factors affect oral HPV persistence and progression to cancer?
- How common is prevalent and persistent oral HPV infection in the general population?
- Do precancerous oropharyngeal lesions exist that could be detected?
- Why is the increase in incidence of oropharyngeal cancer:
- Seen in men but not women?
- Most apparent in younger cohorts?
- Do patients with HPV-negative, P16-positive and HPV-positive, P16-positive oropharyngeal cancers have similar survival outcomes?
- What is the biological mechanism for different survival rates in people with HPV-positive head and neck squamous cell carcinomas who use tobacco versus non-users?
- Should treatment of people with HPV-positive and HPV negative head and neck squamous cell carcinomas be different?

HPV Virus





E1: DNA helicase/ATPase
E2: Transcriptional trans-modulator, replication control
E4: Cytokeratin disruption
E5: Cell proliferation (binds PDGF receptor)
E6: Transforming protein (binds p53)
E7: Transforming protein (binds pRB)
L1: Major capsid protein
L2: Minor capsid protein

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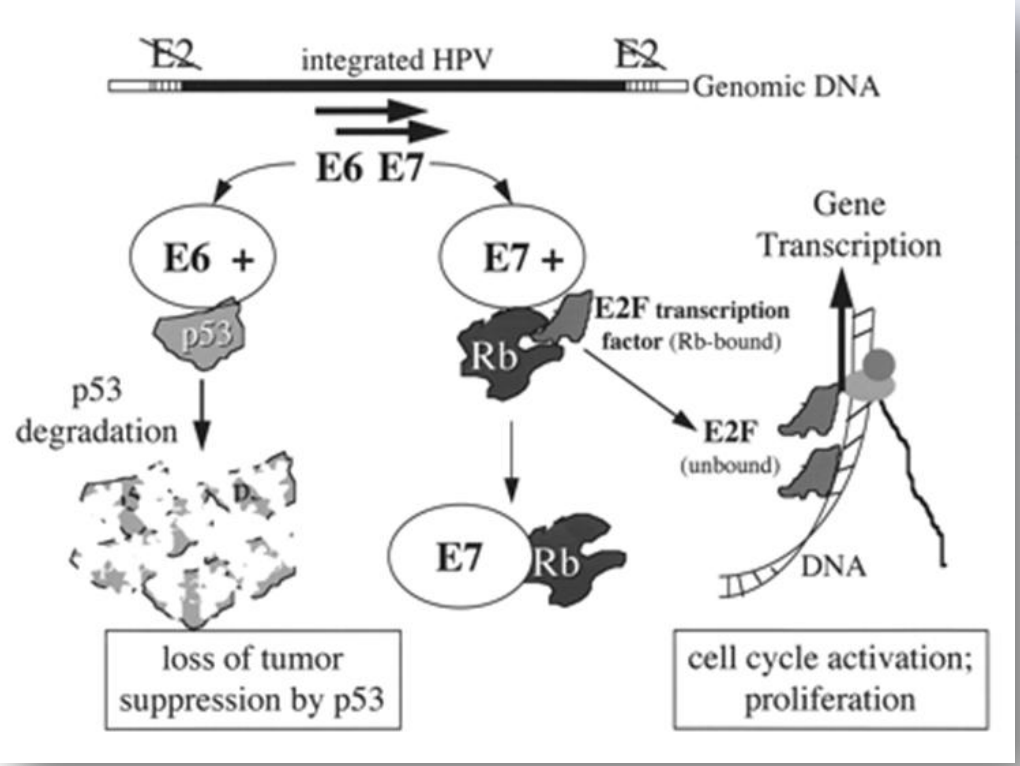

- The E6 and E7 oncoproteins normally under control of E2 and E1 inhibitory genes
- E1 and E2 can be deleted or altered upon integration
  - E6 and E7 then can disrupt the function of Rb and P53
- P53 and Rb are tumor suppressor genes in that they regulate cell-cycle checkpoints at the G1 phase

P53 Mutation in HPV Related HNSCC

- Prevalence of p53 mutations in HPV-positive tumors with the dual presence of HPV DNA and p53 mutations ranging from 0% to 42%
- 48% overall p53 mutations in this study
  - 25% of HPV+ tumors had p53 mutations
  - None were disruptive

HPV16 was detected in 12 of 21 (57%) HNSCCs of the lingual/palatine tonsils

Table 1. p53 mutations and HPV16 positivity in HNSCCs by anatomic site

Site	*p53* mutation (%)	HPV16-positive (%)
Palatine/lingual tonsils	8/21 (38) Disruptive: 1 (13) Nondisruptive: 7 (88)	12/21 (57)
Nontonsillar	37/68 (54) Disruptive: 14 (38) Nondisruptive 23 (62)	0/68 (0)
Oral cavity	22/38 (58) Disruptive: 10 (45) Nondisruptive: 12 (55)	0/38 (0)
Larynx	11/20 (55) Disruptive: 3 (27) Nondisruptive: 8 (73)	0/20 (0)
Hypopharynx	4/6 (67) Disruptive: 1 (25) Nondisruptive: 3 (75)	0/6 (0)
Palate	0/4 (0) Disruptive: 0 Nondisruptive: 0	0/4 (0)

Inverse Relationship between Human Papillomavirus-16 Infection and Disruptive *p53* Gene Mutations in Squamous Cell Carcinoma of the Head and Neck

William H. Westra,[1,2] Janis M. Taube,[1] M.L. Poeta,[2] Shanaz Begum,[1] David Sidransky,[2] and Wayne M. Koch[2]

Clin Cancer Res 2008;14(2) January 15,2008

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Distinct Genetic Signature of HPV Associated OPSCC

HPV+ HNSCC	HPV- HNSCC
Inactivation of p53 (ubiquitination)	
Lower p53 mutations (wild type)	High rate of disruptive p53 mutations
Down regulation of cyclin D	Increased cyclin D
Down regulation of pRb	Normal or increased pRb
Increased p16	Decreased p16 (mutation, methylation, deletion)
Decreased EGFR expression	Elevated PCNA, MIB-1, Survivin

Combined analysis of HPV-DNA, p16 and EGFR expression to predict prognosis in oropharyngeal cancer

Niklas Reimers[1], Hans U. Kasper[2,3], Soenke J. Weissenborn[4], Hartmut Stützer[5], Simon F. Preuss[1], Thomas K. Hoffmann[6], Ernst Jan M. Speel[7], Hans P. Dienes[2], Herbert J. Pfister[3,4], Orlando Guntinas-Lichius[1] and Jens P. Klussmann[1]*

Int. J. Cancer: **120,** 1731–1738 (2007)

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What are the risk factors for HPV+ vs. HPV negative OPC?

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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.

Case-control study of 100 patients with newly diagnosed oropharyngeal cancer and 200 control patients without cancer

Sexual Behavior	Patients with Oropharyngeal Cancer (N=100)	Control Patients (N=200)	Adjusted Odds Ratio (95% CI)†	
			All Patients	HPV-16+ Patients‡
	number (percent)			
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)
Age at first intercourse				
18 yr or older	30 (30)	87 (44)	1.0	1.0
17 yr or younger	70 (70)	113 (56)	1.3 (0.7–2.3)	2.1 (1.1–3.6)
Condom use				
Usually or always	28 (28)	90 (45)	1.0	1.0
Never or rarely	72 (72)	110 (55)	2.2 (1.2–3.8)	2.1 (1.1–4.0)
Sex with same-sex partner				
No	92 (92)	186 (93)	1.0	1.0
Yes	8 (8)	14 (7)	1.0 (0.4–2.6)	1.1 (0.3–3.3)
Sexual partner with history of HPV-associated cancer‡‡				
No	86 (86)	190 (95)	1.0	1.0
Yes	3 (3)	2 (1)	3.0 (0.5–20.5)	3.9 (0.6–25.8)
Unsure	11 (11)	8 (4)	2.3 (0.8–6.5)	2.8 (0.9–8.5)

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Distinct Risk Factor Profiles for Human Papillomavirus Type 16–Positive and Human Papillomavirus Type 16–Negative Head and Neck Cancers

Maura L. Gillison, Gypsyamber D'Souza, William Westra, Elizabeth Sugar, Weihong Xiao, Shahnaz Begum, Raphael Viscidi

J Natl Cancer Inst 2008; 100:407-420

- Case subjects (n=240) diagnosed with HNSCC from 2000 through 2006 stratified by tumor HPV-16 status as determined by in situ hybridization
- Two control subjects (n=322) without cancer were individually matched by age and sex to each HPV-16-positive and HPV-16-negative case subject.

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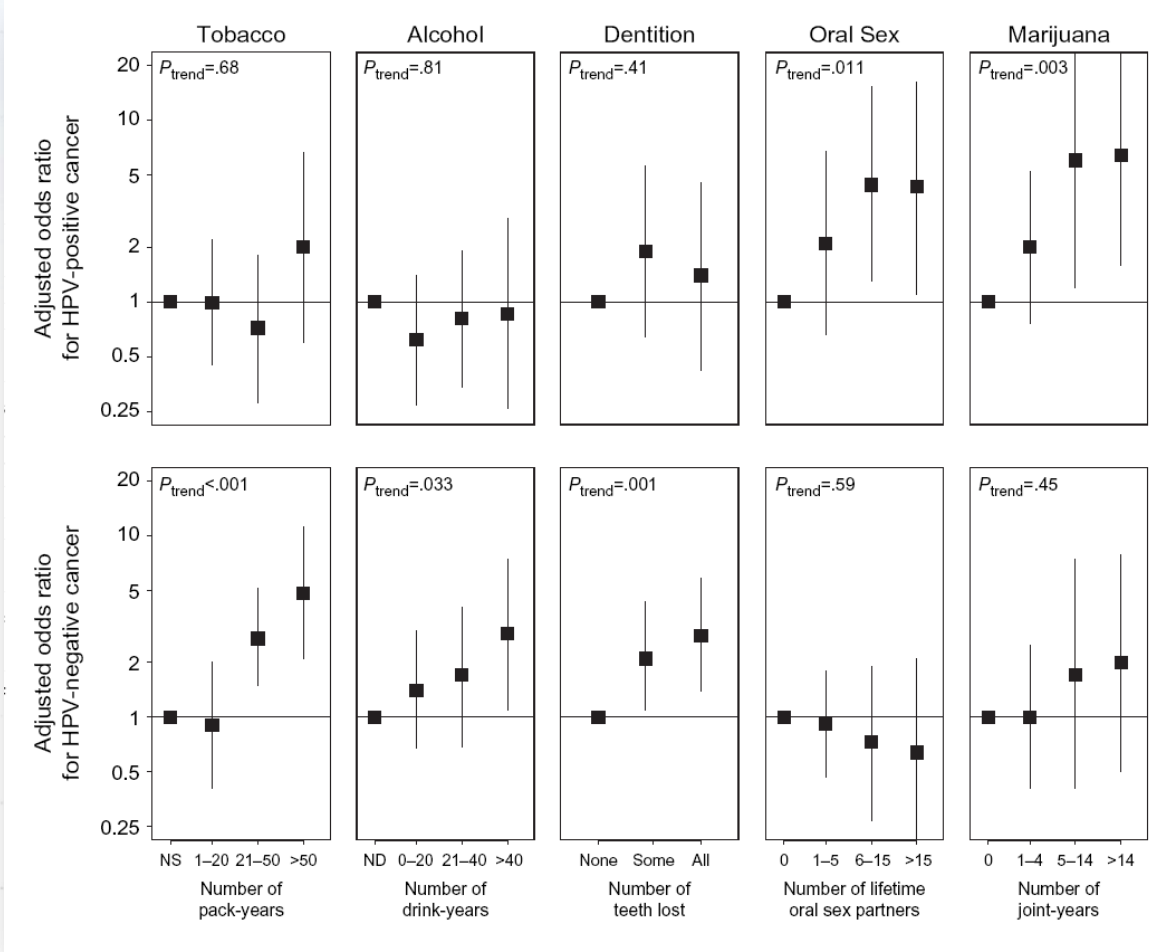
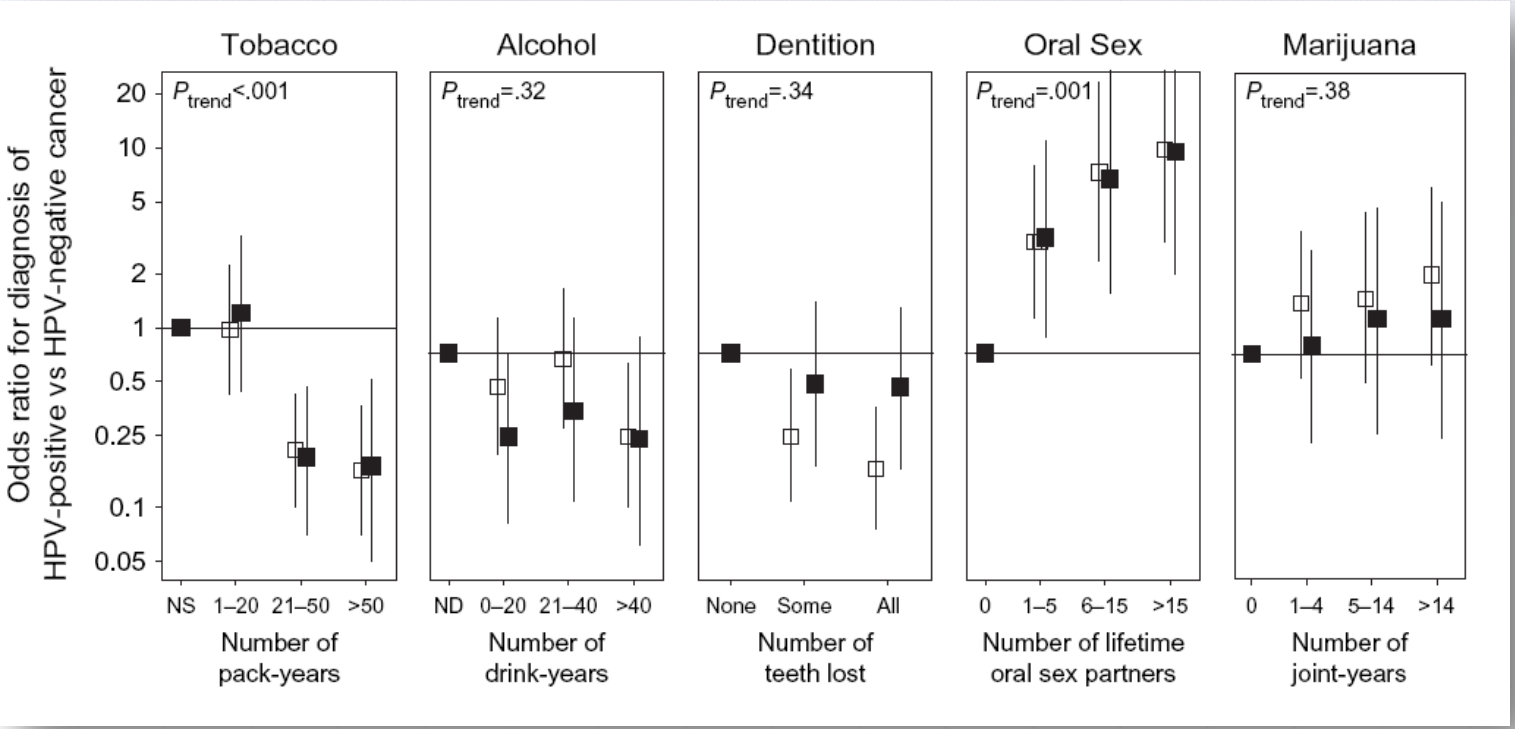
Dose response relationships for tobacco, alcohol, tooth loss, oral sex partners, and marijuana use and odds of human papillomavirus type 16 (HPV-16) positive and HPV-16 negative HNSCCs



J Natl Cancer Inst 2008; 100:407-420

Dose – response relationships for tobacco, alcohol, tooth loss, oral sex partners, and marijuana use and the odds of being diagnosed with HPV-16 positive vs. HPV-16 negative head and neck squamous cell carcinoma.



HPV-16 – positive HNSCCs and HPV-16 – negative HNSCCs have different risk factor profiles.

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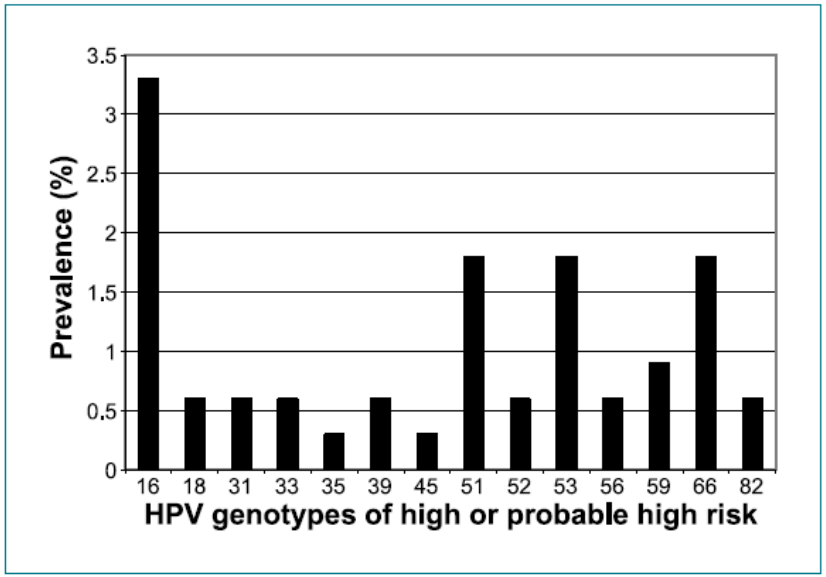
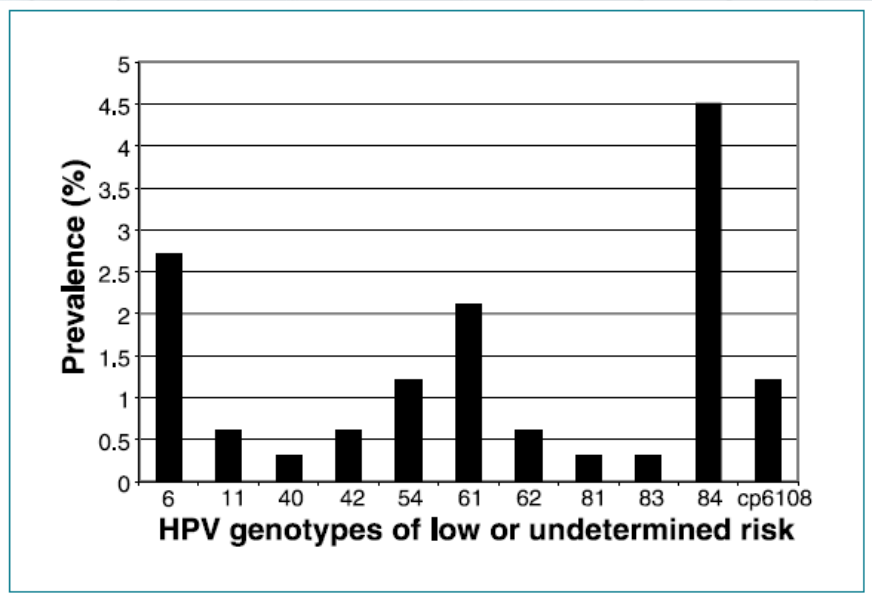
Detection of Genital HPV Types in Fingertip Samples from Newly Sexually Active Female University Students

Rachel L. Winer[1], James P. Hughes[2], Qinghua Feng[3], Long Fu Xi[1,3], Stephen Cherne[3], Sandra O'Reilly[1], Nancy B. Kiviat[3], and Laura A. Koutsky[1]





- High-or probable high-risk type-specific HPV DNA prevalence in 335 fingertip samples collected from 127 women
- HPV prevalence in fingertip samples was 14.3%
- HPV (any type) was detected in 38.5% of genital samples
- 60.4% concordance between fingertips HPV type (58 of 96 types) and genital sample.

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Human papillomavirus (HPV) transmission from oropharyngeal cancer patients to sexual partner.

S. Tsao

- Patients with confirmed OPC and their sexual partners underwent OC/OP swabs/brushings and answered a questionnaire
- HPV genotyping via real-time PCR
- Tested 174 patient-partner pairs
  - 29 HPV-positive OPC patients (17%),
  - 19 partners (66%) had HPV-positive swabs
- All 19 HPV-positive partners (100%) were concordant with the OPC patient for at least one HPV type
- In 4 of the 29 pairs with an HPV-positive patient, a prior history of HPV-related disease occurred in either the patient (1 rectal cancer) or the partner (3 abnormal Pap smears)

Is there a survival difference between HPV+ and HPV- OPC?

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

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

J Natl Cancer Inst 2008;100:261–269

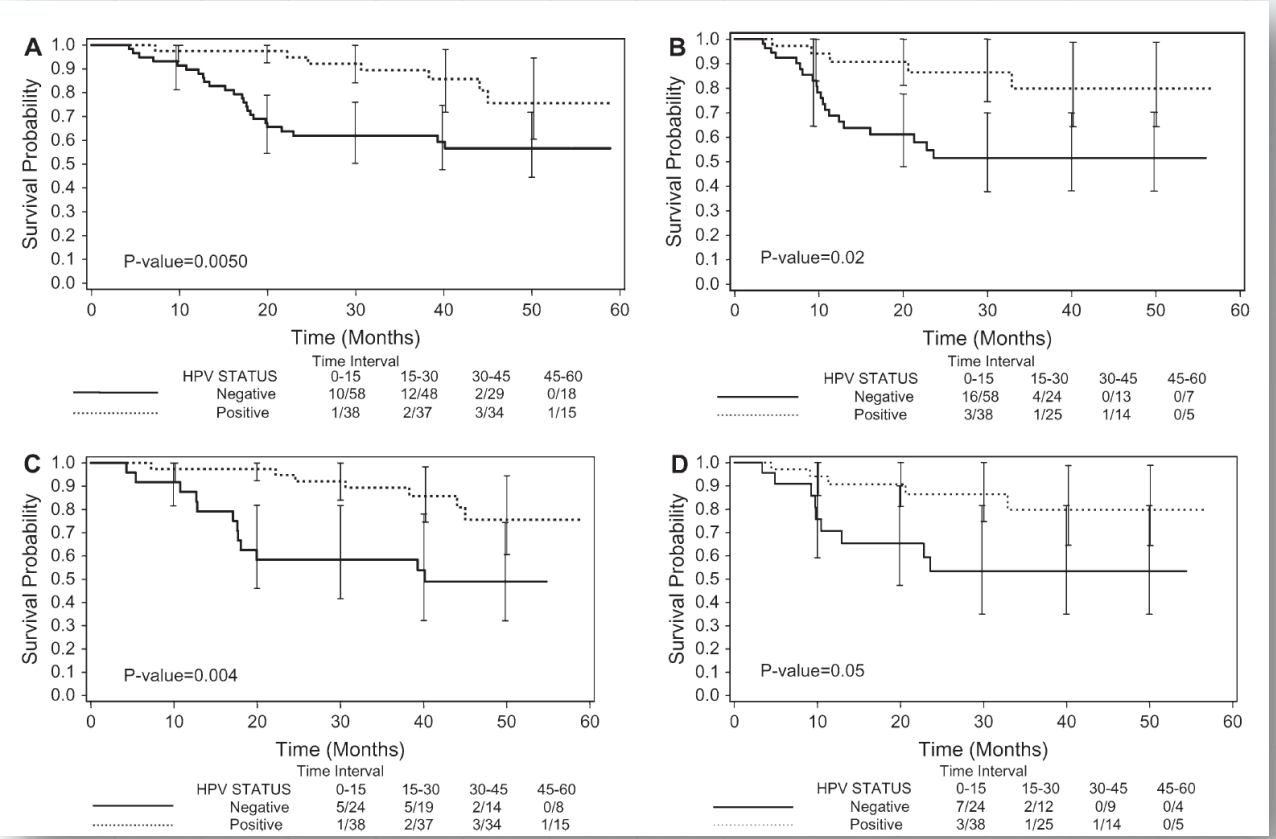
- Prospectively evaluated the association of tumor HPV status with therapeutic response and survival
- 96 patients with stage III or IV HNSCC of the oropharynx or larynx who participated in ECOG 2399 phase II trial

- Received two cycles of induction chemotherapy with intravenous paclitaxel and carboplatin followed by concomitant weekly intravenous paclitaxel and standard fractionation radiation therapy

- The presence or absence of HPV oncogenic types in tumors was determined by PCR and in situ hybridization

- Two-year overall and progression-free survival for HPV-positive and HPV-negative patients were assessed

Survival Results



A) OS (at 2 y 95% vs. 62%, P=0.005%)
B) PFS (at 2 y 86% vs. 53%)
C) OS for patients with oropharynx cancer only
D) PFS for patients with oropharynx cancer only

J Natl Cancer Inst 2008;100:261-269

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Survival of squamous cell carcinoma of the head and neck in relation to human papillomavirus infection: Review and meta-analysis

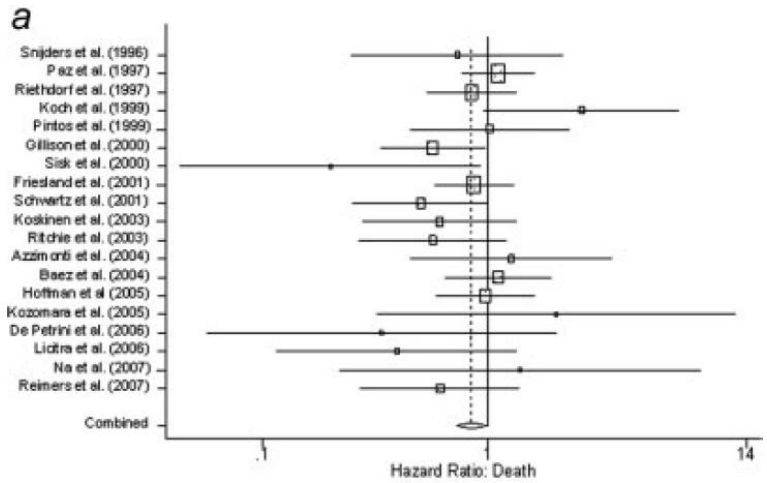
Camille C.R. Ragin[1,2]* and Emanuela Taioli[1,2]

[1]*Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA*
[2]*Division of Cancer Prevention and Population Science, University of Pittsburgh Cancer Institute, Pittsburgh, PA*

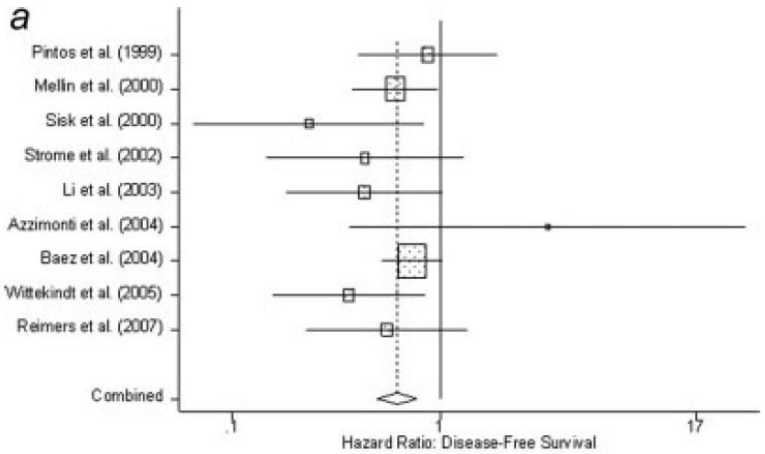
Int. J. Cancer: **121,** 1813–1820 (2007)

Meta-analysis of 23 studies

- 19 provided complete data for OS
  - HPV-positive head and neck tumors had an lower risk of dying than patients with HPV-negative tumors



(a) Overall survival, HPV-positive vs. HPV-negative tumours; meta hazard ratio: 0.85



(a) Disease-free survival, HPV-positive vs. HPV-negative tumours; meta hazard ratio: 0.62,

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OS

Study	N	HPV16 (%)‡	Head and neck subsites	HR	95% confidence interval
Oropharyngeal tumors					
Friesland et al. (2001)[44]	34	100	Tonsil	0.86	0.6–1.3
De Petrini et al. (2006)[40]	20	100	Oropharynx	0.20	0.0–1.0
Licitra et al. (2006)[39]	90	100	Oropharynx	0.39	0.1–1.4
Reimers et al. (2007)[52]	80	97	Oropharynx	0.61	0.3–1.4
Total	224				
Meta*				0.72	0.5–1.0
p value, *Q* test				0.240	
p value, Egger's test			0.011		

DFS

Study	N	HPV16 (%)‡	Head and neck subsites	HR	95% confidence interval
Oropharyngeal tumors					
Mellin et al. (2000)[17]	60	100	Tonsil	0.61	0.4–1.0
Strome et al. (2002)[46]	52	88	Tonsil	0.44	0.2–1.3
Li et al. (2003)[37]	67	90	Tonsil	0.43	0.2–1.0
Wittekindt et al. (2005)[51]	34	94	Tonsil	0.36	0.2–0.9
Reimers et al. (2007)[52]	80	≥96§	Oropharynx	0.55	0.2–1.4
Total	293				
Meta*				0.51	0.4–0.7
p value, *Q* test				0.846	
p value, Egger's test			0.135		

- Patients with HPV-positive oropharyngeal tumours had a 28% reduced risk of death (meta HR: 0.72, 95%CI: 0.5–1.0) in comparison to patients with HPV-negative oropharyngeal tumors
- The HPV-positive patients with oropharyngeal tumours had a 49% lower risk of disease-failure than the patients with HPV-negative oropharyngeal tumours (meta HR: 0.51, 95% CI: 0.4–0.7)
- OS for patients with non-oropharyngeal tumors did not differ by HPV status

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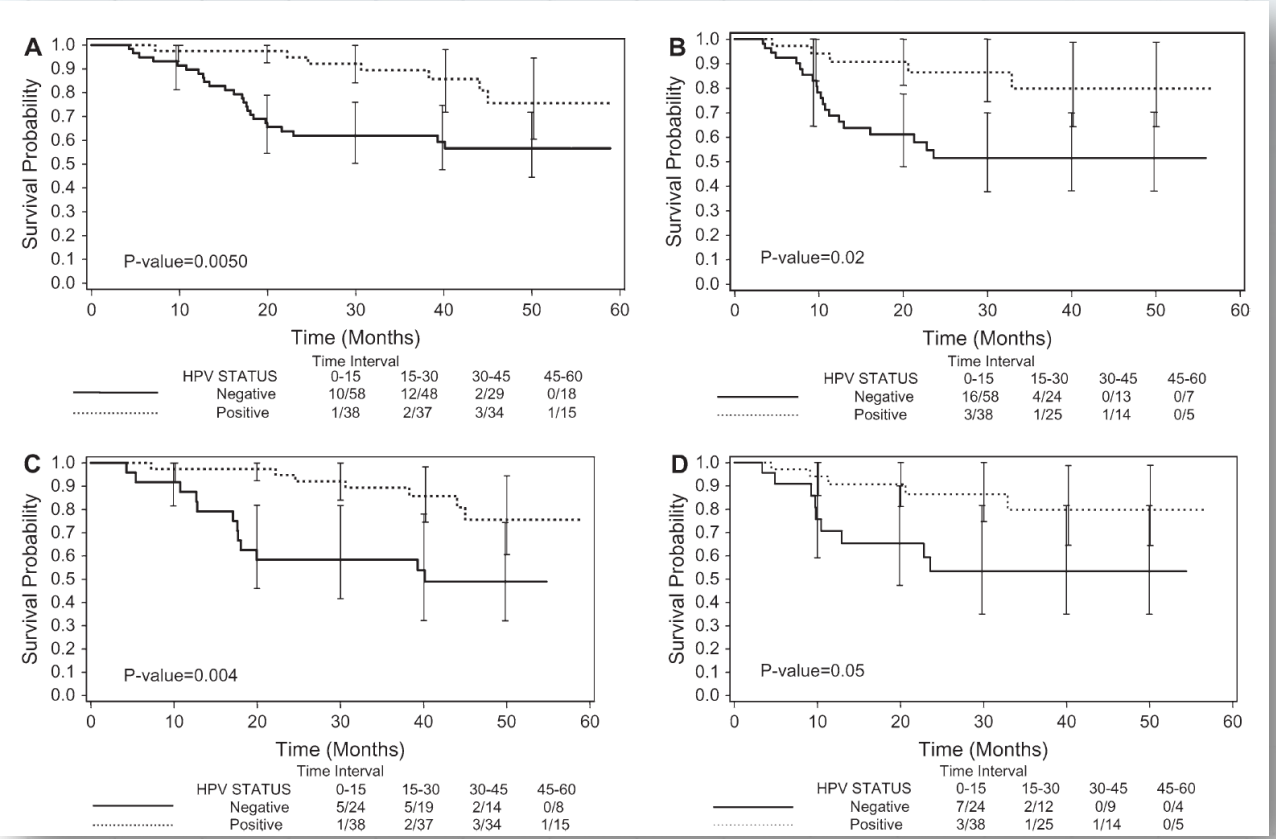
Survival Results



A) OS (at 2 y 95% vs. 62%, P=0.005%)
B) PFS (at 2 y 86% vs. 53%)
C) OS for patients with oropharynx cancer only
D) PFS for patients with oropharynx cancer only

J Natl Cancer Inst 2008;100:261-269

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Oropharynx cancer (OPC) in TAX 324: Human papillomavirus (HPV) and survival.

M.R. Posner

- Prospective randomized, international, phase III trial of sequential therapy (ST) in pts with locally advanced squamous cell cancer of the head and neck
- 111 (42%) had evaluable biopsies
  - 56 (50%) were HPV+ and 55 (50%) were HPV-.
- HPV+ OPC pt characterisitics:
  - younger (54 vs. 58 yrs, p=0.02),
  - Caucasian (96% vs. 84%, p=0.03),
  - T1/T2 primary cancers (49% vs. 20%, p=0.001),

OS*	HPV+ N=56	HPV- N=55
1-yr	93% (82-97)	69% (54-79)
2-yr	89% (78-95)	48% (34-61)
3-yr	87% (75-94)	41% (28-53)
5-yr	82% (69-90)	35% (23-48)
PFS*		
1-yr	85% (73-92)	52% (38-64)
2-yr	83% (70-91)	35% (23-48)
3-yr	81% (68-90)	33% (21-46)
5-yr	78% (64-87)	28% (17-40)

J Clin Oncol 28:15s, 2010 (suppl; abstr 5525)

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Does race matter?

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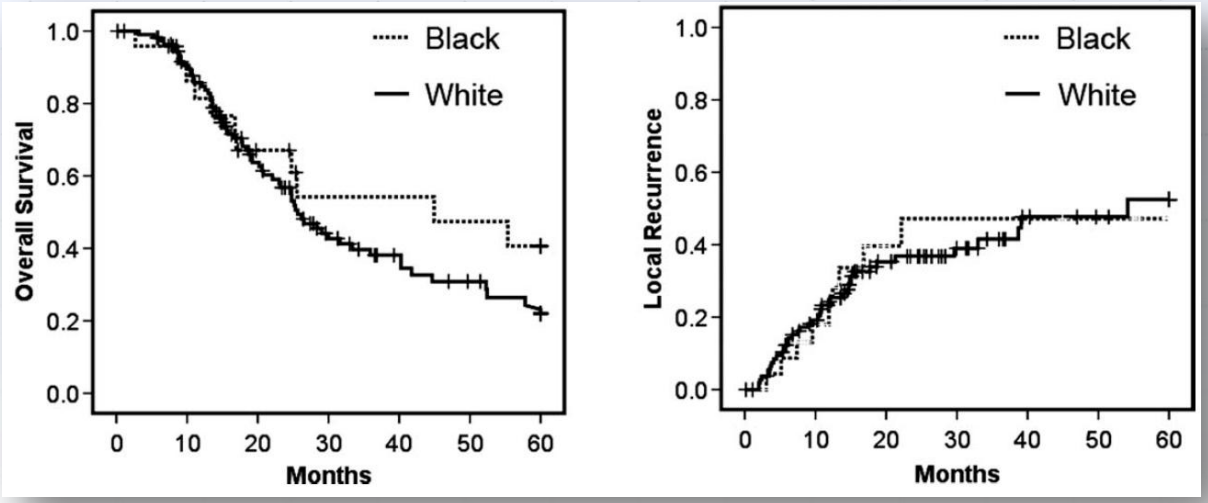
Human Papillomavirus-Active Head and Neck Cancer and Ethnic Health Disparities

Paul M. Weinberger, MD; Mark A. Merkley, BS; Sunny S. Khichi, BS; Jeffrey R. Lee, MD; Amanda Psyrri, MD; Lana L. Jackson, MD; William S. Dynan, PhD

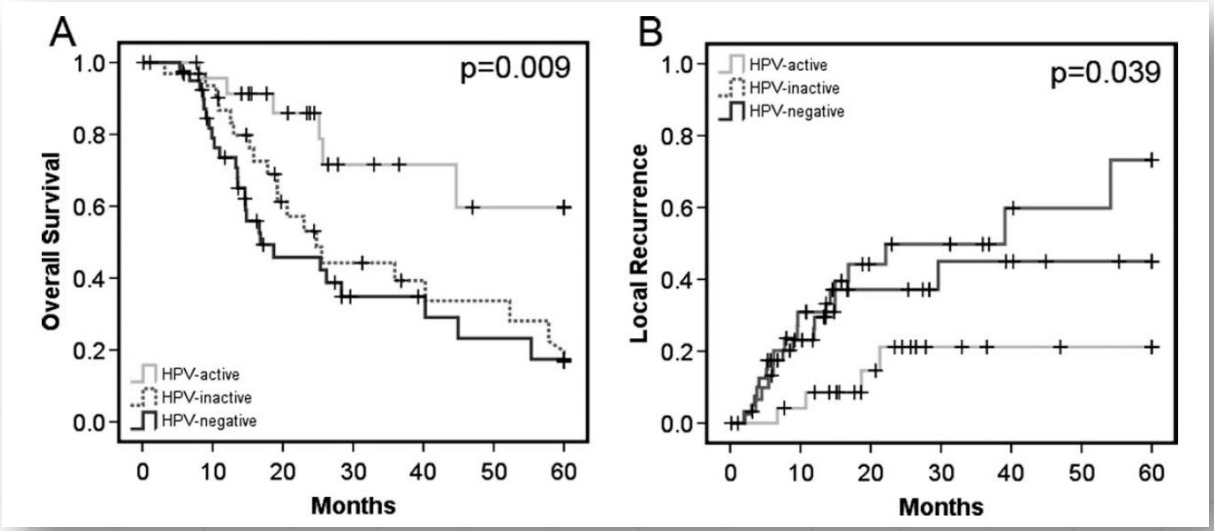
Laryngoscope, 120:1531–1537, 2010

- 140 patients with HNSCC
- RT PCR against E6 and E7 & IHC detection of $p16^{INK4a}$
- Patients were classified:
  - HPV-negative (HPV DNA-negative, $p16^{INK4a}$ low)
  - HPV-inactive (HPV DNA-positive, $p16^{INK4a}$ low)
  - HPV-active (HPV DNA-positive, $p16^{INK4a}$ high)

	HPV DNA-Negative	HPV DNA-Positive
$p16^{INK4a}$ low	HPV-Negative	HPV-Inactive
$p16^{INK4a}$ high	Undefined (not observed)	HPV-Active



Overall survival and local recurrence rates stratified by patient ethnicity.



(A) Overall survival rates for HPV-active, HPV-inactive, and HPV-negative patients as indicated.
(B) Local recurrence rates for patients in each class as indicated.

Laryngoscope, 120:1531-1537,2010

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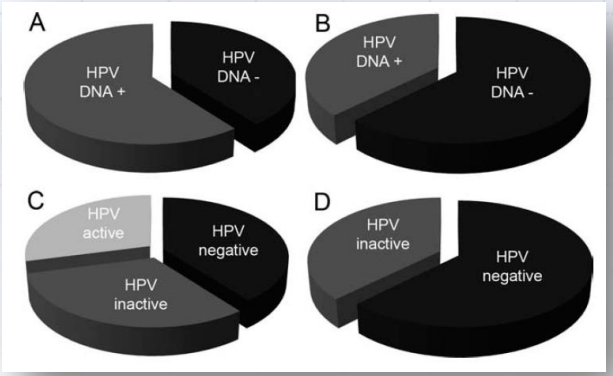
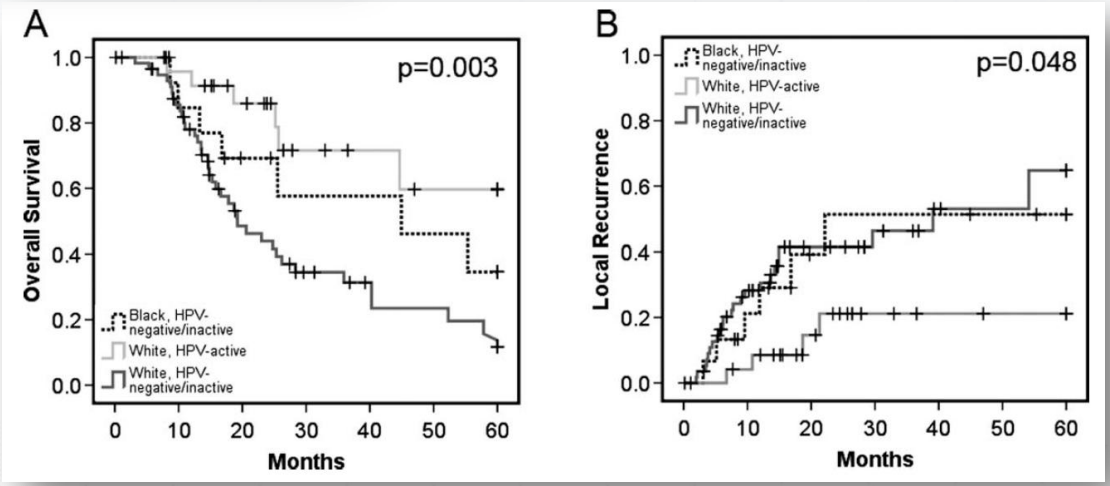


(A, B) Prevalence of HPV 16 DNA in patients stratified by ethnicity; (A) white, (B) black. Difference was not significant (P = 0.12). (C, D) HPV status using three-class system stratified by ethnicity; (C) white, (D) black. Difference in the frequency of the HPV active class between white and black patients was significant (P= .017).



Patients with HPV-active HNSCC had improved 5y OS survival (59.7%) compared to HPV-negative and HPV inactive patients (16.9%) (P = .003). Black patients were less likely to have HPV-active disease (0%) compared to white patients (21%) (P = .017).

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Laryngoscope, 120:1531-1537,2010

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Does smoking affect the outcomes in HPV+ OPC?

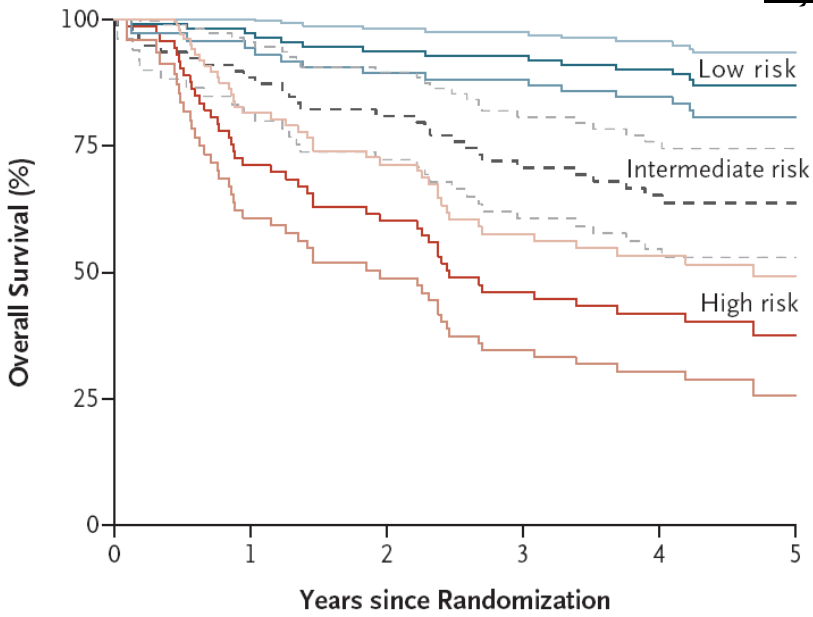
Survival outcomes by tumor human papillomavirus (HPV) status in stage III-IV oropharyngeal cancer (OPC) in RTOG 0129

- Randomized phase 3 trial comparing standard fractionation (FX) radiotherapy (RT) and cisplatin (cis) (100 mg/m2, days 1, 22, 43) to accelerated FX-RT and cis
- HPV16 in situ hybridization (ISH).
- The hazard of death:
  - HPV-neg OPC with ≥ 20 p-y (HR 4.33)
  - HPV-neg OPC with < 20 p-y (HR 2.41)
  - HPV-pos OPC with ≥ 20 p-y (HR 1.79)
  - HPV-pos OPC with <20 p-y (HR set as 1)

HPV and Smoking

RTOG 0129

3-yr survival

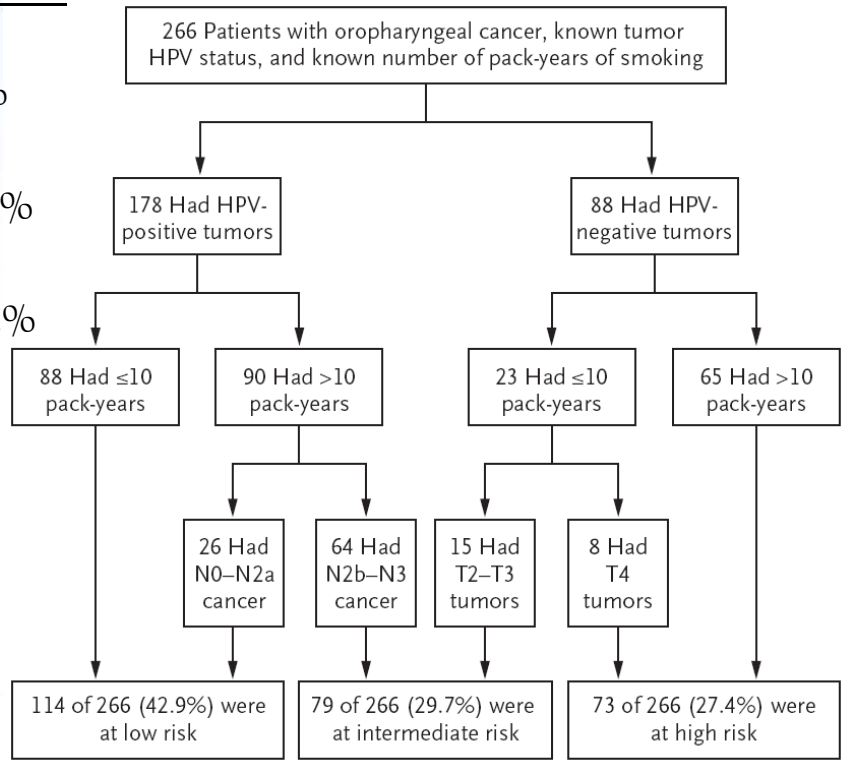


No. at Risk						
Low risk	114	111	106	102	95	46
Intermediate risk	79	70	64	54	44	24
High risk	73	52	43	33	28	8

93%

70.8%

46.2%



The risks of death and cancer relapse or death significantly increased by 1% for each additional pack-year of tobacco smoking for both HPV+ and HPV- patients

Distinctive clinicopathologic characteristics for HPV positive and HPV negative oropharyngeal carcinoma

	HPV-Positive	HPV-Negative
Anatomic site	Tonsil and BOT	All sites
Histology	Non-keratinized/basaloid	Keratinized
Age	Younger cohort	Older
Gender	3:1 men	3:1 men
Stage	Tx, T1-2	Variable
Risk factor	Sexual behavior	Tobacco and Alcohol
Molecular/Genetics	Inactivation of p53 & Rb, ↑P16	p53 mutations, ↓P16
Incidence	Increasing	Decreasing
Survival	Improved	Unchanged

Intensity-Modulated Radiotherapy Outcomes for Oropharyngeal Squamous Cell Carcinoma Patients Stratified by p16 Status

Asal Shoushtari, MD[1]; Mathew Meeneghan, MD[1]; Ke Sheng, PhD[1]; Christopher A. Moskaluk, MD, PhD[2]; Christopher Y. Thomas, MD[3]; James F. Reibel, MD[4]; Paul A. Levine, MD[4]; Mark J. Jameson, MD, PhD[4]; Kimberly Keene, MD[5]; and Paul W. Read, MD, PhD[1]

Cancer June 1, 2010

- Retrospective review of 112 pts with OPC
- Treatments
  - IMRT (66-70 Gy)+ post RT neck dissection ± chemo (55.3% pts)
  - RT + chemotherapy (60.7% pts)

PEG tube placed during treatment	46 (41.0%)
PICC/central line	28 (25.0%)
Chemotherapy	68 (60.7%)
Cisplatin	51 (45.5%)
Carboplatin	15 (13.3%)
Intravenous 5-FU	25 (22.3%)
Capecitabine	26 (23.2%)
Cetuximab	3 (2.6%)
Docetaxel/paclitaxel	17 (15.1%)
Induction chemotherapy	59 (52.6%)
Average no. of induction chemotherapy cycles	2
Average no. of concurrent chemotherapy cycles	3
Concurrent chemotherapy	61 (54.4%)

Planned Postradiation Neck Dissections in Patients with N1 Disease	No.
Total no. patients with neck dissections	62
SND	32
MRND	34
RND	11

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Demographics of Patients Stratified by p16-Status

	All	p16 Status Known		P
No.	112 (100.0%)	72	(64.3%)	
		p16 negative	p16 positive	
p16 status		27 (24.1%)	45 (40.2%)	
				.1330[b]
Mean age, y	57.3	61.9	57.6	
Gender				.1520[c]
Male	91 (81.3%)	20 (74.1%)	39 (86.7%)	
Female	21 (18.8%)	7 (25.9%)	6 (13.3%)	
Primary site				.0201[d]
Tonsil	51 (45.5%)	15 (55.6%)	20 (44.4%)	
Base of tongue	52 (46.4%)	8 (29.6%)	24 (53.3%)	
Soft palate/tonsil pillar	8 (7.1%)	4 (14.8%)	0 (0.0%)	
Lateral pharyngeal wall	1 (0.9%)	0 (0.0%)	1 (2.2%)	
Primary tumor classification				.6862[d]
T1	32 (28.6%)	9 (33.3%)	17 (37.8%)	
T2	47 (42.0%)	12 (44.4%)	20 (44.4%)	
T3	17 (15.2%)	2 (7.4%)	5 (11.1%)	
T4	16 (14.3%)	4 (14.8%)	3 (6.7%)	
Lymph node classification				.0800[d]
N0	19 (17.0%)	6 (22.2%)	4 (8.9%)	
N1	18 (16.1%)	6 (22.2%)	7 (15.6%)	
N2a	12 (10.7%)	1 (3.7%)	6 (13.3%)	
N2b	42 (37.5%)	13 (48.1%)	16 (35.6%)	
N2c	18 (16.1%)	1 (3.7%)	10 (22.2%)	
N3	3 (2.7%)	0 (0.0%)	2 (4.4%)	
Stage group				.2691[d]
I	4 (3.6%)	0 (0.0%)	0 (0.0%)	
II	10 (8.9%)	5 (18.5%)	2 (4.4%)	
III	20 (17.9%)	6 (22.2%)	10 (22.2%)	
IVA	73 (65.2%)	15 (55.6%)	31 (68.9%)	
IVB	5 (4.5%)	1 (3.7%)	2 (4.4%)	
Histology				.2108[d]
Well differentiated	10 (8.9%)	2 (7.4%)	6 (13.3%)	
Moderately differentiated	37 (33.0%)	11 (40.7%)	12 (26.7%)	
Poorly differentiated	53 (47.3%)	9 (33.3%)	25 (55.6%)	
NOS	12 (10.7%)	5 (18.5%)	2 (4.4%)	

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3 year survival data

Patients with p16+ tumors:

- 89.5% and 87.5% pathologic complete response (CR) on neck dissection with and without chemotherapy, respectively.

Patients with p16- tumors:

- 66.7% and 25.0% pathologic CR on neck dissection with and without chemotherapy, respectively

80% of cohort experienced grade 3 mucositis during treatment and peak grade 1 xerostomia at 6 months after IMRT.

Overall	Overall N=112	p16+ N=45	p16- N=27	P
Local PFS				
All	90.5%	97.8%	73.3%	.007
ChemoRT	93.4%	100%	77.8%	.011
RT alone	85.5%	94.1%	70.5%	.241
Regional PFS				
All	93.8%	97.1%	79.1%	.017
ChemoRT	96.9%	100.0%	77.8%	.011
RT alone	88.5%	90.5%	79.4%	.402
Locoregional PFS				
All	90.5%	97.8%	73.5%	.006
ChemoRT	93.5%	100.0%	77.8%	.011
RT alone	85.2%	94.1%	70.4%	.245
DFS				
All	81.7%	88.2%	61.4%	.004
ChemoRT	86.5%	94.3%	65.8%	.01
RT alone	74.0%	75.3%	58.9%	.30
Overall survival				
All	76.5%	87.8%	47.6%	<.001
ChemoRT	85.1%	100.0%	57.8%	<.001
RT alone	60.1%	65.7%	44.3%	.174
CSS				
All	86.4%	92.7%	65.1%	.016
ChemoRT	92.4%	100.0%	72.2%	.010
RT alone	77.0%	77.8%	63.3%	.420
Distant metastasis-free survival				
All	88.4%	92.4%	74.2%	.004
ChemoRT	91.9%	93.6%	85.7%	.355
RT alone	82.8%	89.5%	68.1%	.140
LN pathologic CR				
All	77.4%	88.9%	42.9%	.003
ChemoRT	84.4%	89.5%	66.7%	.234
RT alone	58.8%	87.5%	25.0%	.020
N0 LN control				
All	97.3%	100%	92.6%	.137
ChemoRT	98.5%	100%	100.0%	1.000
RT alone	95.5%	100%	88.9%	.257

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Outcomes in HPV-Associated Oropharyngeal Squamous Cell Carcinoma After Postoperative or Definitive Nonsurgical Therapy

C.R. Spencer

- Washington University approach for OPSCC
  - minimally invasive transoral laser microsurgery (TLM) with postoperative (PO) IMRT based radiation therapy (RT) or CRT or definitive RT
- 187 patients with OPSCC treated from 1997 to 2009
  - 124 received PO therapy
  - 63 received definitive nonsurgical therapy.

	Definitive	%	Post-Op	%
Stage I, II	3	5%	7	6%
Stage III, IVA	42	72%	111	90%
Stage IVB	13	22%	6	5%
	2 yr	5 yr	2 yr	5 yr
p16+ OS	74%	45%	88%	82%
p16- OS	38%	21%	65%	32%
p16+ RFS	83%	83%	96%	96%
p16- RFS	50%	50%	94%	84%

J Clin Oncol 28:15s, 2010 (suppl; abstr 5544)

2010 ASCO Annual Meeting

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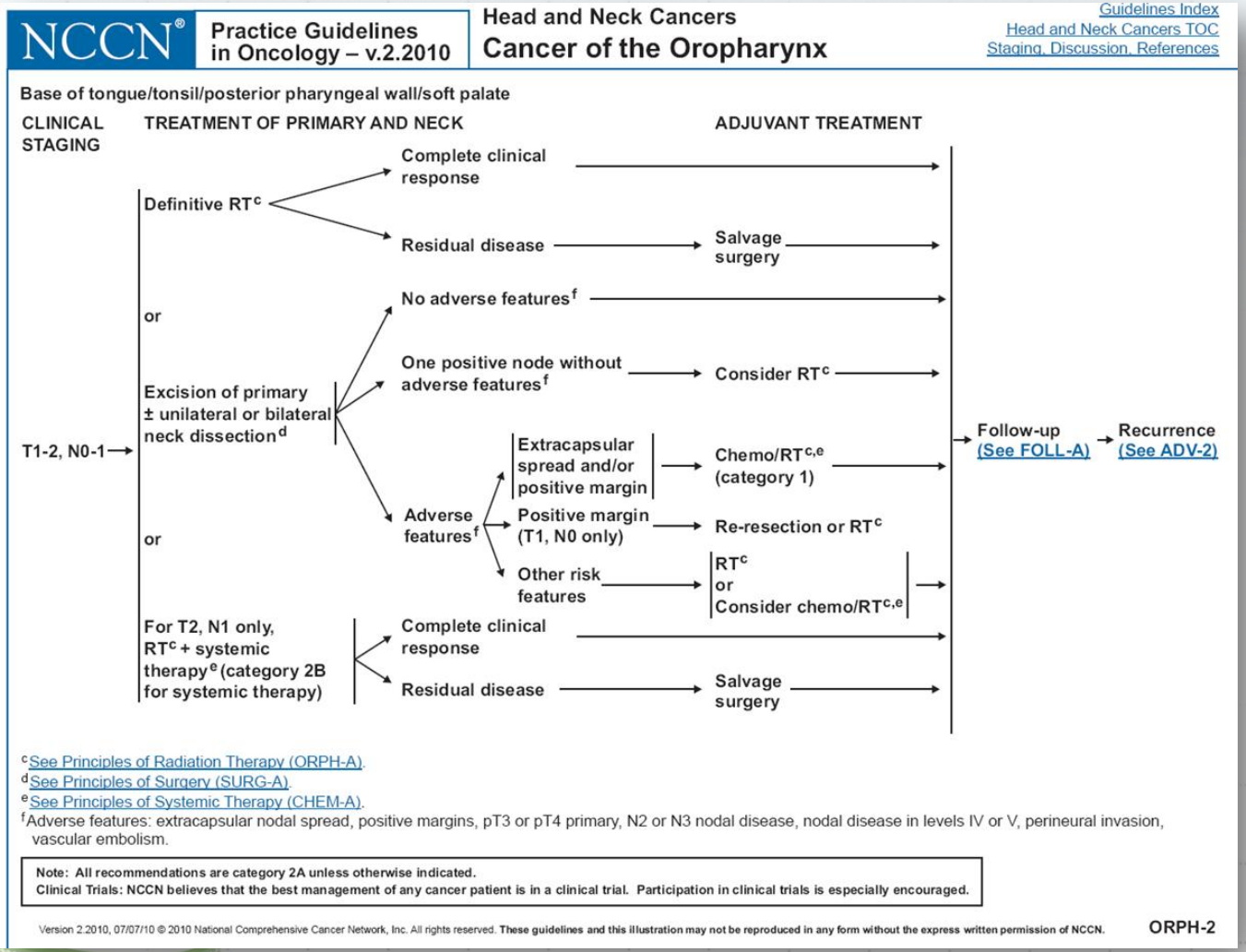
Current Treatment Guidelines



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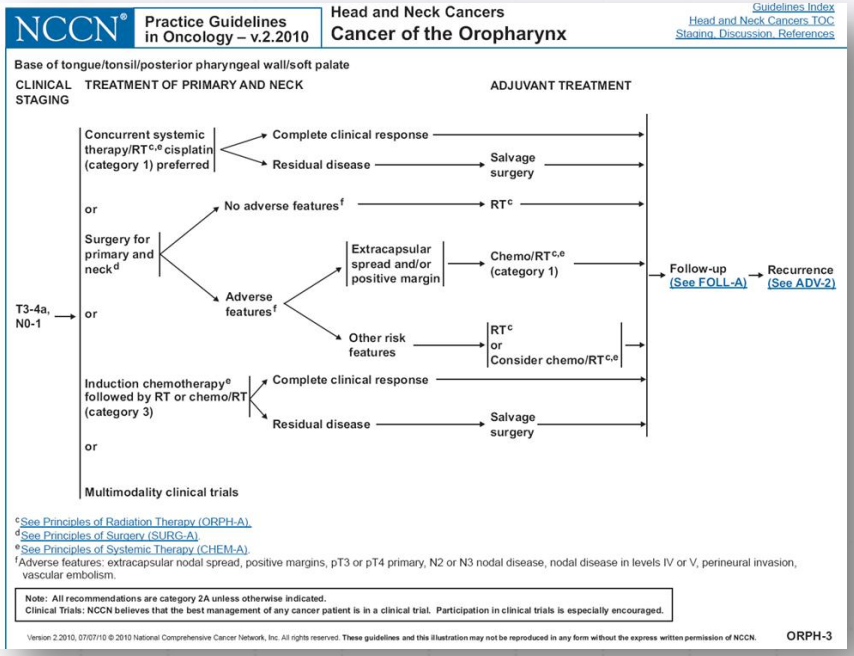
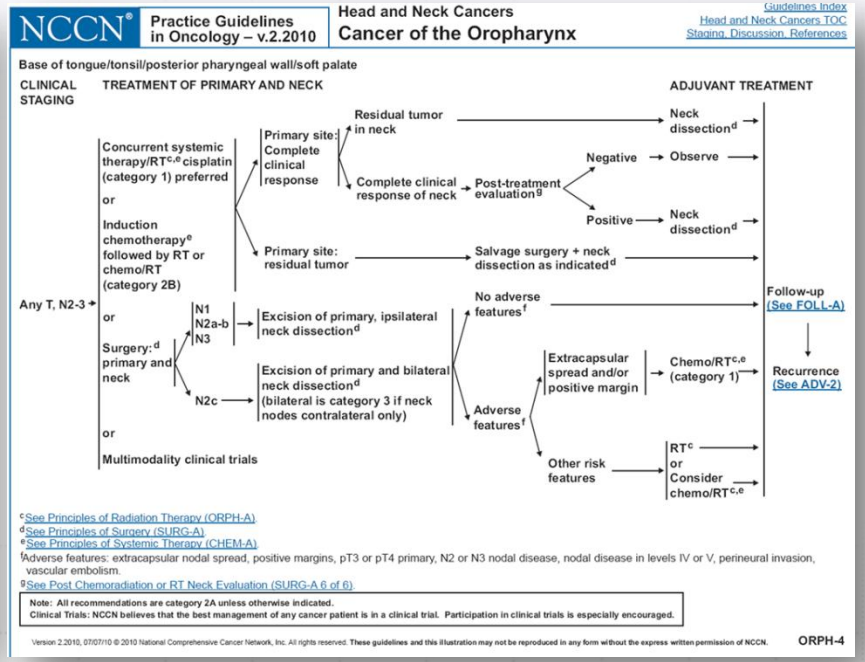
Current Treatment Guidelines





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Questions need to be answered

- What is the natural history of oral HPV?
- What is the duration of time from oral HPV infection to cancer?
- Do precancerous oropharyngeal lesions exist that could be detected?
- Why is the increase in incidence of oropharyngeal cancer:
  - Seen in men but not women?
  - Most apparent in younger cohorts?
- What is the biological mechanism for different survival rates in people with HPV-positive head and neck squamous cell carcinomas who use tobacco versus non-users?
- Should treatment of people with HPV-positive and HPV negative head and neck squamous cell carcinomas be different?
- Would inhibition of E6 and E7 in HPV+ OPC increase the effectiveness of current therapy/decrease dose?
- What is the most effective and least toxic treatment option?
- Do we need to intensify therapy for HVP-/p16- OPC?

Current Trials

- A Phase II Trial of Induction Chemotherapy Followed by Cetuximab (Erbitux) With Low Dose vs. Standard Dose IMRT in Patients With HPV-Associated Resectable Squamous Cell Carcinoma of the Oropharynx (Hopkins)

Arms	Assigned Interventions
Group 1: Experimental Patients undergo low-dose intensity-modulated radiotherapy (IMRT) 5 days per week for approximately 5 weeks (27 fractions). Patients also receive cetuximab IV over 1-2 hours once weekly for 6 weeks. Interventions: • Biological: cetuximab • Radiation: intensity-modulated radiation therapy	Biological: cetuximab Given IV Radiation: intensity-modulated radiation therapy Patients undergo low-dose radiotherapy
Group 2: Experimental Patients undergo standard-dose IMRT 5 days per week for approximately 6 weeks (33 fractions). Patients also receive cetuximab IV over 1-2 hours once weekly for 7 weeks. Interventions: • Biological: cetuximab • Radiation: intensity-modulated radiation therapy	Biological: cetuximab Given IV Radiation: intensity-modulated radiation therapy Patients undergo low-dose radiotherapy

129 centers

DISEASE CHARACTERISTICS:

- Histologically or cytologically confirmed squamous cell carcinoma of the oropharynx as determined by H&E staining
- Newly diagnosed disease
- Resectable disease OR disease that is expected to become resectable after study treatment Stage III, IVA, or IVB disease as determined by imaging studies (CT scan with IV contrast or MRI required) and a complete head and neck exam

- HPV-associated disease is defined as p16 IHC-positive and/or HPV-16 ISH-positive
- Non-HPV-associated disease is defined as p16 IHC-negative

Primary Outcome Measures: 2-year progression-free survival
Secondary Outcome Measures: Toxicity, Overall survival, Objective response,
Quality of life as assessed at baseline and at 1, 6, 12, and 24 months after completion of study treatment, Correlative biomarker studies

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Current Trials

A Phase II Study of Docetaxel/Cisplatin/5-Fluorouracil (TPF) Induction Chemotherapy Followed by Concurrent Chemoradiotherapy Using a Modified Radiation Dose in Patients With Newly Diagnosed HPV Positive, Locally Advanced Squamous Cell Carcinoma of the Oropharynx (Harvard)

Condition	Intervention	Phase
Squamous Cell Carcinoma of the **Head** and **Neck** **Human Papilloma Virus**	Drug: docetaxel Drug: Cisplatin Drug: 5-fluorouracil Radiation: Intensity modulated radiation therapy Drug: carboplatin Drug: cetuximab	Phase II

Primary Outcome Measures: ●Local-regional Control (5 years)]
To determine the local-regional control at 2 and 5 years in patients with advanced HPV related oropharynx cancer or unknown primary.

Secondary Outcome Measures: ●Progression Free Surviva
To determine progression free survival at 2 and 5 years

●Overall Survival (overall survival at 2 and 5 years)

●Toxicity

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Thank you

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