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No Common Cold: Viruses Can Cause HPV-Related Cancers

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Assistant Professor

11/2/2020

Disclosures

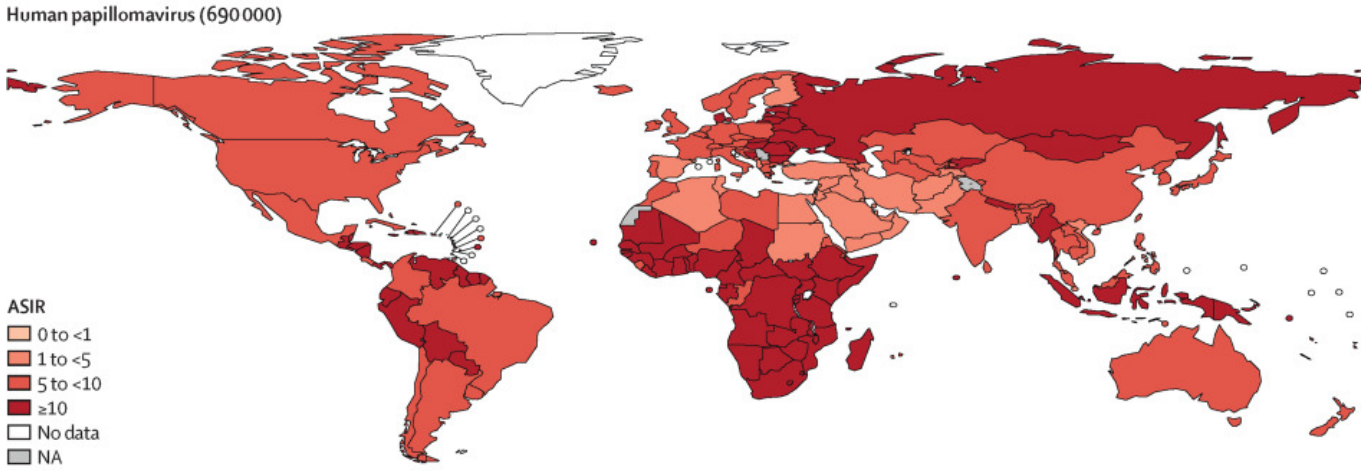
- None

Learning Objectives

- Understand how head and neck cancers caused by HPV differ from those caused by smoking
- Understand the key role of radiotherapy in the treatment of HPV-associated oropharyngeal cancers
- Become familiar with UCSF's leading efforts in reducing side effects and improving quality of life in the treatment of HPV-associated oropharyngeal cancers

Infections responsible for 13% of cancers

- Most common are H. pylori, human papillomavirus (HPV), hepatitis B (HBV), and hepatitis C (HCV)



de Martel, The Lancet Global Health, 2020

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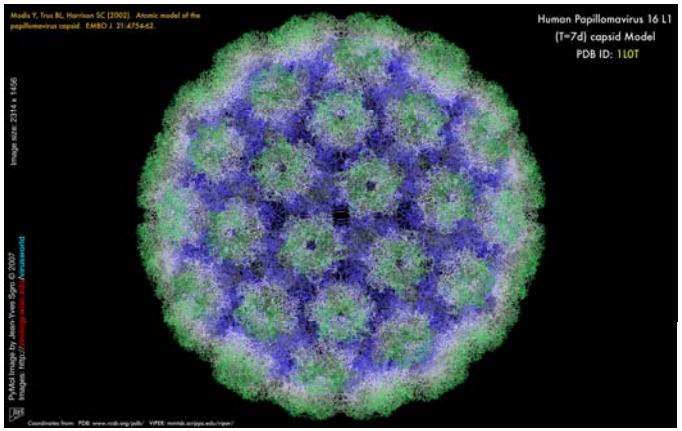
Human Papillomavirus (HPV)

- Group of non-enveloped DNA Viruses
- Infect human epithelial (surface) cells
- Some strains cause warts
- Some strains cause cancer



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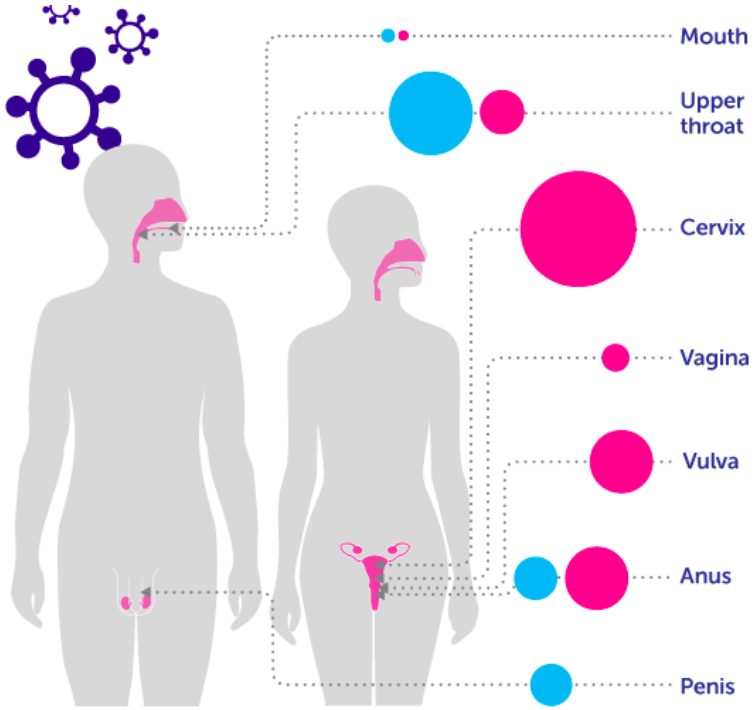
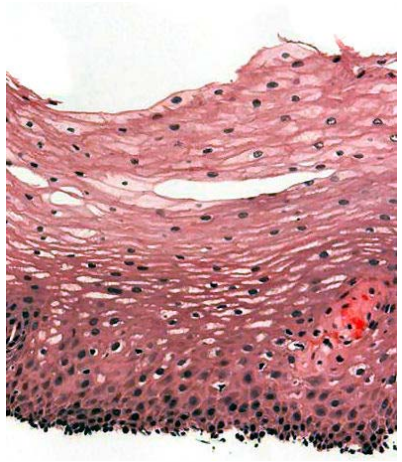
HPV causes uncontrolled growth of surface cells



- Virus makes proteins E6 and E7
- Unregulated growth of epithelial cells of the skin and mucous membranes



Squamous cells

Mature and divide

Basal cells

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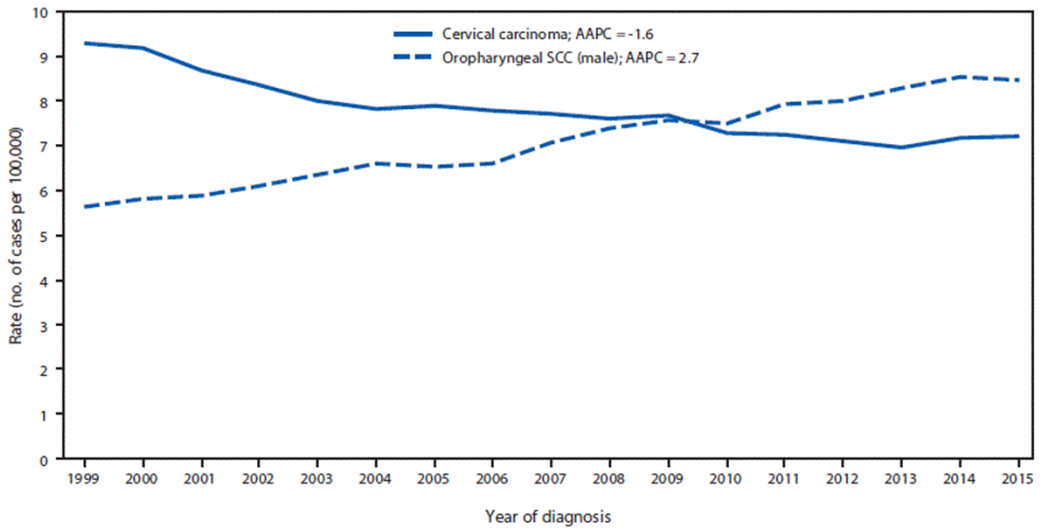
Rising incidence of HPV-associated oropharyngeal cancer

- Most head and neck cancers with decreasing incidence
- One notable exception – oropharynx
- Has overtaken cervical cancer as the most common HPV-related cancer in the United States



Chaturvedi, J Clin Oncol 2010
Van Dyne, CDC Weekly 2018

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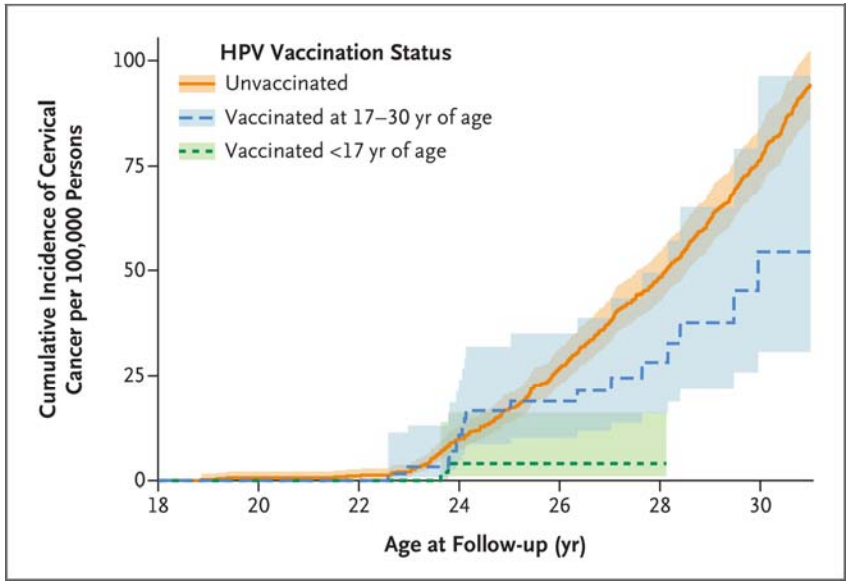
June 2020: HPV vaccine approved for oropharyngeal cancers

ORIGINAL ARTICLE

HPV Vaccination and the Risk of Invasive Cervical Cancer

Jiayao Lei, Ph.D., Alexander Ploner, Ph.D., K. Miriam Elfström, Ph.D., Jiangrong Wang, Ph.D., Adam Roth, M.D., Ph.D., Fang Fang, M.D., Ph.D., Karin Sundström, M.D., Ph.D., Joakim Dillner, M.D., Ph.D., and Pär Sparén, Ph.D.



JAMA Network Open

Original Investigation | Pediatrics

Risk of Oral Human Papillomavirus Infection Among Sexually Active Female Adolescents Receiving the Quadrivalent Vaccine

Nicolas F. Schlecht, PhD; Martin Masika, MD; Angela Diaz, MD, PhD; Anne Nucci-Sack, MD; Anthony Salandy, PhD; Sarah Pickering, MPH; Howard D. Strickler, MD, MPH; Viswanathan Shankar, DrPH; Robert D. Burk, MD

Table 3. Association Between Vaccine Status at Enrollment and Detection of Quadrivalent HPV Vaccine Types in the Oral Cavity[a]

Vaccine Status	No. of Participants (% HPV Positive)	Odds Ratio (95% CI)[b]	Odds Ratio (95% CI)[c]
No. of doses			
0	192 (2.1)	1 [Reference]	1 [Reference]
>1	1067 (0.4)	0.17 (0.04-0.68)	0.20 (0.04-0.998)

Abbreviation: HPV, human papillomavirus.

[a] Quadrivalent HPV vaccine types include HPV-6, HPV-11, HPV-16, and HPV-18.

- HPV vaccine was approved for cervical cancer in 2006
- Oropharyngeal cancer incidence likely to decrease like cervical cancer

Lei, NEJM 2020

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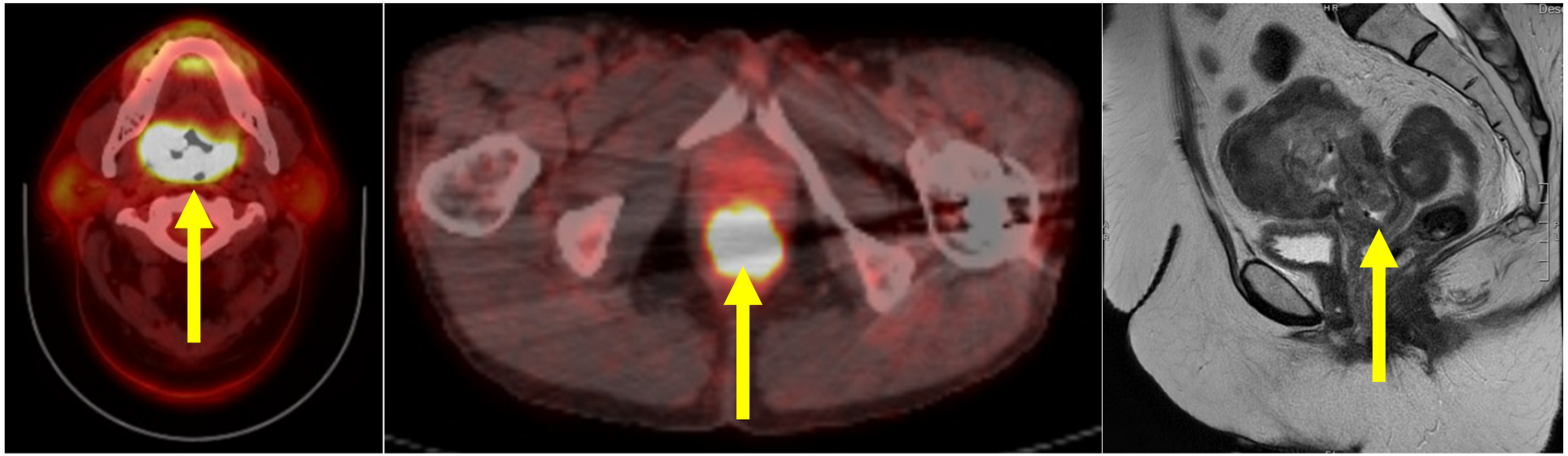
HPV-Associated Squamous Cell Carcinomas

Same culprits: HPV-16 ~90%, HPV-18 ~5%



Oropharynx | Anus | Cervix

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HPV-Associated Squamous Cell Carcinomas

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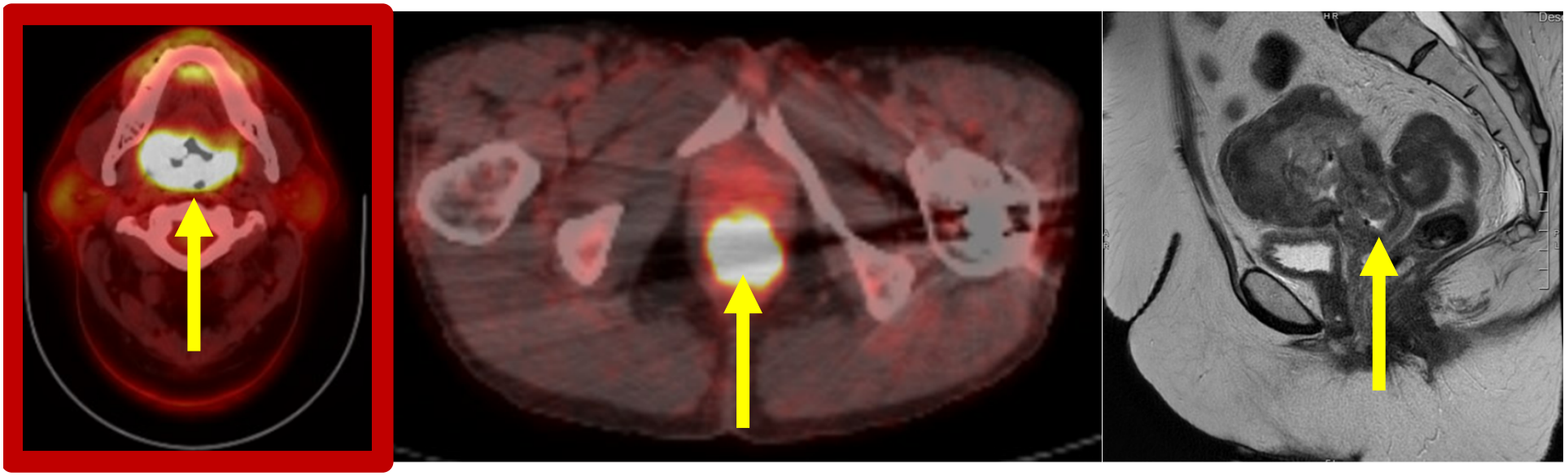

Oropharynx | Anus | Cervix

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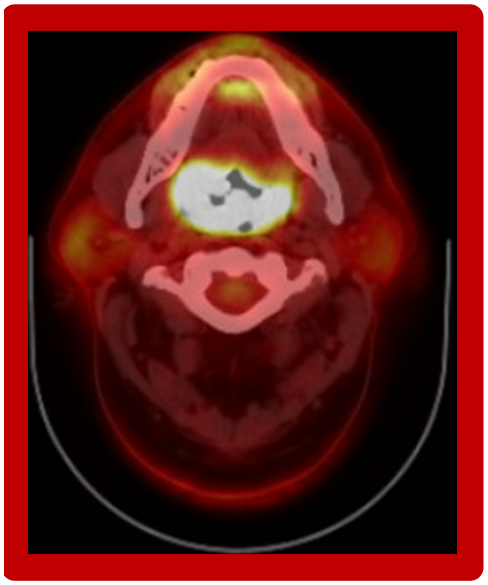
Oropharynx Cancer Treatment



- **Early Stage**
  - **RT** alone
  - Surgery ± post-operative **RT** ± chemo
- **Locally advanced**
  - **RT** + chemo
  - Surgery ± post-operative RT ± chemo

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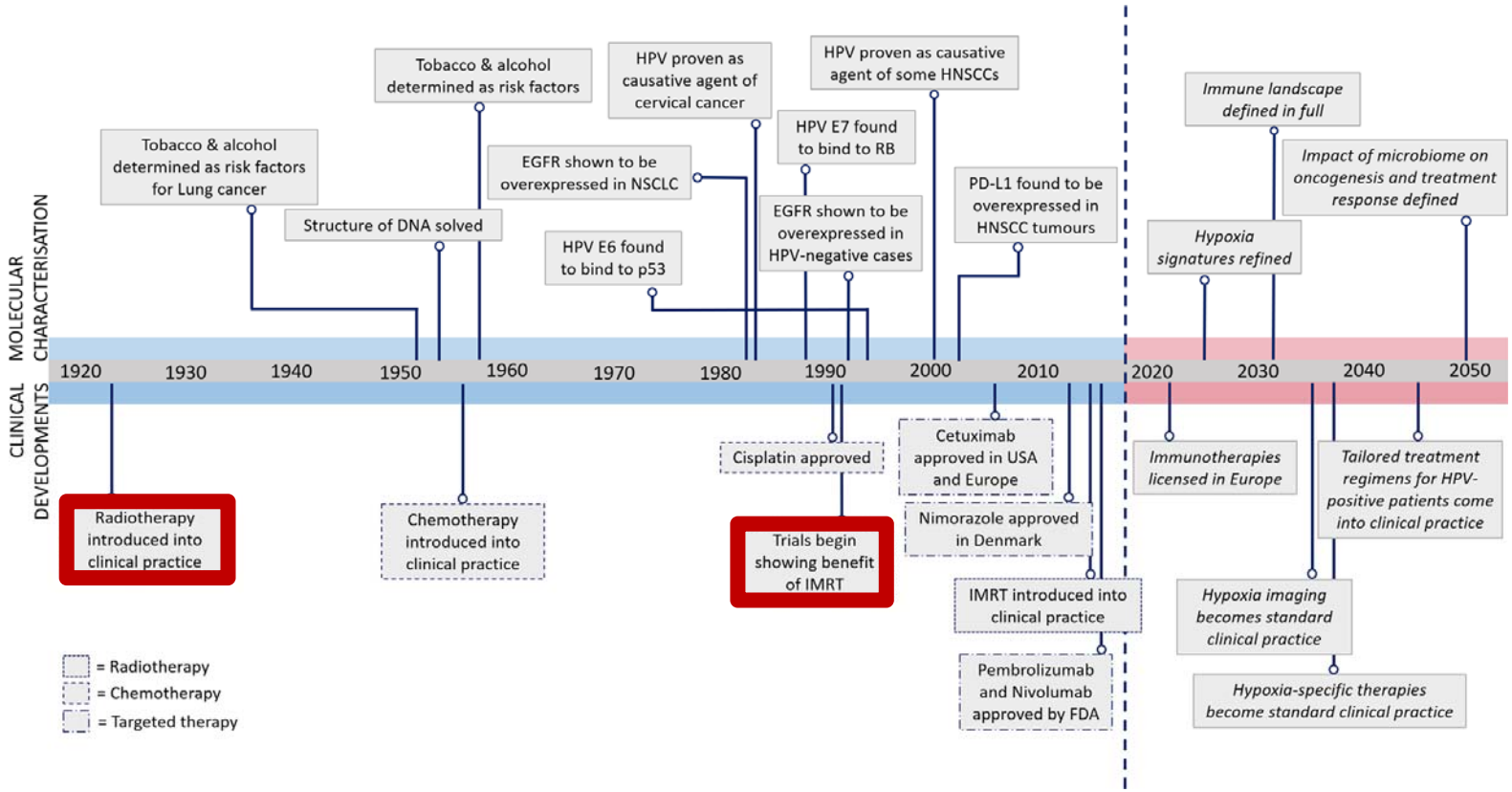
Head and Neck SCC Treatment Evolution



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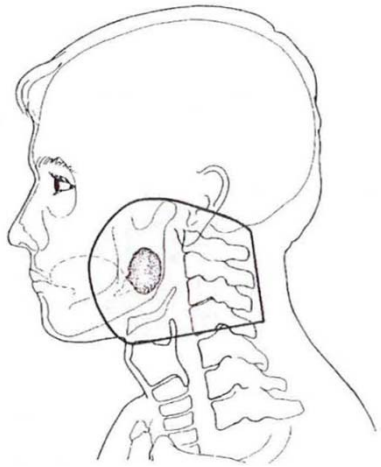
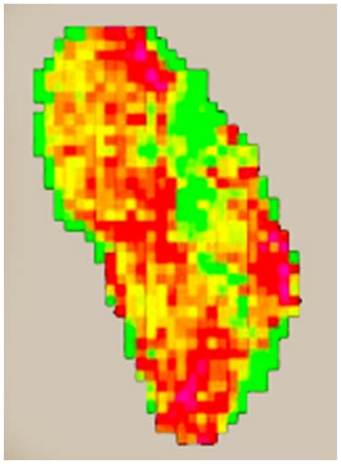
UCSF was an early-adopter of IMRT (since 1997)



Old techniques of radiation therapy



Intensity-modulated radiation therapy

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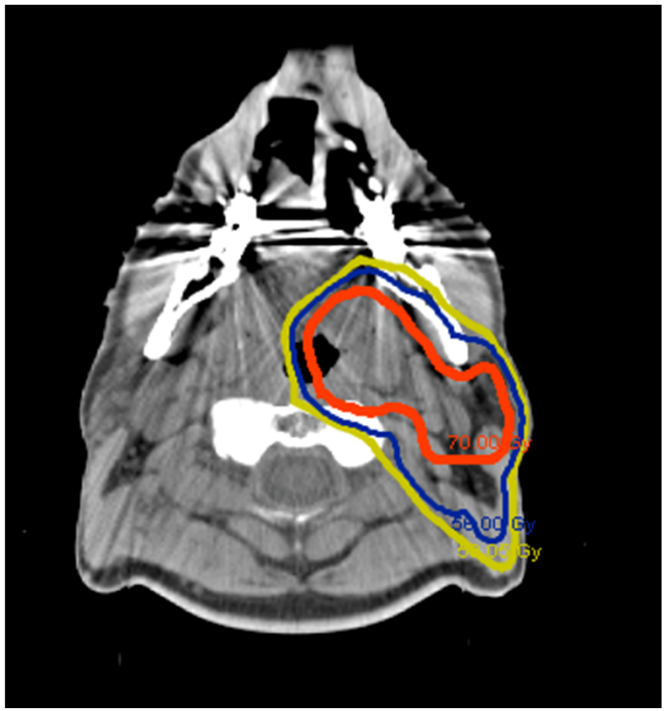
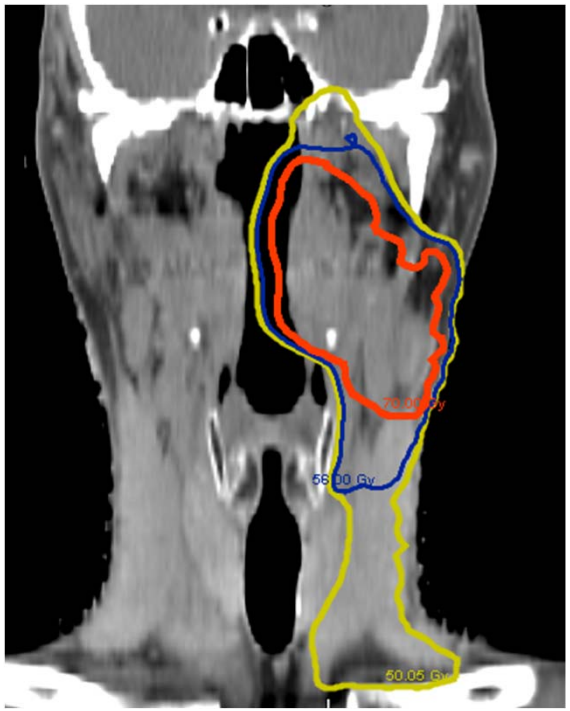
70 Gy with High-Dose Cisplatin

Current standard of care irrespective of HPV status





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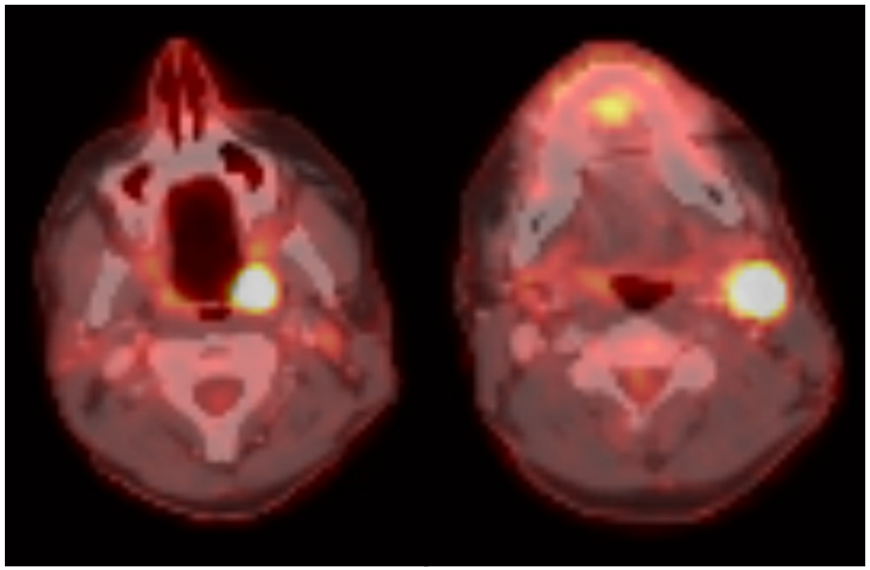
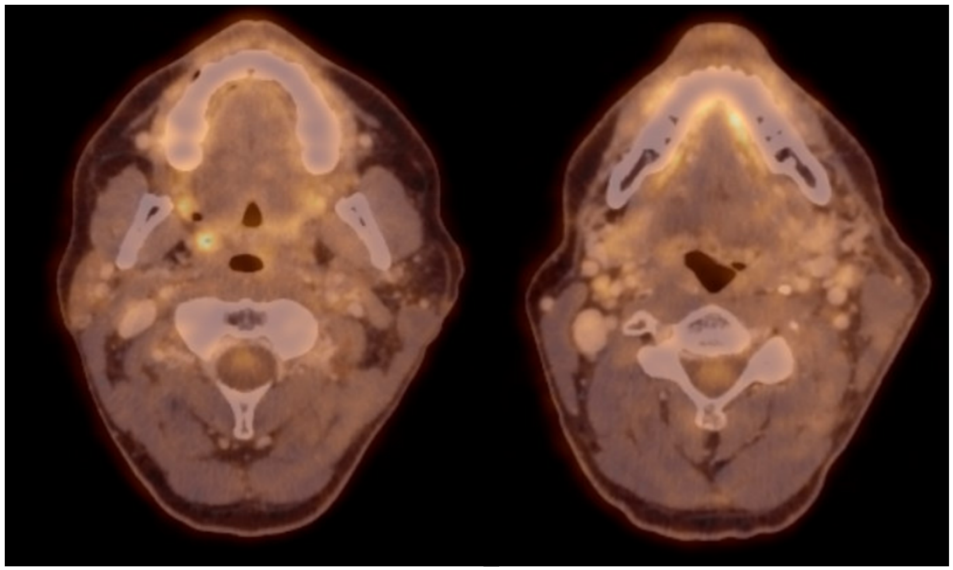
Treatments render most patients disease-free

Pre-treatment



3 month follow-up



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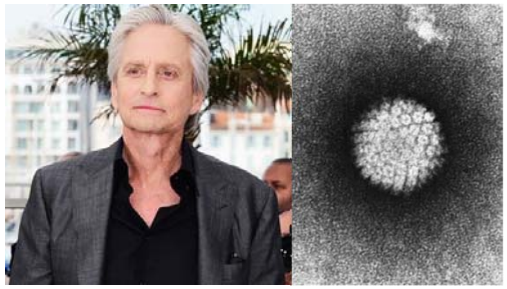
HPV vs. Smoking Head and Neck Cancers



Cause	HPV	Smoking
Site	Oropharynx	Any
Age	Younger	Older
Socioeconomic Status	High	Low
Risk Factors	Sexual behavior	Alcohol, tobacco
Survival	> 80% at 3 years	50% at 3 years
Incidence	Increasing	Decreasing

2001: HPV associated with oropharynx cancer

ORIGINAL ARTICLE

Human Papillomavirus Infection as a Risk Factor for Squamous-Cell Carcinoma of the Head and Neck

Jon Mork, M.D., A. Kathrine Lie, M.D., Eystein Glattre, M.D., Sarah Clark, D.Phil., Göran Hallmans, M.D., Egil Jellum, Ph.D., Pentti Koskela, Ph.D., Bjørn Møller, M.Sc., Eero Pukkala, Ph.D., John T. Schiller, Ph.D., Zhaohui Wang, M.D., Linda Youngman, Ph.D., et al.

Site†	Seropositive Patients	Seropositive Controls	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)‡	Patients Positive for HPV-16 DNA§
	no./total no. (%)				no./total no. (%)
Lips (code 140)	2/57 (4)	21/307 (7)	0.5 (0.1–2.4)	0.5 (0.1–2.1)	0/32 (0)
Tongue (code 141)	9/57 (16)	22/302 (7)	2.7 (1.2–6.4)	2.8 (1.2–6.6)	4/29 (14)
Floor of mouth (code 143)	0/23 (0)	15/125 (12)	—	—	0/15 (0)
Oral cavity, not otherwise specified (code 144)	2/19 (11)	2/104 (2)	5.4 (0.8–38.8)	3.6 (0.5–26.3)	0/15 (0)
Oropharynx (code 145)	10/26 (38)	14/137 (10)	8.6 (2.6–28.5)	14.4 (3.6–58.1)	9/18 (50)
Nasopharynx (code 146)	0/10 (0)	2/60 (3)	—	—	1/7 (14)
Hypopharynx (code 147)	0/16 (0)	3/81 (4)	—	—	0/8 (0)
Nose and paranasal sinuses (code 160)	2/7 (29)	3/36 (8)	3.5 (0.6–20.7)	3.4 (0.6–20.8)	0/4 (0)
Larynx (code 161)	9/76 (12)	20/411 (5)	2.5 (1.1–5.8)	2.4 (1.0–5.6)	1/32 (3)
All sites	35/292 (12)	102/1568 (7)	2.1 (1.4–3.2)	2.1 (1.4–3.2)¶	15/160 (9)

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2007: different risk factors than other HN cancers

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.

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

Sexual Behavior	Patients with Oropharyngeal Cancer (N=100)	Control Patients (N=200)	Adjusted Odds Ratio (95% CI)†	
			All Patients	HPV-16+ Patients‡
	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)**

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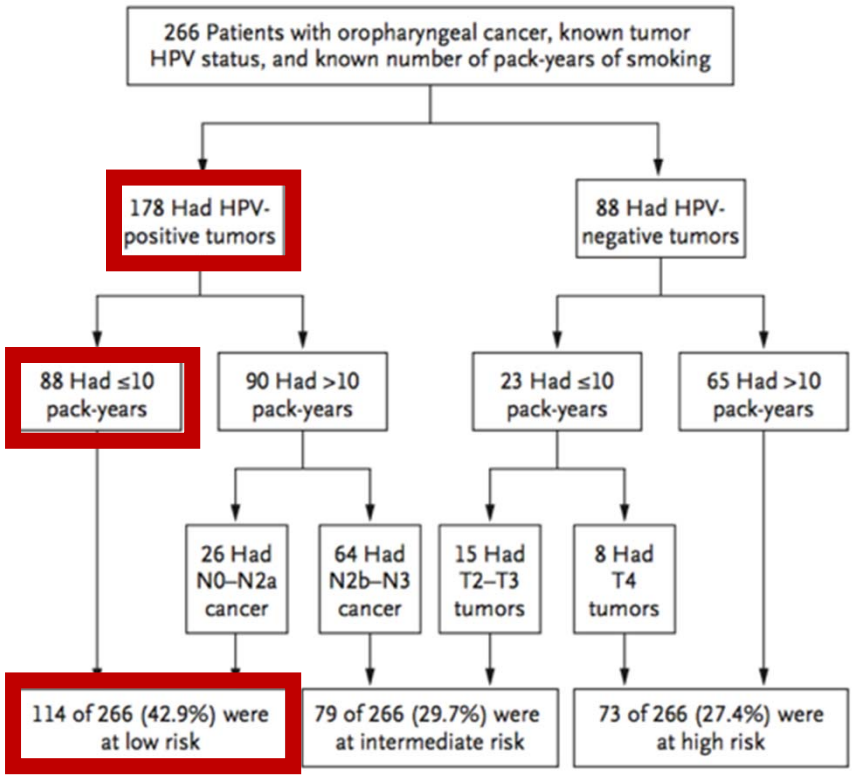
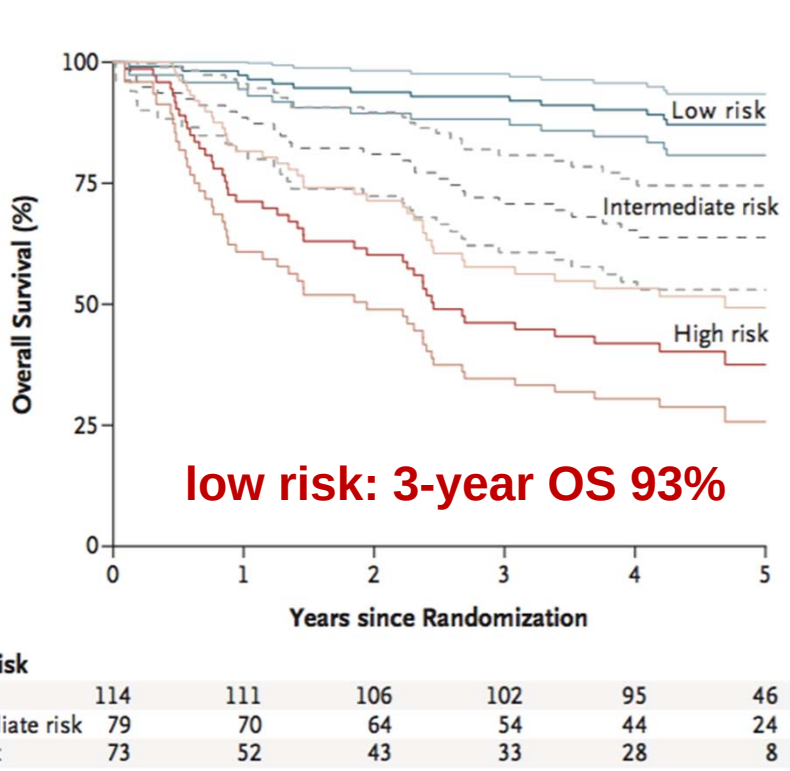
2010: HPV status linked to longer survival





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

Ang, NEJM 2010

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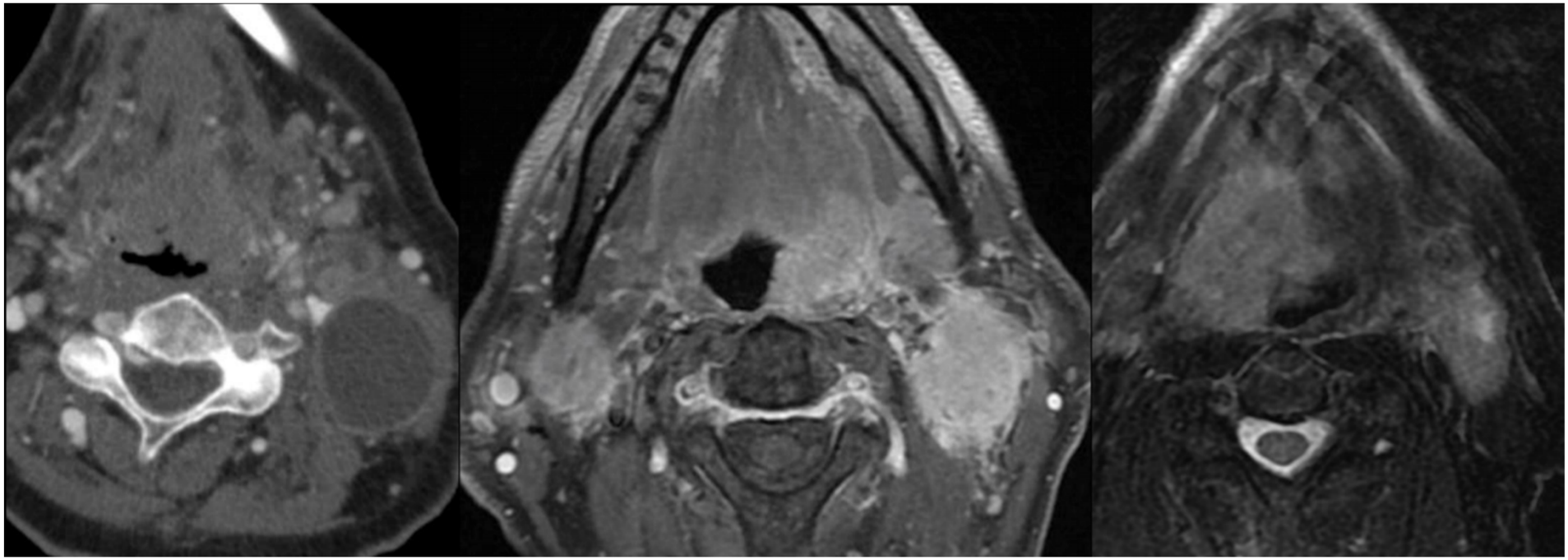
HPV Status Included in Latest Staging Guidelines

All three AJCC7 Stage IVA



AJCC8 Stage I | AJCC8 Stage II | AJCC8 Stage III

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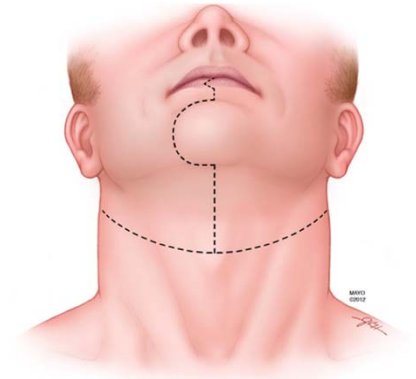
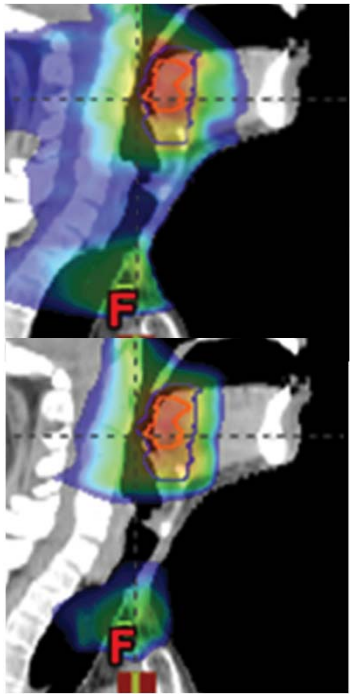
De-Intensification

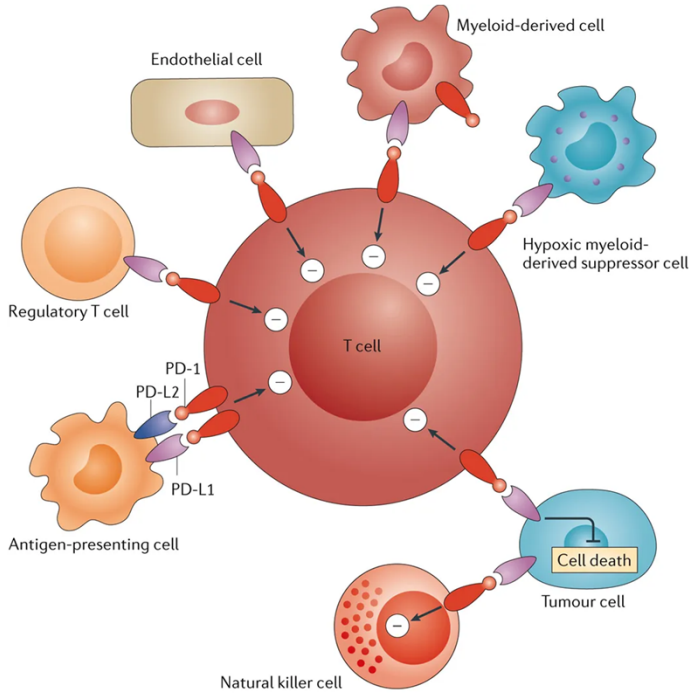
Maintain high cure rates while reducing long-term toxicities



Surgery



Radiation



Systemic

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Need to test hypothesis rigorously

Cannot substitute Cisplatin with Cetuximab

RTOG 10-16
5-year OS 85% → 78%

De-ESCALaTE
2-year OS 98% → 89%

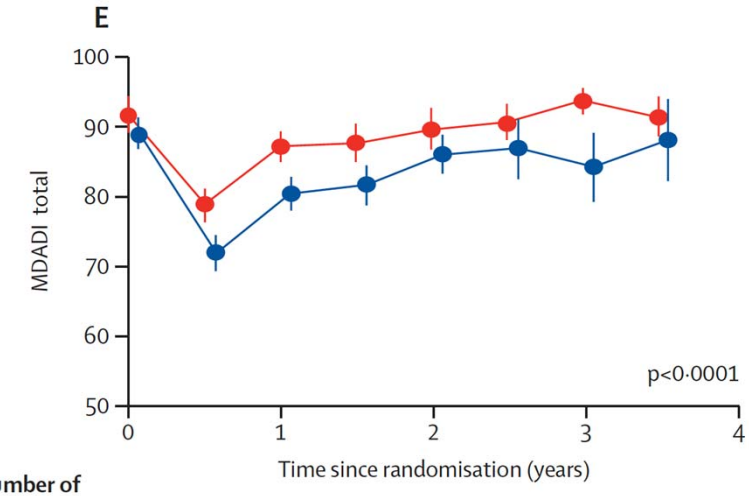
Worse overall survival
Similar acute and late toxicities

Nichols, Lancet Oncol 2019

Need to test hypothesis rigorously

Cannot assume transoral surgery is less morbid than radiotherapy

Primary RT (68% chemo) had statistically superior swallowing scores, less pain and trend toward less shoulder dysfunction at 1 year compared to primary surgery (caveat: 71% had post-op RT)



Number of completed surveys									
RT group	32	29	27	20	14	10	8	7	..
TORS + ND group	31	33	30	21	17	11	9	6	..

 Nichols, Lancet Oncol 2019

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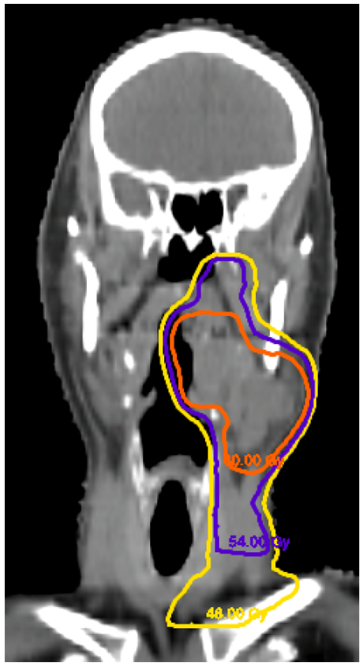
Many promising ways to de-intensify RT

Reduce definitive RT dose	UNC/UFL: 60 Gy + cisplatin
	HN002 (PI Dr. Sue Yom): 60 Gy ± cisplatin
	ECOG 1308: chemoselection for 54 Gy vs. 70 Gy
	UC Davis: chemoselection for 54 Gy vs. 60 Gy
Reduce post-op RT dose	ECOG 3311: omission of RT, 50 vs. 60 Gy, 66 Gy
	Mayo: 30-36 Gy
Reduce RT target size	Penn: omit RT to primary site

NRG HN-002 (Closed)
PI: Sue Yom



Schema

N = 308 randomized

Eligibility

- OP SCC
- ≤10 pack-year
- T1-T2 N1-N2b
- T3 N0-N2b

REGISTER

Central review
p16+ IHC

STRATIFY

Declare Intent
Unilat vs Bilat Neck XRT

RANDOMIZE

Arm 1: 60 Gy XRT (2Gy/fx) in 6 weeks + cisplatin 40 mg/m2 weekly x 6 cycles

Arm 2: 60 Gy XRT (2 Gy/fx) at 6 fractions/week for 5 weeks

NRG ONCOLOGY™

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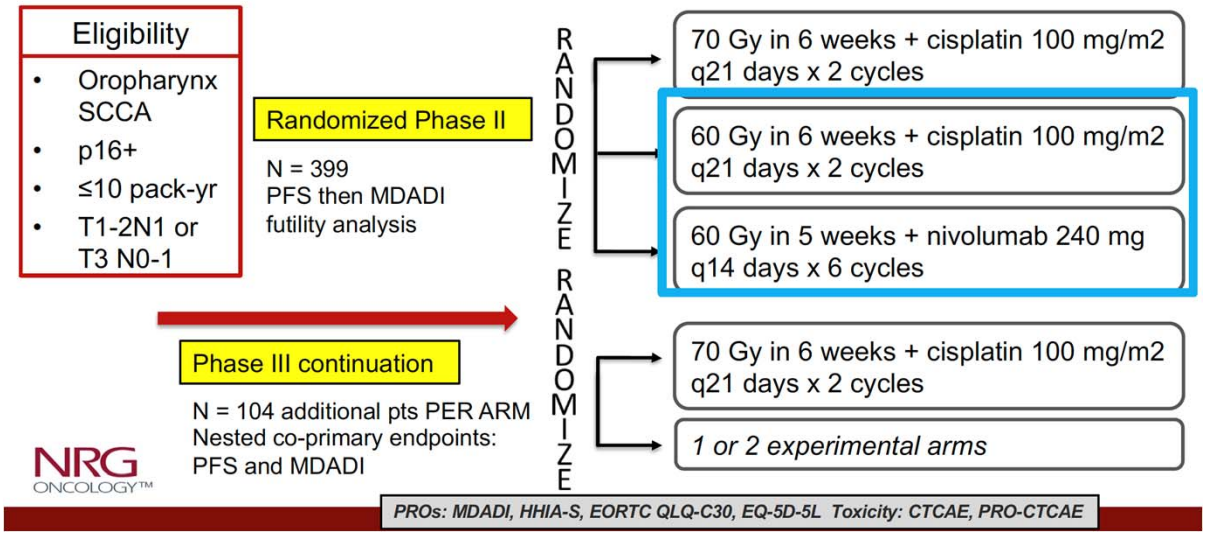
NRG HN-005 (Open)
PI: Sue Yom

The next NRG Oncology phase II study with two new experimental arms:

NRG-HN005: A Randomized Phase II/III Trial of De-intensified Radiation Therapy for Patients with Early Stage, p16-Positive, Non-Smoking-Associated Oropharyngeal Cancer



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Takeaways

- Standard of care chemoradiation for locally advanced HPV-associated oropharyngeal cancer is associated with life-long debilitating side effects
- Patients with HPV-associated oropharyngeal cancers tend to be younger, healthier, with less smoking history
- UCSF is a leader in developing future standards for oropharyngeal cancer treatments