



# Human Papillomavirus in Head and Neck Cancer

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ACLI Medical Section Meeting 2019

# Disclosures

## Employment Relationship

- University of Florida

## Compensation, Remuneration, Funding

- None applicable

## Ownership or Investment Interests

- None applicable

## Leadership Positions

- Only within UF

# Disclosures

Hang out at your own risk



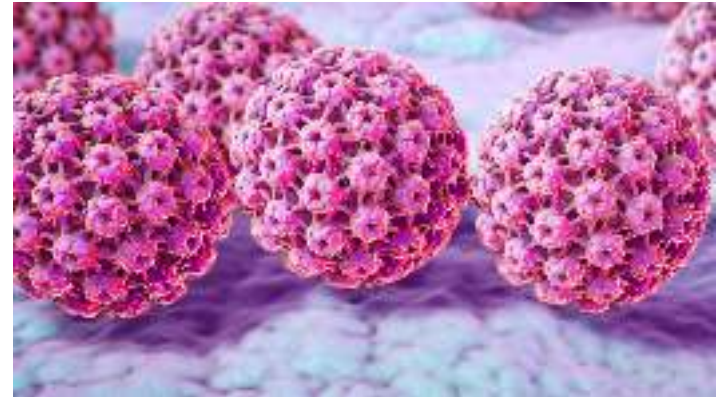
# In this talk

HPV: background

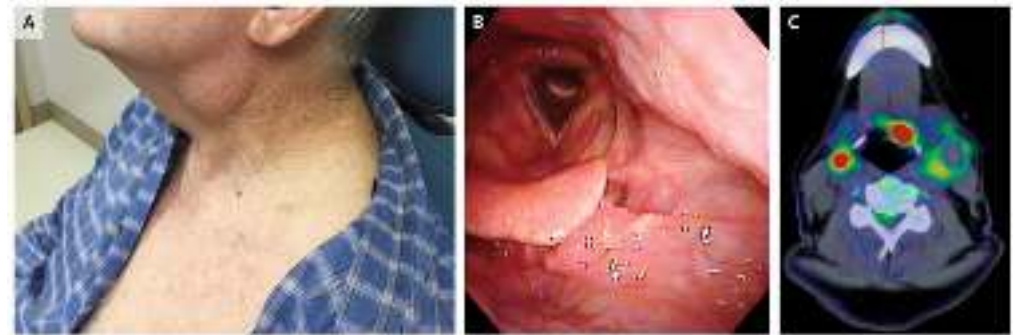
Head and neck cancer

HPV in head and neck cancer

Treatment decisions



ABCnews.com



Holtzman Hitchcock NEJM 375 2016

# What we won't discuss today

Head/neck cancers other than squamous cell carcinoma (SCCa)

Detailed molecular biology

# Background: HPV

# What is human papillomavirus (HPV)?



<https://www.skepticalraptor.com>

Double-stranded DNA virus

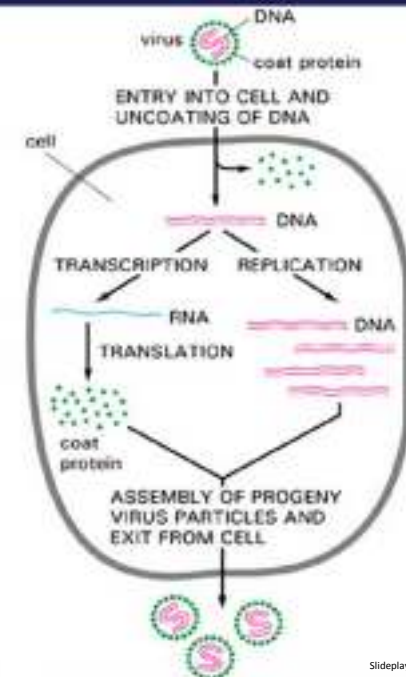
Highly species specific

About 200 varieties in humans

Only 13 cause cancer:

- HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68
- HPV **16** and **18** cause 63% of HPV-associated cancers
- HPV types 31, 33, 45, 52, and 58 cause an additional 10%
- HPV **16** is the most likely to both persist and to progress to cancer

## Life cycle of DNA virus



Slideplayer.com Yang Xu College of Life Sciences

# What is human papillomavirus (HPV)?

Recall that HPV is also responsible for genital warts

- “Low-risk” strains, such as HPV 6 and 11, cause about 90%



MedicalFoxy.com



U. Of Iowa College of Dentistry



Open-i.com

If there is any connection to cancer it's weak



# What is human papillomavirus (HPV)?

Non-sexually transmitted warts are also from HPV

HPV 1, 2 & 4: plantar and common warts

HPV 3 & 10: flat warts

HPV 2 & 7: butcher's warts

HPV 6&11: recurrent respiratory papillomatosis



# How do people get HPV?

Respiratory form transmitted during childbirth

Casual contact and shared objects sufficient

Genitourinary and oral infections through intimate skin-skin or –mucosa contact

Essentially everyone who has sex gets HPV

Every year in the United States there are  
**~14 million new HPV infections.**



About 50%  
of them are in 15- to 24-year-olds.

That's about 19,000  
teens and young adults each day.

Merckengage.com

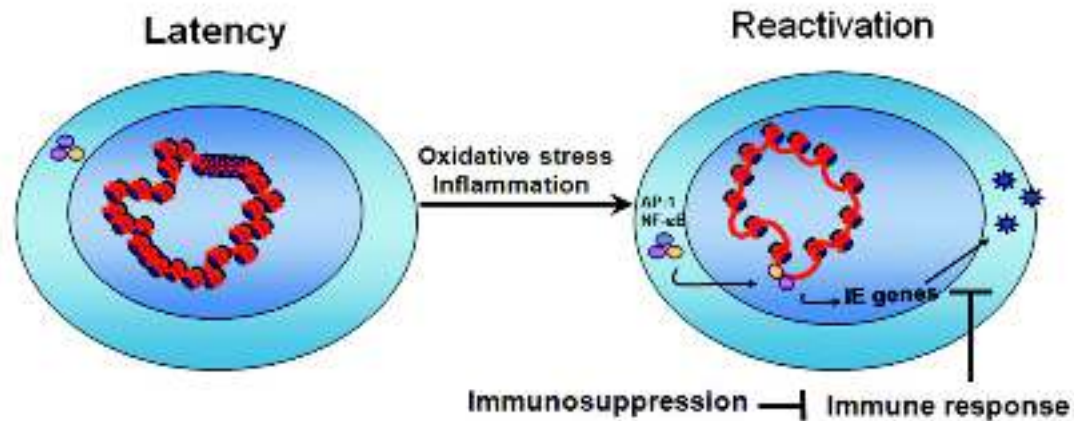
# How do people get HPV?

Most infections resolve within 12-24 months

Can have latent period with symptoms months+ later

There is some suggestion that the virus can reactivate later in life

Connection to cancer unclear



MDPI.com

# How can we prevent transmission of HPV?

Condoms reduce transmission but don't eliminate

- Uncovered skin is sufficient



Scroguard.com

The only real solution is the **vaccine**:

Gardasil 9 (earlier versions: Gardasil and Cervarix)

- HPV 16 and 18 - most common in cancer
- HPV 31, 33, 45, 52, and 58 - cancer
- HPV 6 and 11 - 90% of genital warts

Ages 9-14: 2 shots (6 months apart)

Ages 15-45: 3 shots (2, 4 months apart)

**~100% effective in preventing cancer and warts if given **BEFORE SEXUAL CONTACT****

**0% effective if given after exposed to virus**

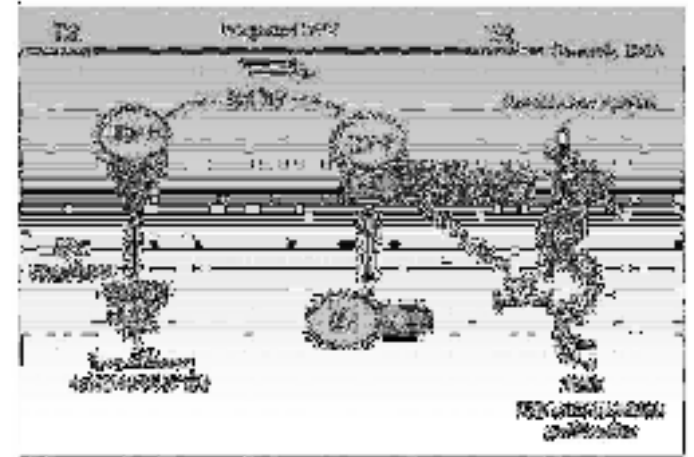
# How does HPV cause cancer?

Virus makes proteins E6 and E7 that make human cells live longer

- Turn off brakes on the cell cycle (ex. p53 and pRB)

These same proteins cause human DNA to mutate more

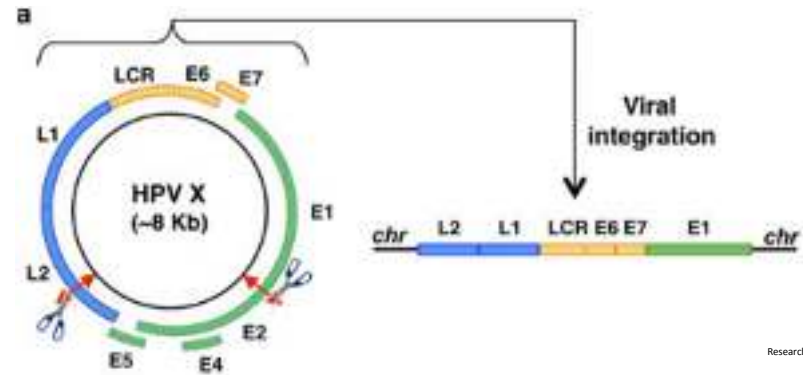
- Inhibit DNA repair
- Suppress apoptosis



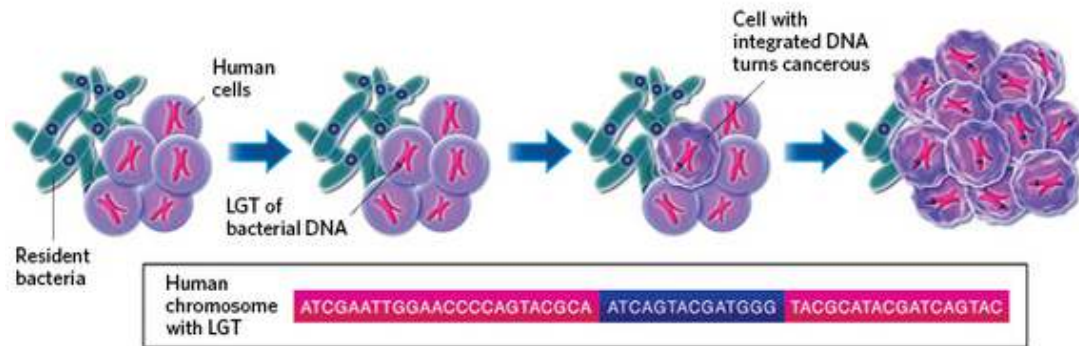
ResearchGate

# How does HPV cause cancer?

HPV performs lateral gene transfer, but no evidence cancer results from this



Researchgate.net



TheScientistMagazine.com

Fun fact: As much as 8% of the human genome is ancient viruses passed down in this way

# How does HPV cause cancer?

## Co-risk factors

- #1: Smoking
- #2: Alcohol

[Cancer Epidemiol Biomarkers Prev. 2009 Feb;18\(2\):541-50. doi: 10.1158/1055-9965.EPI08-0347. Epub 2009 Feb 3.](#)

### **Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium.**

[Hashibe M<sup>1</sup>, Brennan P, Chuang SC, Boccia S, Castellsague X, Chen C, Curado MP, Dal Maso L, Daudt AW, Fabianova E, Fernandez L, Wunsch Filho V, Franceschi S, Hayes RB, Herrero R, Kelsey K, Kollman S, La Vecchia C, Lacerus P, Levi F, Lence JJ, Mates D, Malos E, Meneses A, McClean MD, Muscat J, Elul-Neto J, Olishan AF, Purdue M, Rudnai P, Schwartz SM, Smith E, Sturgis EM, Szeszenia-Dabrowska N, Talamini R, Wei Q, Winn DM, Shangina O, Pilarska A, Zhang ZF, Ferro G, Berthiller J, Boffella P.](#)

Pooled data: 11,221 cases and 16,168 controls

Calculated population attributable risks:

Alcohol\* or tobacco: 72% (95% CI 61-79%)

- 4% alcohol alone
- 33% tobacco alone
- 35% alcohol and tobacco combined
- 74% for men
- 57% for women
- 33% for cases <45 years
- 73% for cases >60 years
- 84% in Europe
- 83% in Latin America
- 51% in North America

\*3+ drinks per day Hashibe J Nat Can Inst 99(10) 2007

# How does HPV cause cancer?

## Co-risk factors

#1: Smoking

#2: Alcohol

Poor hygiene

Mechanical irritation

Gastroesophageal reflux

Chronic infection

Immunosuppression

Poor nutrition

Wood dust

Metal vapors

## Nasopharynx cancer: Epstein-Barr Virus (EBV)

Specific subtype that resembles lymphoma

Extremely common in Asia

Rare here EXCEPT in Asian immigrant population





# Which cancers?

1. HPV causes all or many

Uterine cervix

Anal canal

Penis

Vagina, vulva

2. HPV causes some, presence is **prognostic**:

Oropharynx

3. HPV sometimes present, role unclear:

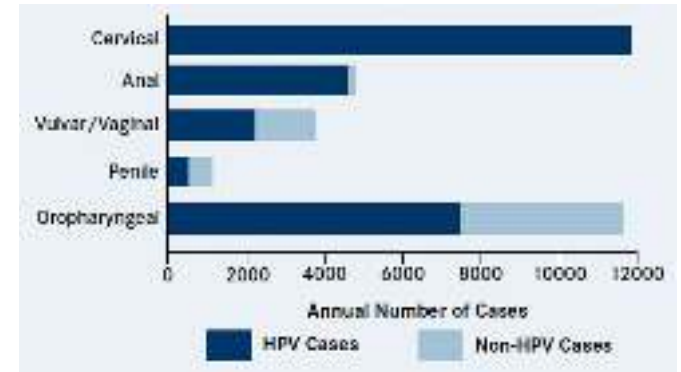
Skin: basal, squamous, and melanoma

Oral cavity

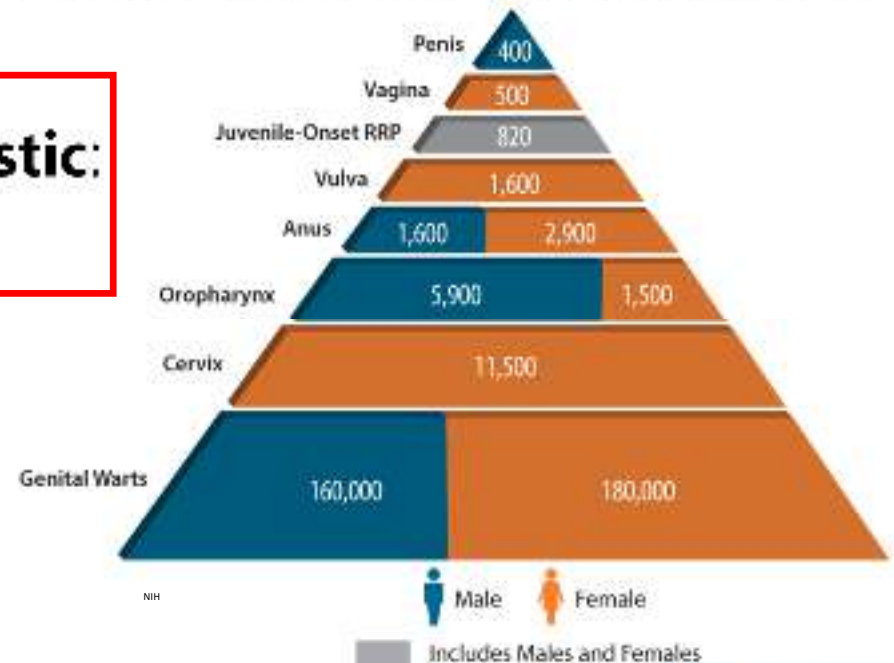
Larynx, hypopharynx

Nasopharynx

OnLive



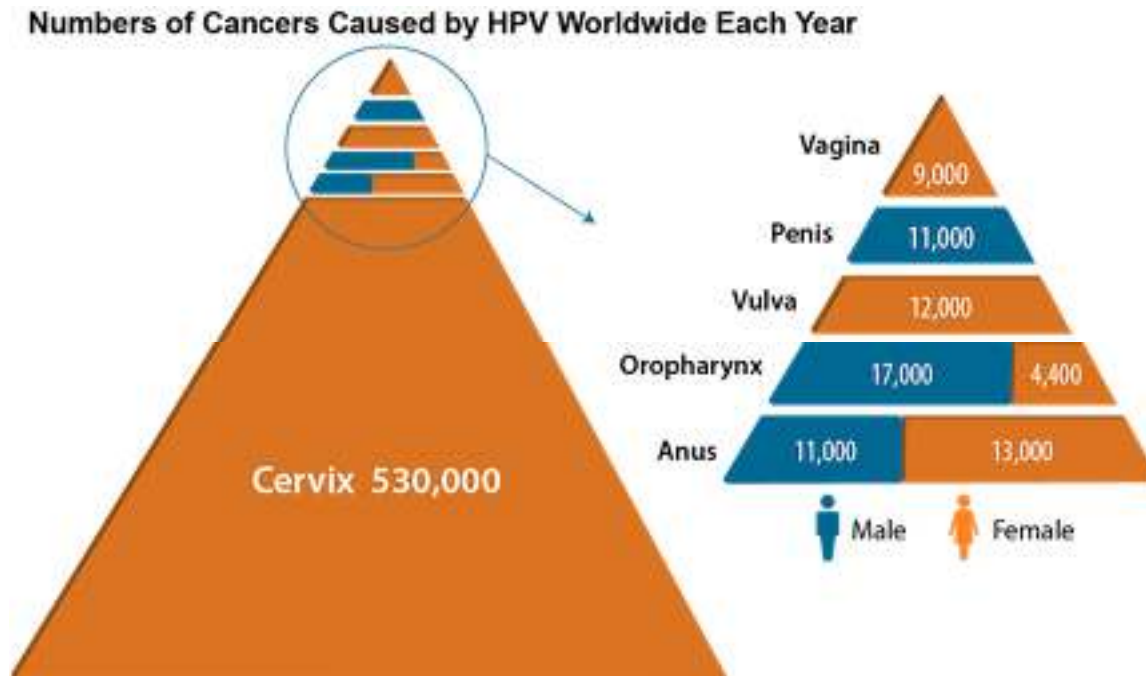
Numbers of U.S. Cancers and Genital Warts Attributed to HPV Infections



NIH  
Includes Males and Females

# Worldwide picture quite different from U.S.

Routine Pap testing and now vaccine have changed the HPV landscape



# Head & neck cancer

# Cancers of the head and neck

65,000 in U.S. in 2017

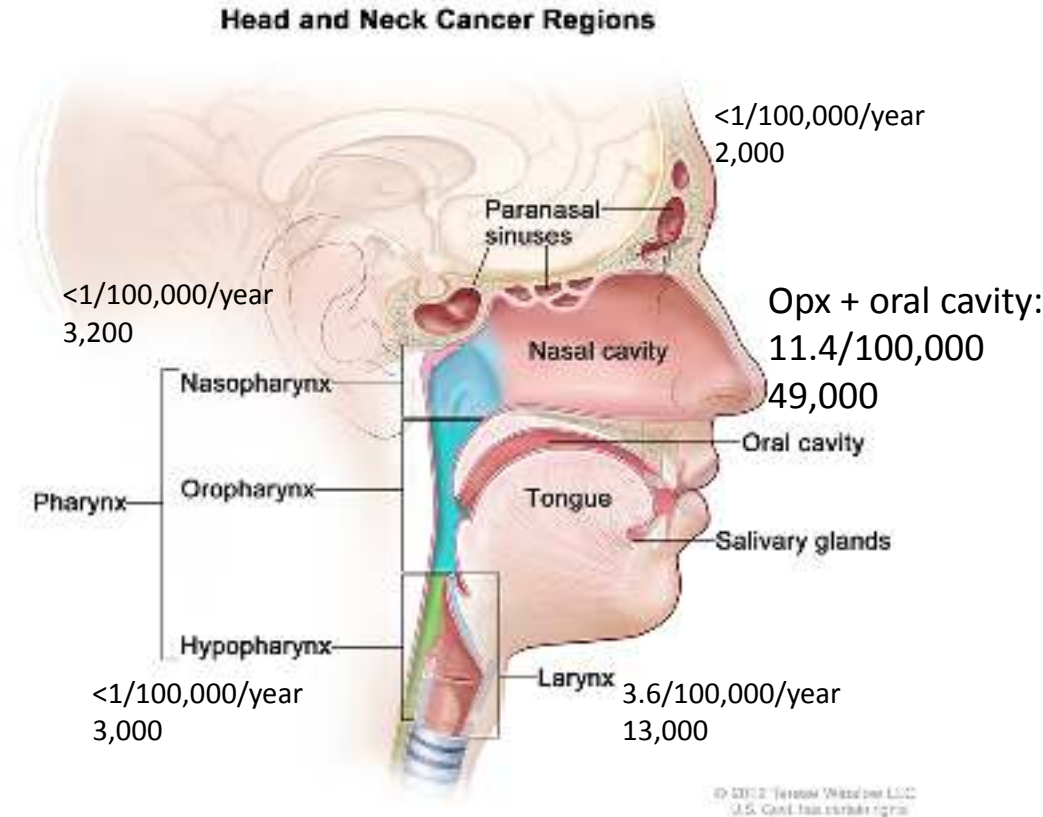
Average age at diagnosis is 62

>90% are squamous cell carcinoma

>75% associated with tobacco exposure and/or alcohol

Overall declining as smoking does

However rise in rates of HPV-associated cancers rising



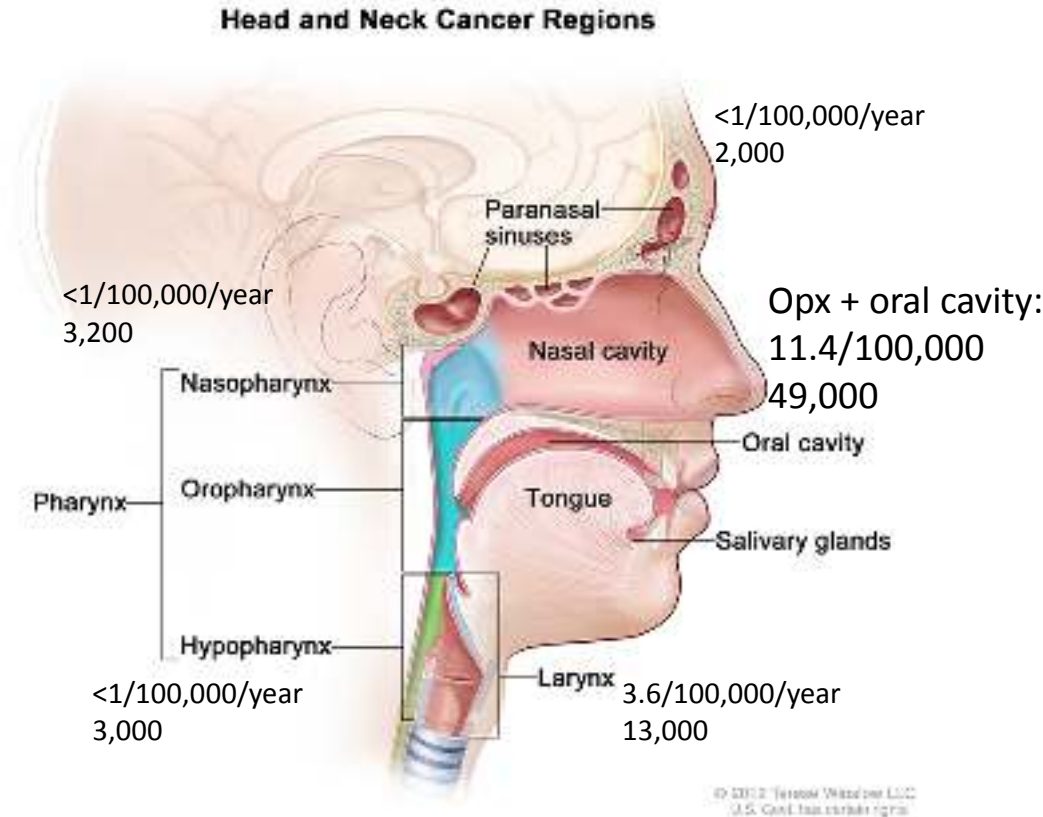
# Cancers of the head and neck

About 70% test positive for HPV

2008-2012:

12,638 of 15,738 HPV positive were in males

1988 – 2004 there was a **225%** increase in HPV-positive cancers



# Cancers of the head and neck: Treatment

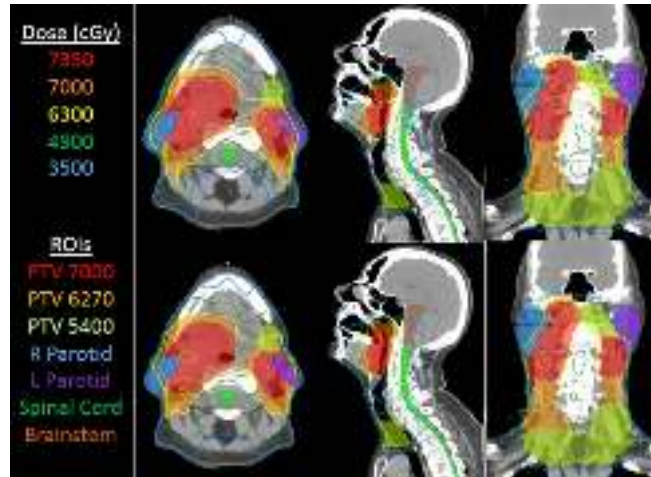
Surgery

Radiation therapy

Chemotherapy

Can sometimes omit chemo

- If small
- If not in lymph nodes



Physicsworld.com



Hanasono JAMA 139(11) 2013

Can sometimes omit a local therapy

- Done empirically – depends on site



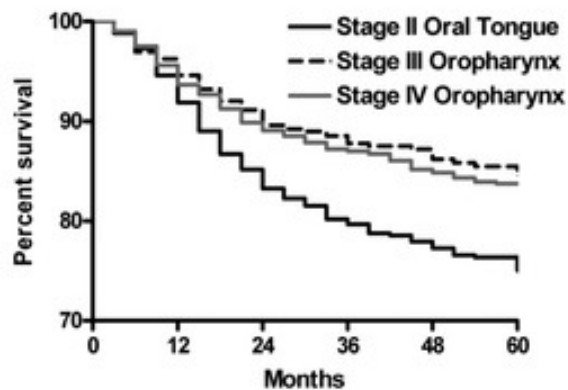
NPR.org

# Oropharynx vs oral cavity: a lesson in biology

Orophx: Radiation is primary treatment

OrCav: Surgery is primary treatment

Oral cavity has worse cause-specific survival



Rusthoven Cancer 112(2) 2008



Orophx: HPV status prognostic

OrCav: HPV does **not** affect outcomes



# An example of why you should not extrapolate

Tonsil versus retromolar trigone

Tonsil region:

LRC at 5 years: 75%

Best first treatment: radiotherapy

HPV prognostic

Mendenhall Am J Oncol 18(11) 2000



ghorayeb.com

RMT:

LRC at 5 years: 60%

Best first treatment: surgery

HPV not prognostic

Hitchcock Am J Otol 36(20) 2015

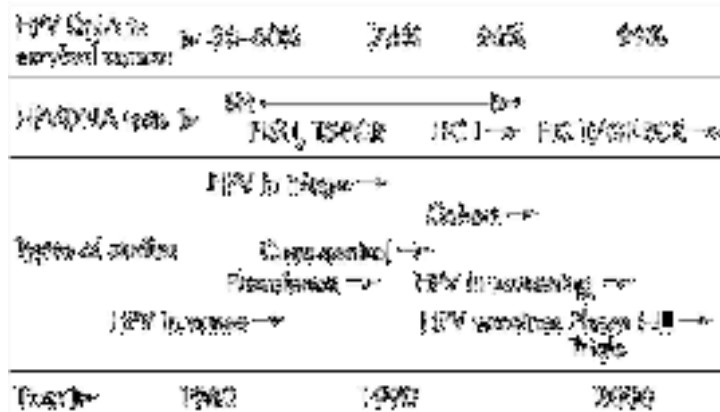


Scielo.br



# HPV in head and neck cancer

# How we learned about HPV: cervical cancer



Bosch J Clin Pathol 55(4) 2002

Later converted to testing p16 instead of HPV DNA  
 p16 protein expression changed by HPV  
 p16 test shown to be just as reliable  
 Test much cheaper

Early testing poor – hard to establish relationship  
 As soon as testing reliable, used for screening  
 Immediate work on vaccine begun

What about those other mucosal squamous cancers?

# We learned HPV was present in H&N cancers

Journal of the National Cancer Institute

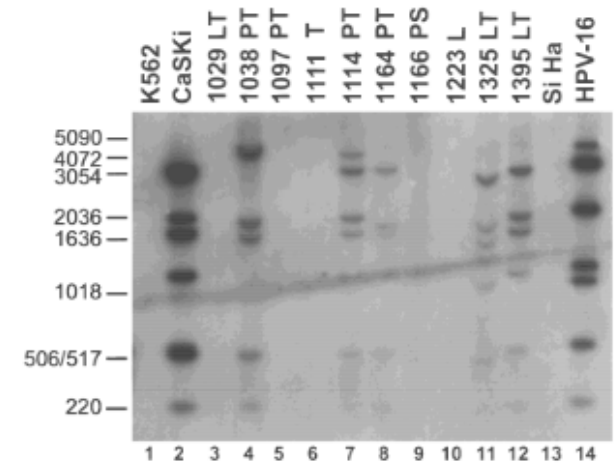
Endicott JF, et al. Detection of human papillomavirus in head and neck squamous cell carcinoma: a multicenter study. *J Clin Oncol* 2000;18:1632-42.

Endicott JF, et al. Detection of human papillomavirus in head and neck squamous cell carcinoma: a multicenter study. *J Clin Oncol* 2000;18:1632-42.

Published in 2000.

Relationship not understood. Causal?  
Associative?

They did know oropharynx was the site  
where it mattered



Gillison et al looking for HPV in  
different sites

# Where it got traction: a big study rescued



## RTOG 0129

Oral cavity, oropharynx, hypopharynx, larynx: 721 patients

Testing different methods of radiotherapy

**Negative study** - no difference in outcomes – big problem for authors

BUT

**HPV status determined in 74.6% of oropharynx patients**

# Where it got traction: a big study rescued

[J Clin Oncol. 2014 Dec 15;32\(24\):3958-3967.](#)  
Published online: 2014 Nov 3. doi: [10.1200/JCO.2014.52.7325](#)

PMCID: PMC4239204  
PMID: [25255500](#)

Randomized Phase III Trial to Test Accelerated Versus Standard Fractionation in Combination With Concurrent Cisplatin for Head and Neck Carcinomas in the Radiation Therapy Oncology Group 0129 Trial: Long-Term Report of Efficacy and Toxicity

RTOG 0129

HPV status determined in 74.6% of oropharynx patients

HPV+ more common in

- non- or light smokers
- younger age
- Caucasians
- smaller primary tumors at diagnosis

# Where it got traction: a big study rescued

RTOG 0129

HPV(+) and HPV(-) arms balanced for other factors

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer

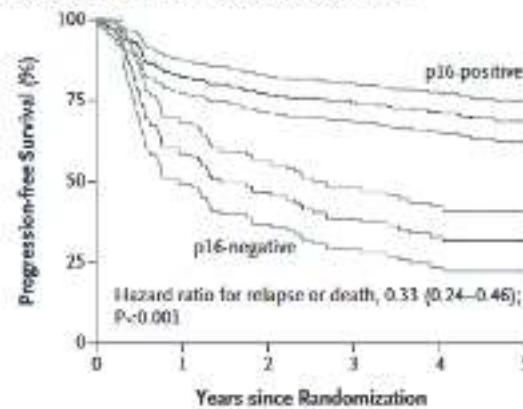
K. Kian Ang, M.D., Ph.D., Jonathan Harris, M.S., Richard Wheeler, M.D., Randal Weber, M.D., David I. Rosenthal, M.D., Phuc Felix Nguyen-Tân, M.D., William H. Westra, M.D., Christine H. Chung, M.D., Richard C. Jordan, D.D.S., Ph.D., Charles Lu, M.D., Harold Kim, M.D., Rita Axelrod, M.D., C. Craig Silverman,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

C Overall Survival According to p16 Expression



No. at Risk	0	1	2	3	4	5
p16-positive	213	203	190	176	162	77
p16-negative	101	73	60	49	34	15

D Progression-free Survival According to p16 Expression



No. at Risk	0	1	2	3	4	5
p16-positive	213	177	164	156	143	66
p16-negative	101	59	46	37	25	11

3 year overall survival: 84% vs 51%

3 year progression-free survival: 74% vs 38%

# Where it got traction: a big study rescued

Recursive partitioning analysis used to create risk groups

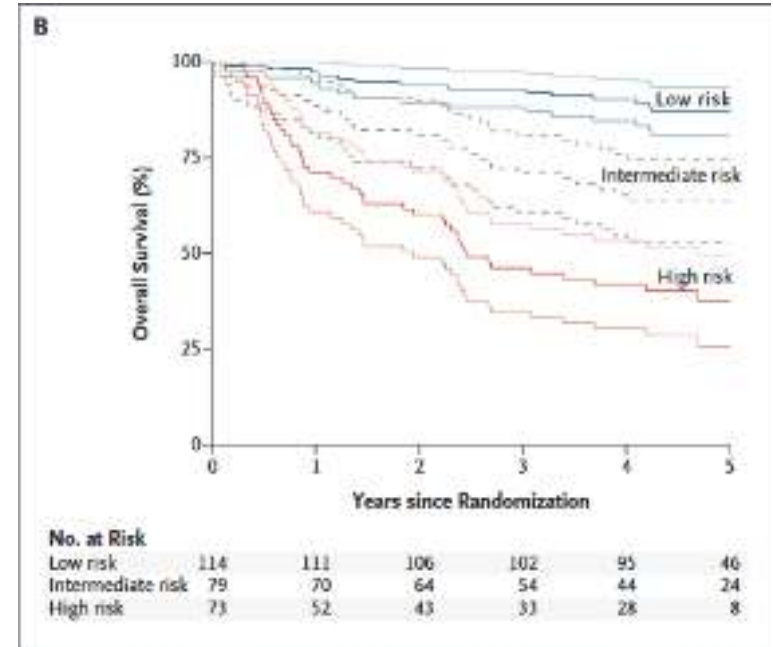
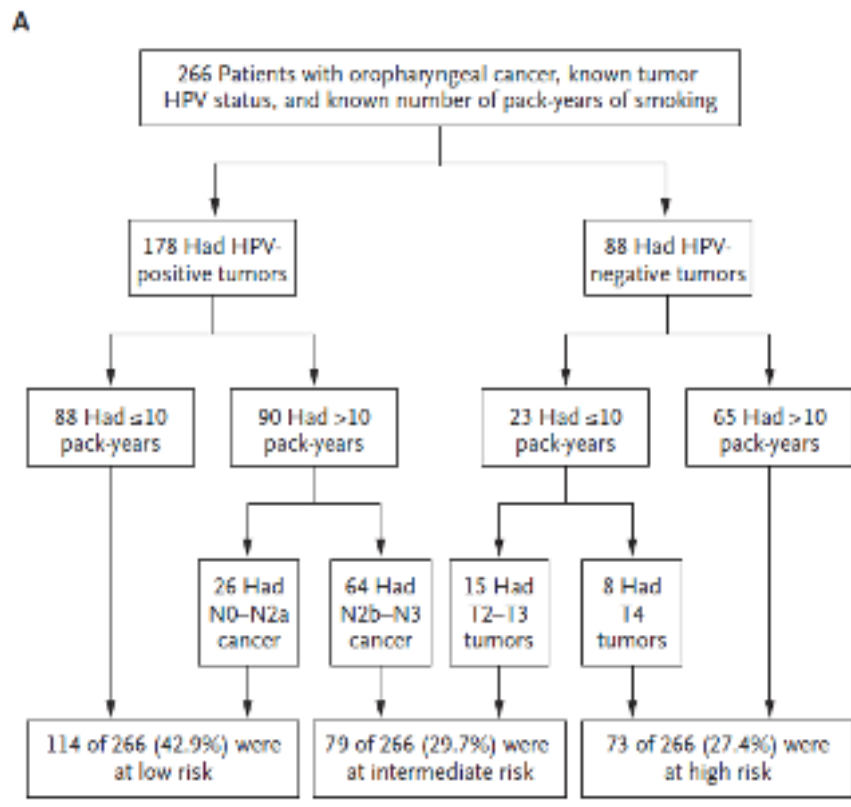
**Smoking remained a powerful predictor of survival**

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

## Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer

K. Kan Ang, M.D., Ph.D., Jonathan Harris, M.D., Richard Wessler, M.D.,  
 Paula Weber, M.D., David L. Zoroff, M.D., Phuc Leb Nguyen-Tan, M.D.,  
 William H. West, M.D., Christine H. Chung, M.D.,  
 Edward C. Jorhan, D.D.S., Ph.D., Charles Lu, M.D., David Kim, M.D.,  
 Mia Andron, M.D., U. Craig Siderman, M.D., Kevin P. Recimard, M.D.,  
 and Naama L. Gillman, M.D., Ph.D.



## HPV negative OPX SCCA



Smoker

Median age early 60s

Less likely to be white

Diagnosed at later stage

## HPV positive OPX SCCA



Non-smoker

Median age early 50s

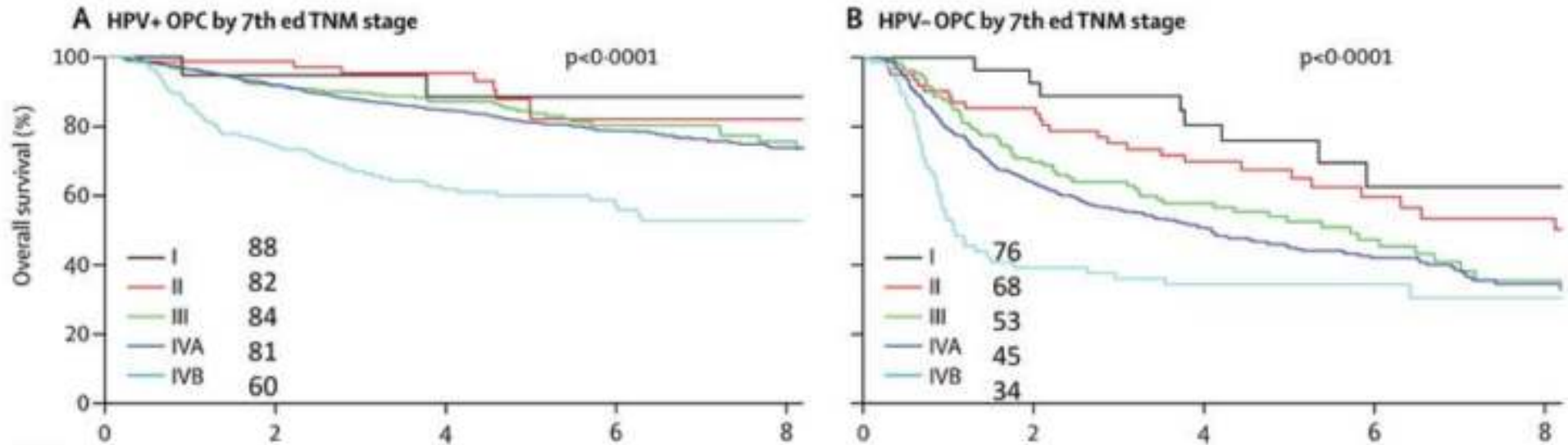
More often white

Diagnosed at early stage

No gender difference (~80% male both)



# Now our staging system is broken! AJCC 7<sup>th</sup> Ed.



O'Sullivan Lancet Onc 2016

For HPV(+) SCCa of the oropharynx, stage was no longer predictive of outcome

# Improved staging for oropharynx: AJCC 8<sup>th</sup> Edition

Different staging for HPV(+) and HPV(-)

**TABLE 3. Clinical N Category Human Papillomavirus-Associated (p16-Positive) Oropharyngeal Cancer, 8th Edition Staging Manual<sup>a</sup>**

N CATEGORY	N CRITERIA
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One or more ipsilateral lymph nodes, none larger than 6 cm
N2	Contralateral or bilateral lymph nodes, none larger than 6 cm
N3	Lymph node(s) larger than 6 cm

So for example, multiple ipsilateral nodes is staged:

HPV(+): N1

HPV(-): N2b (or N3b if cancer outside node!)

**TABLE 4. Clinical N Category for Non-Human Papillomavirus-Associated (p16-Negative) Oropharyngeal Cancer, 8th Edition Staging Manual<sup>a</sup>**

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 or smaller in greatest dimension and ENE-negative
N2	Metastasis in a single ipsilateral lymph node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE-negative; or metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE-negative; or metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE-negative
N2a	Metastasis in a single ipsilateral lymph node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE-negative
N2b	Metastasis in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE-negative
N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE-negative
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE-negative; or metastasis in any lymph node(s) and clinically overt ENE-positive
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE-negative
N3b	Metastasis in any node(s) and clinically overt ENE-positive

Courtesy of Dr. Eddy Yang, UAB, via slideplayer.com

# Improved staging for oropharynx: AJCC 8<sup>th</sup> Edition

**TABLE 6. Anatomic Stage and Prognostic Groups for Clinical TNM Grouping of Human Papillomavirus-Associated (p16-Positive) Oropharyngeal Cancer, 8th Edition Staging Manual\***

T CATEGORY	N CATEGORY			
	N0	N1	N2	N3
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

\*Any M1 is stage IV.



No Stage IV Subdivision

**TABLE 8. Anatomic Stage and Prognostic Groups for Clinical and Pathologic TNM Grouping of Non-Human Papillomavirus-Associated (p16-Negative) Oropharyngeal Cancer, 8th Edition Staging Manual\***

T CATEGORY	N CATEGORY			
	N0	N1	N2a,b,c	N3a,b
T1	I	II	IVA	IVB
T2	II	III	IVA	IVB
T3	III	III	IVA	IVB
T4a	IVA	IVA	IVA	IVB
T4b	IVB	IVB	IVB	IVB

\*Any M1 is stage IVC.

# We're learning there is more to the story

8 years since HPV identified as a key factor

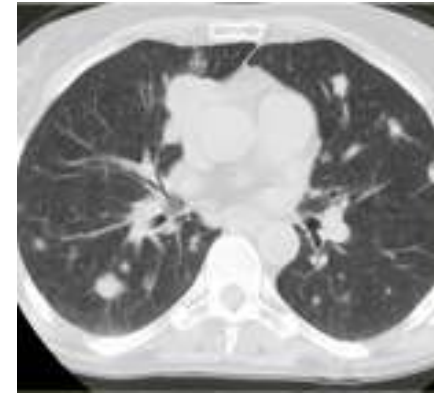
5 years since routinely tested

Outcomes remain excellent for HPV(+)

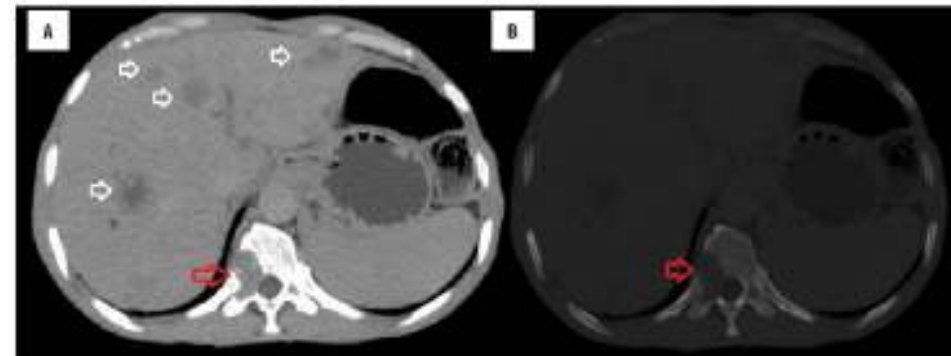
Same rate of distant mets as HPV(-): ~10%

Unusual pattern of distant metastasis

- More often multi-organ
- Especially in bone
- **LATE**: many after 3 years (versus >90% within 2y)
- Have better salvage rates (11% vs 4% @2 years\*)



vs



\*Huang Oral Oncology 49(1) 2013

# If this cancer recurs, can they be salvaged?

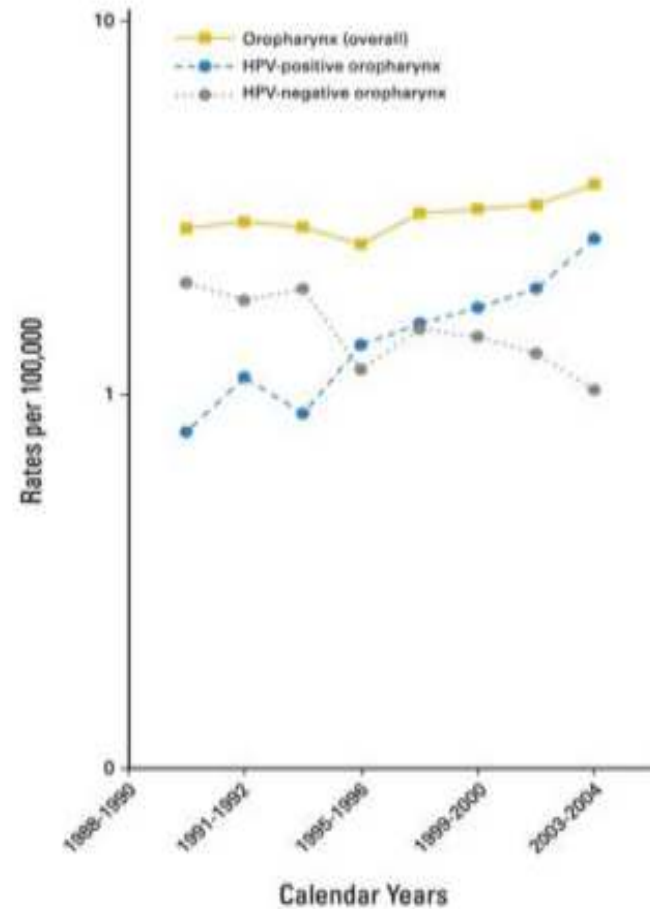
Salvage Success Rates			
Site of Recurrence	No. of Patients	Procedure Success (successful/attempted)	Salvage Success (successful/all LR recurrences)
Primary site only	85	50% (15/30)	18%* (15/85)
Neck only	36	10% (1/10)	3%* (1/36)
Primary and neck	16	0% (0/3)	0% (0/16)
<b>Total</b>	<b>137</b>	<b>37% (16/43)</b>	<b>12% (16/137)</b>
Abbreviation: LR, local-regional		*p=0.02	

Hitchcock Appl Rad Onc 7(3) 2018

Overall salvage rate in those without distant mets = 12%

# Rates of HPV(+) oropharynx cancer are rising

Many theories, little data



Chaturvedi JCO 29(1) 2011

# HPV is present in SCCa in other sites

Skin  
Oral cavity



No apparent connection  
to outcomes



Tufaro The Clinicopathologic and Molecular Aspects of Non-Melanoma Skin Cancer

Hypopharynx  
Larynx



May be prognostic but  
unproven



Entusa.com

How does HPV impact  
treatment decisions?



# Initially, enthusiasm for surgery as monotherapy

Trans Oral Robotic Surgery (TORS)

Was hope that we could offer surgery alone

Early data from ongoing trials shows **~90% of people still need radiation**

Holsinger Ellis J Clin Oncol 33(29)2015



White JAMA 136(12) 2010

RT versus RT and surgery:

same cure rate

side effects both treatments >>>> one treatment

# What's new in HPV(+) SCCa? De-intensification

Multiple institutions (including UF)  
looking at less treatment in HPV(+)

60 Gy instead of 70 Gy radiotherapy

Same cure rate, significantly decreased  
toxicity



International Journal of Radiation

Oncology\*Biological\*Physics

Volume 93, Issue 5, 1 December 2015, Pages 876-885



Clinical Investigation

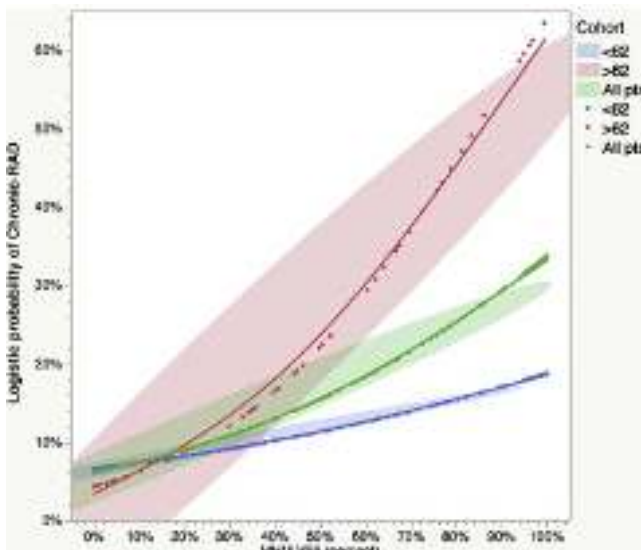
Phase 2 Trial of De-intensified Chemoradiation Therapy for  
Favorable-Risk Human Papillomavirus–Associated  
Oropharyngeal Squamous Cell Carcinoma

Bhishanji S. Chera MD<sup>\*,†,‡,§,¶</sup>, Robert J. Anders MD<sup>\*,†,§,¶</sup>, Jed Tepper MD<sup>\*,†,§,¶</sup>, Bahjat Gajjar PhD<sup>\*,†,§,¶</sup>, Rebecca Green MSW<sup>†,§,¶</sup>, Stacey L. Auner MA<sup>\*,†,§,¶</sup>, Neil Hayes MD, MPH<sup>†,§,¶</sup>, Jared Weiss MD<sup>†,§,¶</sup>, Janaka Chiller-Olsen MD<sup>†,§,¶</sup>, Adam Zanation MD<sup>\*,†,§,¶</sup>, Trevor Rockman MD<sup>\*,†,§,¶</sup>, William Furthauer MD<sup>\*,†,§,¶</sup>, Nathan Sheets MD<sup>†,§,¶</sup>, Mark Winkler MD<sup>\*,†,§,¶</sup>, William Mendelhall MD<sup>\*,†,§,¶</sup>

# Why should the ACLI Medical Section care about 10 Gy?

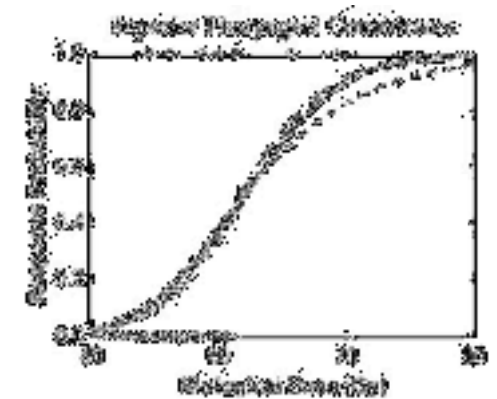
Cost of treatment (time)

Cost of managing short- and long-term effects (both \$ and morbid/mort)



Probability of dysphagia versus volume irradiated and dose – Red >62 Gy, Blue <62 Gy

Variable	Cohorts	
	<62 Gy	>62 Gy
Number of patients	20	19
Mean dose	50.6 Gy	59.5 Gy
Mean dose	48.8 Gy	58.8 Gy
Mean dose	50.6 Gy	59.5 Gy



Doses in patients with and without side effects during head/neck cancer treatment

# What about chemo – do HPV(+) still need it?

The jury is still out on this

Culturally, oncology research is pro-chemo

We suspect HPV(+) outcomes may not be improved as much with chemotherapy

Nobody is testing this at present



# People with HPV(+) oropharynx cancer, compared to other head and neck cancers:

Have much better overall and disease-free survival

Are diagnosed 10-15 years earlier, on average

Have great outcomes even with extensive lymph node disease

May experience recurrence >3 years, especially distant mets

- More often salvaged when they do, but rate still low

# Objectives of this talk

- 1) Discuss the epidemiology of oral HPV infection and HPV-related oropharyngeal cancers
- 2) Discuss diagnostic and clinicopathologic features of HPV-related oropharyngeal cancers
- 3) Discuss the updated AJCC staging criteria for HPV-related oropharyngeal cancers
- 4) Compare and contrast treatment options and prognosis for HPV-related oropharyngeal cancers with those for other oropharyngeal cancers