



Head & Neck Case Clinic: HPV, Gone Viral!

Preeti Dalawari, MD, MSPH, ALMI

Vice President & Medical Director

Michelle Privett, MS, RN, FALU, FLMI, ACS

Vice President, Education & Training

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What is your favorite medical TV drama of all time?



Nobody has responded yet.

Hang tight! Responses are coming in.

RGIA

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New Amsterdam



Dr. Eric Manheimer and Fictional Dr. Max Goodwin

Case 1

- 64-year-old male, non-smoker
- 150K
- Hx of heavy ETOH in past but rarely drinks now
- Dx with “small spot/cancer” on tongue with excision 1 year prior
- APS: Squamous cell CA



What is the first thing you need to know to assess risk?

Image by <https://www.vectorportal.com>. creative commons 4.0



What is the FIRST thing you need to know to assess risk?

A. Family history

0%



B. Location of Tumor

0%



C. Tumor Size

0%



D. p16 status

0%

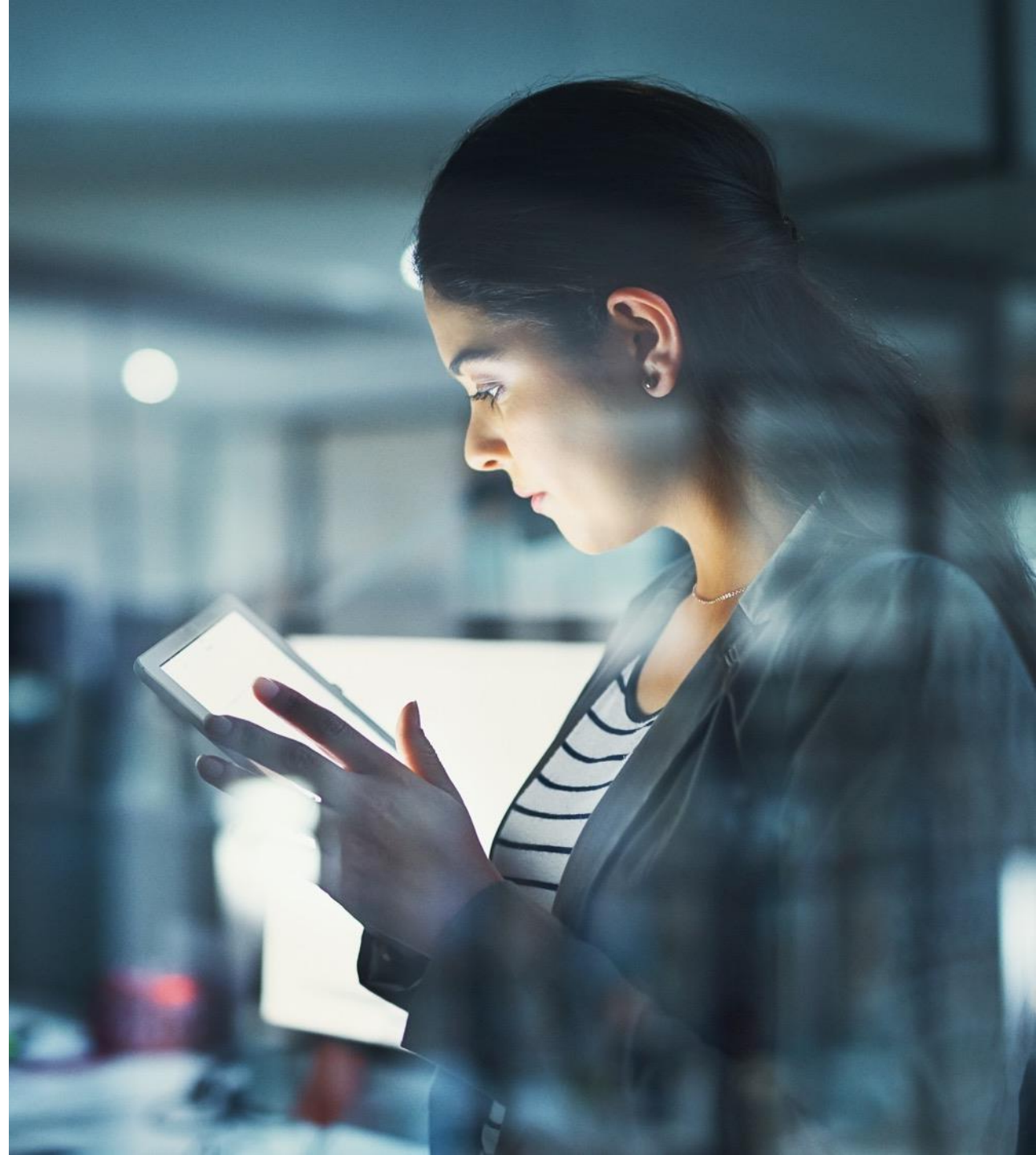


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Anatomy of Head and Neck Cancers



Anatomy

Squamous cell carcinomas

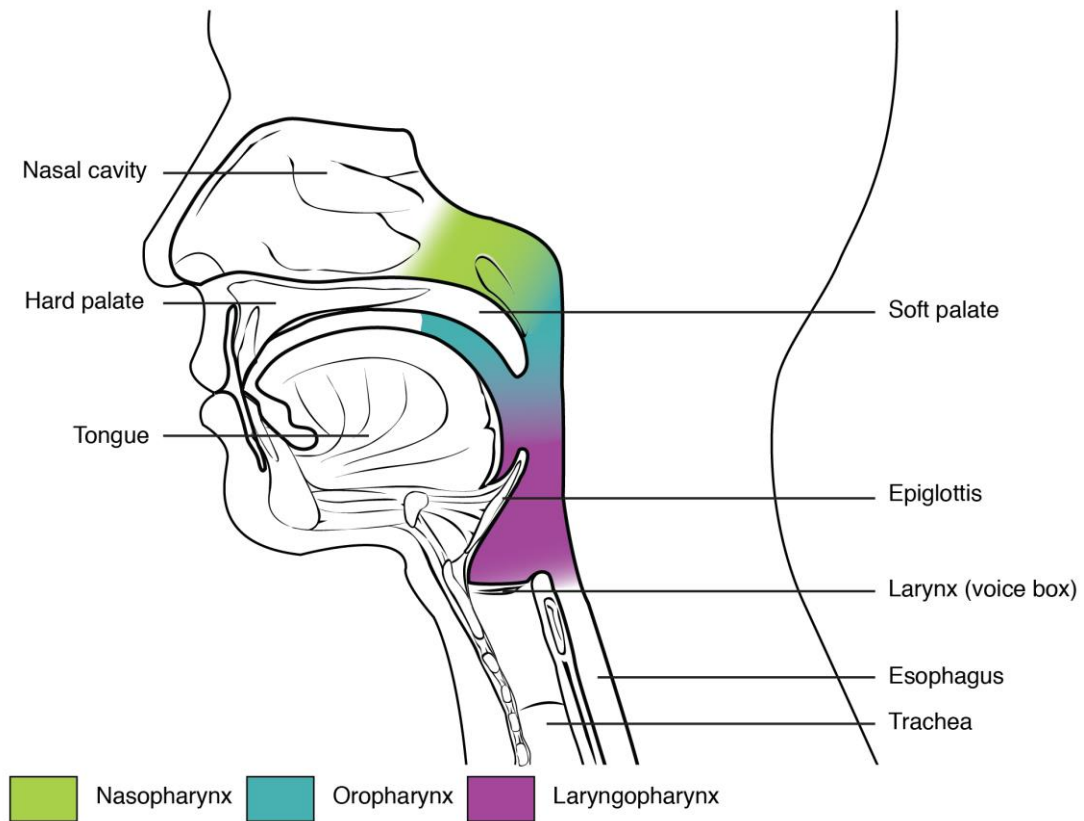
- Cancers arise from squamous cells that line the moist mucosa (inner lining of mouth, throat, nose)



https://commons.wikimedia.org/wiki/File:PLoS_oral_cancer.png

Anatomy

Head and neck cancers



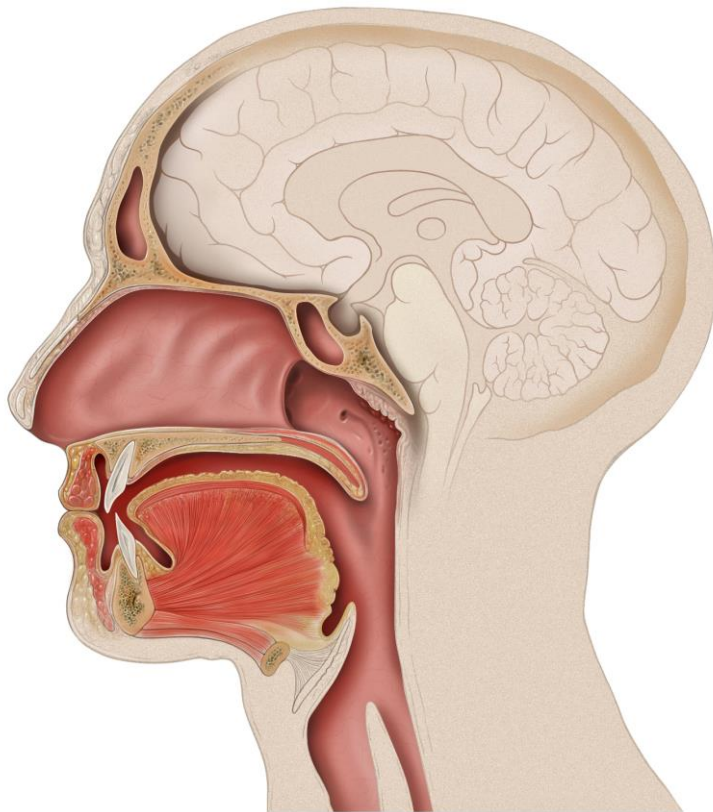
- Nasal cavity/paranasal sinus
- Nasopharynx
- **Oropharynx**
- **Oral cavity**
- Hypopharynx
- Larynx

Wikimedia commons: https://commons.wikimedia.org/wiki/File:2305_Divisions_of_the_Pharynx.jpg

Anatomy

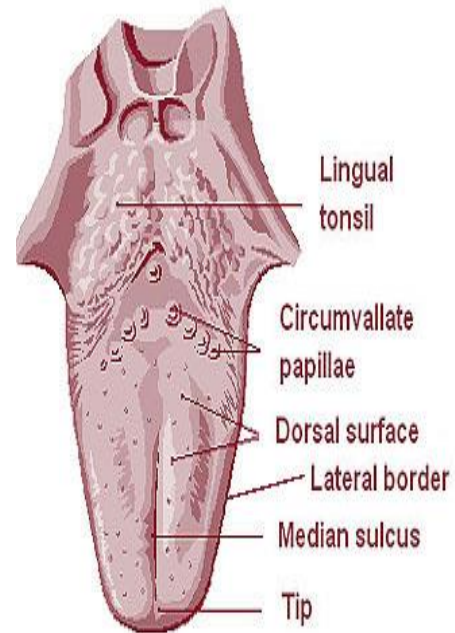
Oral cavity

Sagittal Section



https://commons.wikimedia.org/wiki/Category:Human_tongue_anatomy#/media/File:Illu04_tongue.jpg
https://commons.wikimedia.org/wiki/File:Head_lateral_mouth_anatomy.jpg

Tongue



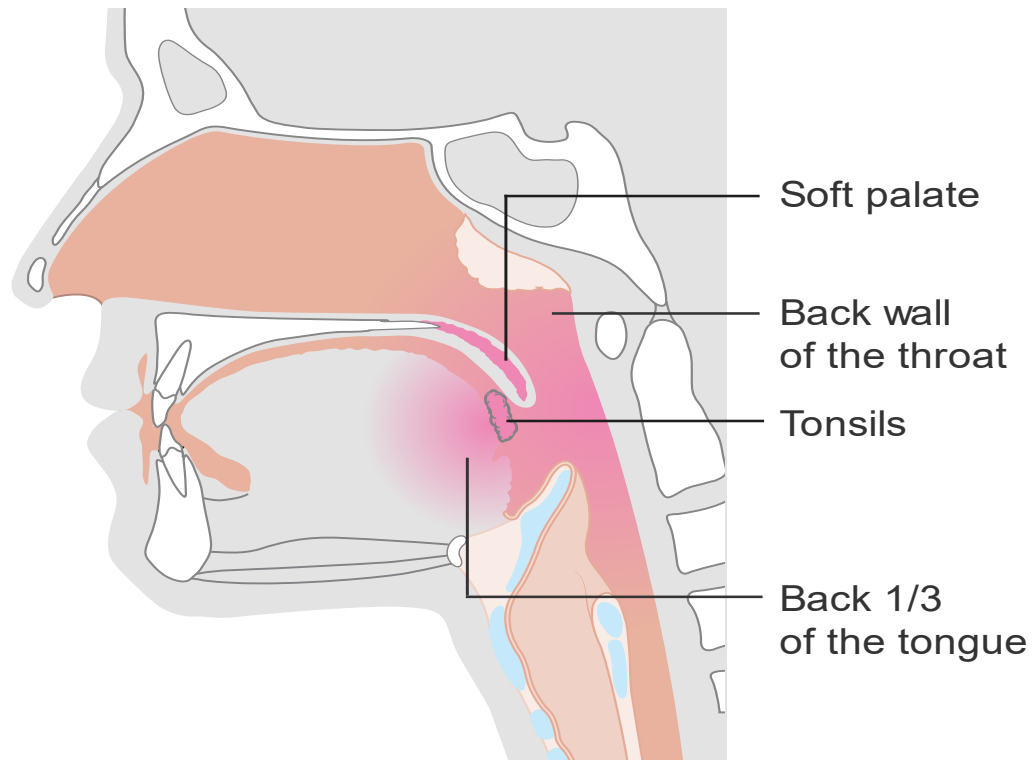
Borders

- Junction of the soft and hard palate - bony front of roof of mouth
- Retromolar trigone - area behind wisdom teeth
- Front 2/3 of tongue (to line but not including of circumvallate papillae)
- Gingiva - gums
- Buccal mucosa (inner lining of lips - starts at wet border - and cheek)
- Floor of mouth and tongue

Anatomy

Oropharyngeal cancer (OPO)

Sagittal Section



Borders

- Anterior/Superior
 - Tongue **base** (circumvallate papillae) - posterior 1/3rd
 - Soft palate
 - Tonsil
- Lateral and posterior aspects: pharyngeal wall

[https://commons.wikimedia.org/wiki/File:Diagram showing the parts of the oropharynx CRUK 332.svg](https://commons.wikimedia.org/wiki/File:Diagram_showing_the_parts_of_the_oropharynx_CRUK_332.svg)

Case 1 Conclusion

- 64-year-old male, nonsmoker
 - 150K
 - Hx of heavy ETOH in past but rarely drinks now
 - Dx with “small spot/cancer” on tongue with excision
 - Squamous cell CA
 - pT1N0M0: Stage One
- What is the **FIRST** thing you need to know?
 - Family history
 - **Location of tumor**
 - Size of tumor
 - p16 status



Epidemiology

Head and Neck Cancers

Epidemiology

Prevalence

- 3-4% of cancers in U.S.
- 1.5% of cancer deaths

Cancer sites according to AJCC 8th edition

- Mucosal lip and oral cavity
- Salivary glands
- Nasopharynx
- Nasal cavity and sinuses
- Oropharynx HPV+
- Hypopharynx and OPO HPV-
- Larynx
- Mucosal melanoma of head and neck
- Unknown primary tumor/cervical nodes

<https://www.cancerstaging.org/About/Pages/8th-Edition.aspx>

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Epidemiology

Incidence and survival by site

Cancer Site	Incidence per 100,000 Person Years	5–Year Survival
Nasopharynx	0.7	46% (keratinized SCC)
Oral Cavity/OPO	11.2	65% (combined)
Hypopharynx	0.7	26%
Laryngeal	3.0	61%

https://www.cancer.gov/types/head-and-neck/hp/oral-prevention-pdq#link/_159Presentation

Epidemiology

Risk factors

- More common in men (2X) than women
- Age at diagnosis > 50 years, median age at diagnosis for most sites is in the 60s
- Risk factors include:
 - Tobacco use/smoking
 - Alcohol use (especially heavy)
 - Viruses: HPV, EBV

Symptoms

Diverse dependent on anatomy

- Prolonged sore throat
- Difficulty swallowing
- Prolonged hoarseness
- Lump/sore that doesn't heal
- White patches that don't heal (leukoplakia) on tongue or mouth

<https://www.cancer.gov/types/head-and-neck/head-neck-fact-sheet#what-are-cancers-of-the-head-and-neck>

Treatment

Varies by site

Options

- Surgery
- Radiation
- Chemotherapy
- Combination

Anatomical Distinction

- OPO: Radiation is primary treatment
- Oral Cavity: Surgery is primary treatment

Case 2 Question 1

- 54-year-old male, nonsmoker
- Left base of tongue cancer
- Squamous cell carcinoma
- Chemo and radiation in 2015
- Stage 4a noted in APS





What is the FIRST thing you want to know to assess risk?



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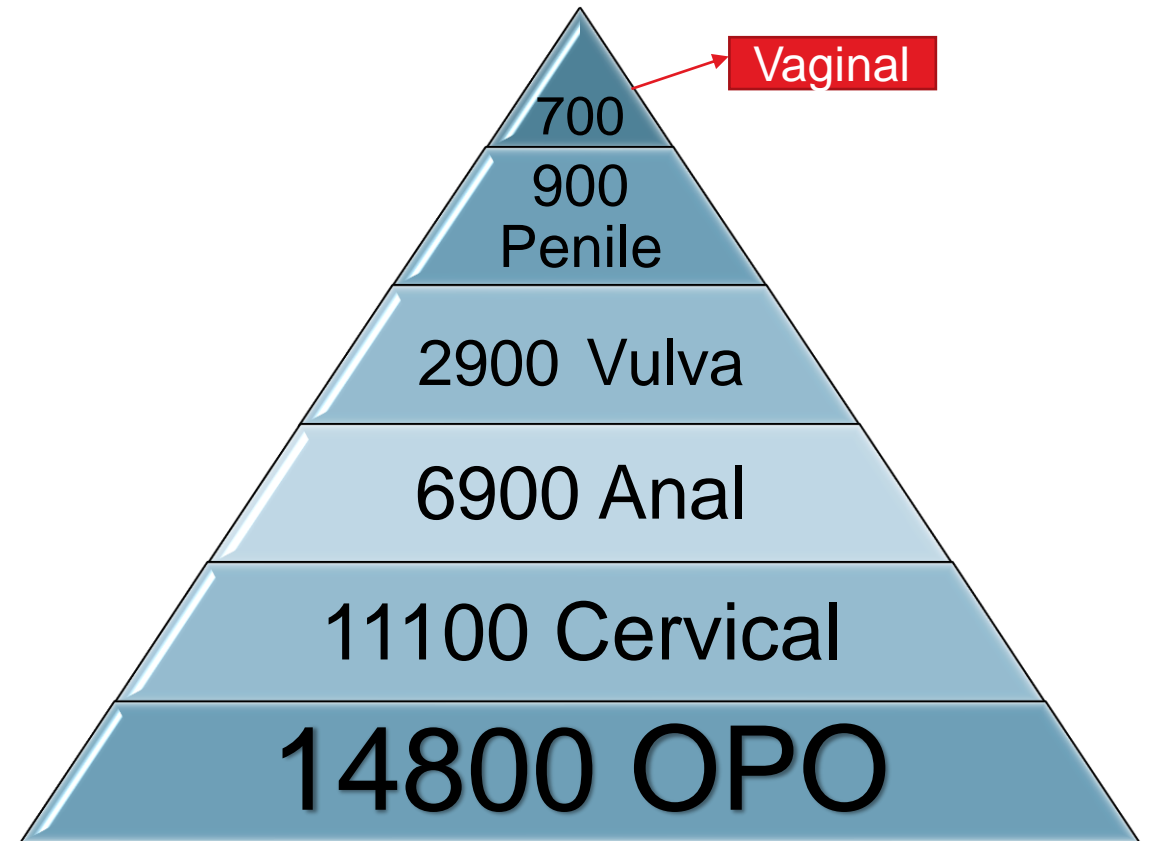
Human Papilloma Virus

Why HPV?

HPV-associated cancers

- Human Papilloma Virus (HPV) associated oropharyngeal (OPO) cancer
 - Incidence of OPO by HPV increasing
 - 70% of OPO tested positive for HPV

Estimated number of HPV-associated cancer



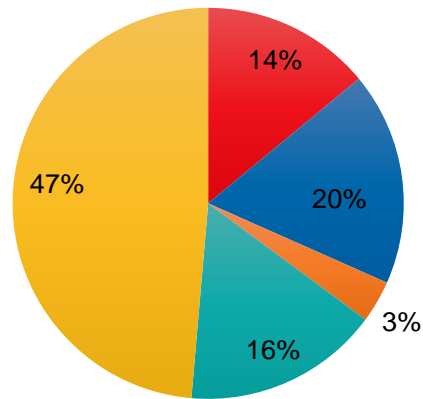
<https://www.cdc.gov/cancer/hpv/statistics/cases.htm>

US Incidence 2015–2019

HPV associated cancer by gender

HPV Associated Cancer - Women

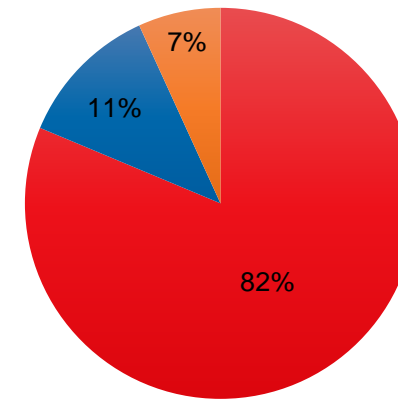
■ Oropharynx ■ Anus ■ Vagina ■ Vulva ■ Cervix



- Total: 26,177/year
- Oropharynx 3,617

HPV Associated Cancer - Men

■ Oropharynx ■ Anus ■ Penis



- Total: 21,022/year
- Oropharynx 17,222

<https://www.cdc.gov/cancer/uscs/about/data-briefs/no31-hpv-assoc-cancers-UnitedStates-2015-2019.htm>

Pathophysiology

What is HPV?

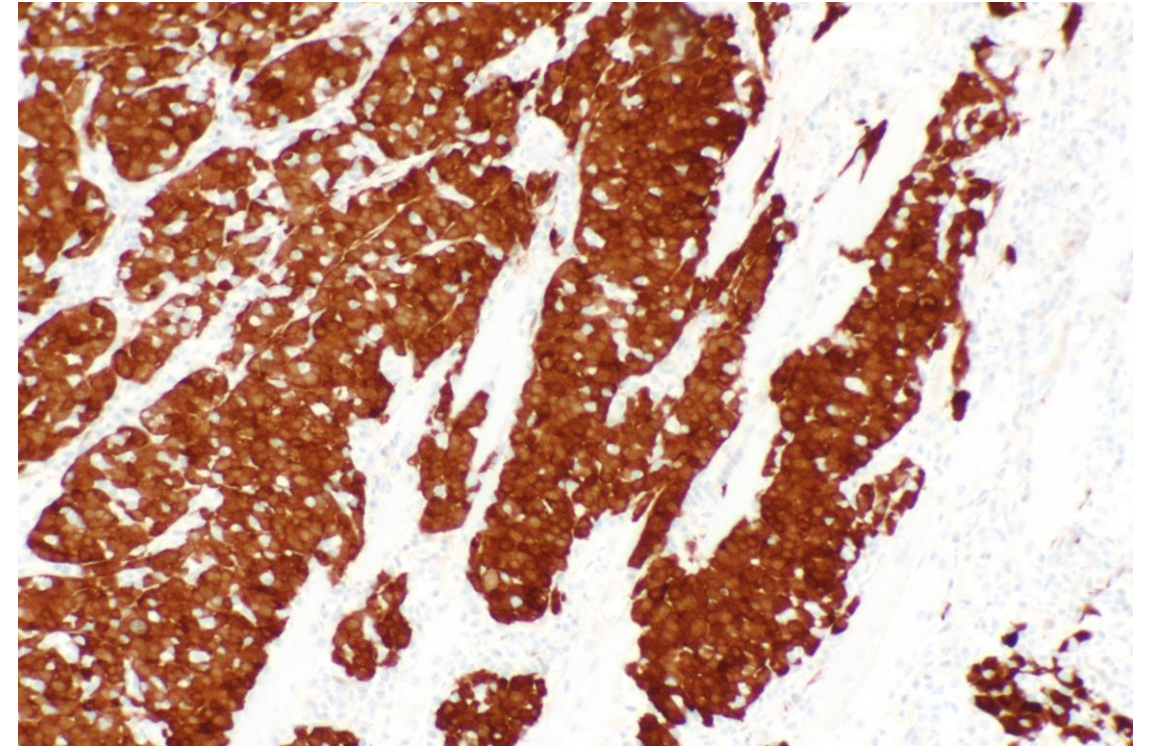
- Most common viral infection of the reproductive tract
- Greater than 100 types; at least **15** are cancer - causing (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 82)
- Almost all men or women will have at least one type of HPV in their lifetime
- Acquired through vaginal, oral, or anal intercourse, but penetrative intercourse is *NOT* required

HPV associated OPO risk factors

- Number of lifetime oral sex partners
- May partially account for observed gender disparity

HPV Testing

- Needs to be inexpensive, available, reproducible
- Protein **p16** is overexpressed
 - AKA cyclin dependent kinase inhibitor 2A
 - Correlated with HR HPV subtypes 16,18, 31, 33 and others
 - Immunohistochemical marker for p16 used (stain)
 - Can't tell difference between transcriptionally active or not
 - **Best used in conjunction with HPV DNA or in situ hybridization**



Lewis et al. p16 Positive Oropharyngeal Squamous Cell Carcinoma: An Entity with a Favorable Prognosis Regardless of Tumor HPV Status. Am J Surg Pathol. 2010; 34(8).

Panwar et al. 2017. Oncology Journal, Head and Neck Cancer. <https://www.cancernetwork.com/article/emergence-novel-staging-system-oropharyngeal-squamous-cell-carcinoma-based-hpv-status/page/0/1>

Case 2 Question 2

- 54-year-old male, nonsmoker
- Left **base** of tongue cancer
- Squamous cell
- Chemo and radiation in 2016
- Stage 4a noted in APS





Can you offer?

Nadda, nodes are positive

0%



Yup, let's do it

0%



Beats me

0%



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TNM Classification

Kaplan-Meier Curve of Survivability

- AJCC changes 7th to 8th Ed: Different staging system based on HPV status
 - Five-Year Survival

Stage	HPV+ OPO	HPV- OPO
1	88%	76%
2	82%	68%
3	84%	53%
4a	81%	45%
4b	60%	34%

O'Sullivan et al. Development and Validation of a Staging System for HPV-related oropharyngeal cancer by the International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S): a multicentre cohort study. *Lancet Oncol.* 2016;17(4): 440-451.

High Risk HPV+ OPO Cancer

Epidemiologically, pathologically, and clinically distinct!

HPV+ compared to HPV- OPO:

- Earlier onset (median age early 50s vs 60s)
- More common in Caucasians
- Earlier stage of diagnosis
- Less likely to have traditional risk factors (e.g., smoking & ETOH)
- More likely to have smaller tumors with greater cervical LN metastasis
- **LN enlargement** is the *initial presenting symptom* in half HPV+ OPO patients (smaller tumor stage but higher LN stage).
- **HPV+ is prognostic finding**
 - Respond better to chemo and rtx
 - Less likely to have secondary tumors

HPV- OPO

TNM Staging

T	N	M	Stage
Tis	N0	M0	0
T1	N0	M0	1
T2	N0	M0	2
T3	N0	M0	3
T1,T3,T3	N1	M0	3
T4a	N0, N1	M0	4A
T1,T2,T3,T4a	N2	M0	4A
Any T	N3	M0	4B
T4b	Any N	M0	4B
Any T	Any N	M1	4C

HPV+ OPO

TNM Categories

Tumor

Category	Criteria
T0	No primary
T1	≤ 2 cm
T2	>2 cm but ≤ 4 cm
T3	>4 cm or extension to lingual surface of epiglottis
T4	Advanced and invading

Node-Clinical

Category	Criteria
cNx	Not assessed
cN0	No nodes
cN1	Ipsilateral, ≤ 6 cm
cN2	Contralateral/bilateral, ≤ 6 cm
cN3	>6 cm

Nodes-Pathologic

Category	Criteria
pNx	Not assessed
pN0	No nodes
pN1	≤ 4 nodes
pN2	≤ 6 nodes

Metastasis

Category	Criteria
M0	None
M1	Distant

<https://www.cancernetwork.com/article/emergence-novel-staging-system-oropharyngeal-squamous-cell-carcinoma-based-hpv-status/page/0/1>

HPV+ OPO

TNM Staging

Clinical Staging

T	N	M	Stage
T0,T1,T2	N0,N1	M0	1
T0,T1,T2	N2	M0	2
T3	N0,N1,N2	M0	2
T0,T1,T2, T3,T4	N3	M0	3
T4	N0,N1,N2, N3	M0	3
Any T	Any N	M1	4

Pathologic Staging

T	N	M	Stage
T0,T1,T2	N0,N1	M0	1
T0,T1,T2	N2	M0	2
T3,T4	N0,N1	M0	2
T3,T4	N2	M0	3
Any T	Any N	M1	4

Case 2 Presentation

- Left otalgia and left sided neck mass
- FNA of left neck mass **p16 positive** squamous cell carcinoma
- PET-CT focal asymmetric uptake in left base of tongue and 2 enlarged hypermetabolic left level 2 cervical nodes
- cT1N1M0
- Treated: Concurrent chemoradiation with Cisplatin
- Now we are 7 years out, good follow-up, no evidence of recurrence

HPV in Head and Neck Cancer

HPV+

- Is a prognosticator only for **OPO** cancer of all the HNC
- Has a **better** prognosis

Take Away

- **HPV** is prognostic in **oropharyngeal cancer** but *NOT* in the other HNC.
- **Anatomy** is extremely important; the tongue is divided into two groups:
 - Anterior 2/3rd is oral cavity.
 - Posterior 1/3rd is oropharyngeal.
- There are **two different staging systems** for oropharyngeal cancer based on p16 stain (HPV status).
 - Due to the complexity in staging, consider referring case to your Medical Director.



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