Updates on HPV- (high risk) Related Head and Neck Carcinomas

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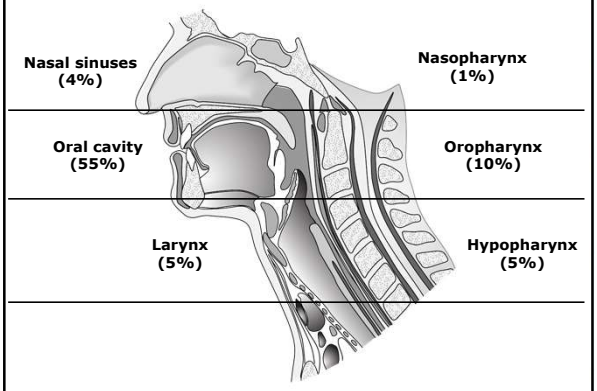
LIFE CHANGING MEDICINE



High Risk HPV- OPC

- Epidemiology: increasing incidence / HPV-16 genotype/ 80% of oropharyngeal cancers
- Pathogenesis: distinct molecular profiles (more stable genome; HPV-negative associated with EGFR overexpression and amplification)
- Presentation: young, with neck mets at dgn (T1/2 N2/N3)
- Dgn: DNA/ RNA ISH, RT-PCR E6/E7mRNA, IHC (p16)
- Prognosis: significantly better prognosis than HPV-neg OPC both at initial diagnosis and after disease recurrence.

Treatment: requires multidisciplinary evaluation and individualized decision-making.

Early-stage disease (I/II)- single modality treatment (surgery and XRT similar local control and survival rates, similar morbidity; upfront XRT as organ preservation); TORS and TLM; elective neck

Locally advanced disease (III-IVB)- surgical or non-surgical approach; XRT w/ concurrent cisplatin or cetuximab; IMRT, induction chemo; de-intensification (of XRT, systemic tx)

Recurrent or metastatic disease (IVC)- salvage re-XRT or surgery and combined chemo; palliative systemic therapy; EXTREME trial cetuximab+cisplatin+5FU

Novel Therapeutic Targets

- PI3K pathway- most commonly genomically altered pathway in HPV-OPC (trials evaluate PI3K inhibitors alone or in combination with EGFR inhibitors)
- Proteomic profiling identified high levels of E2F1 and its targets (Bcl-2 and DNA repair proteins)
- Immune response: PD-1 expressing T cells; checkpoint blockade (pembrolizumab anti-PD1)

Histologic Typing

Keratinizing/ Nonkeratinizing/ Nonkeratinizing with maturation

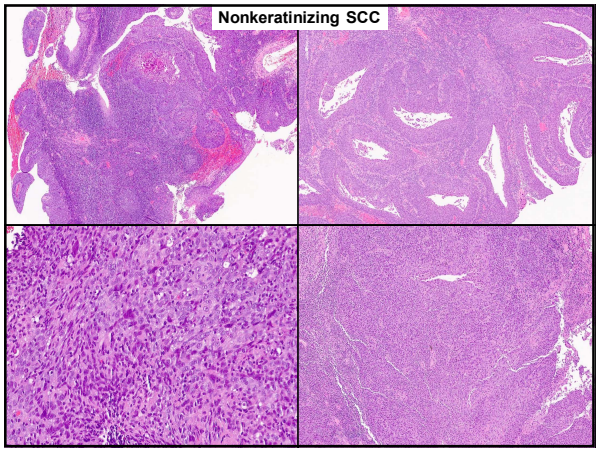
- HPV-related oropharyngeal SCC- nonkeratinizing (majority, 50% OPC)
- Non-HPV oropharyngeal SCC- keratinizing, with desmoplasia (25% OPC)
- Hybrid (nonkeratinizing with maturation) (25% OPC)- also HPV, less frequently detected

Microscopic Features of HPV-HNSCC

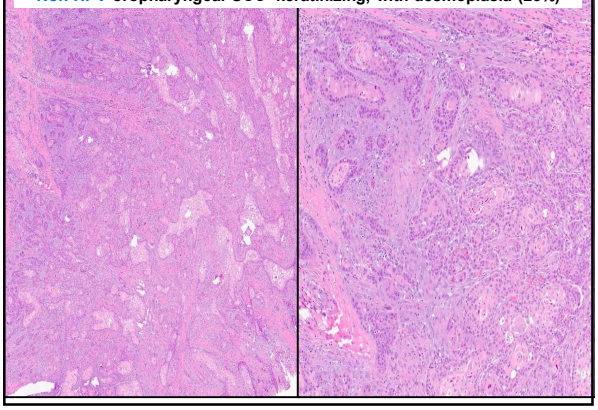
- The histologic features of reticulated epithelium are retained, to varying degrees.
- Involvement of tonsilar surface (when occurs) is a secondary spillover from the tonsilar cypts.
- The transition between HPV-HNSCC and adjacent surface epithelium is abrupt, without precursor lesions.
- Infiltrative without desmoplastic response, with sheets, ribbons; central necrosis gives rise to cystic degeneration.

Microscopic Features of HPV-HNSCC (cont)

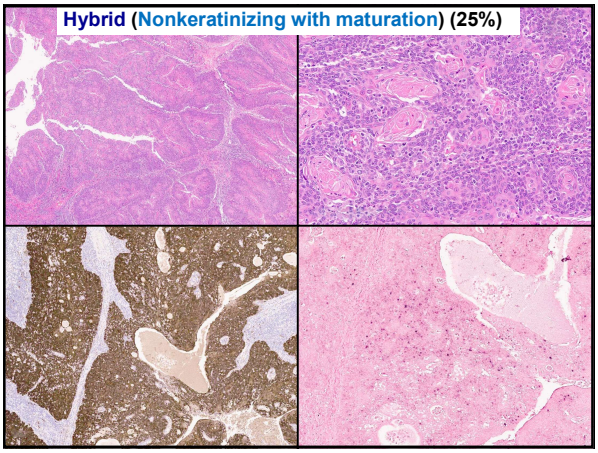
- Tumor nests associated with lymphoid cells (TILS)
- "Lymphoepithelial appearance"
- Cytology: syncytial, basaloid appearance
- LN metastasis: cystic degeneration, mistaken for branchial cleft cysts



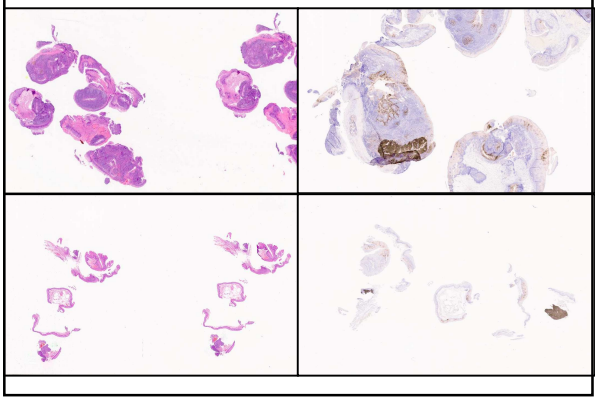
Non-HPV oropharyngeal SCC- keratinizing, with desmoplasia (25%)



Hybrid (Nonkeratinizing with maturation) (25%)



HPV-OPC: Small T1, Bulky LN mets (N2b,c)



7. Chapter 6: Oropharyngeal tumours

- Oropharyngeal tumours: Introduction
- **Benign oropharyngeal lesions**
  - Hamartomatous polyps
- **Epithelial tumours**
  - *Squamous cell carcinoma*
    - Squamous cell carcinoma, HPV-associated
    - Squamous cell carcinoma, HPV-independent

Oropharyngeal SCCs are sub-classified by HPV status in the WHO 4, 5 editions

Issues Unique to HPV+ OPSCC

- **Grading**

  Oropharyngeal HPV SCC should not be graded

- **Invasion**

  ALL oropharyngeal HPV+ SCC are invasive

Variants of HPV(+)ve OPC

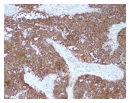
- **Basaloid**
- **Lymphoepithelial-like**
- **Papillary**
- **Adenosquamous**
- **Ciliated adenosquamous**
- **Sarcomatoid**
- **Neuroendocrine carcinoma- NEC variants of OPC HPV+ are aggressive**
  - **Small cell NEC**
  - **Large cell NEC**

HPV Testing

- Tumor classification/ Dgn
- Prognosis
- Eligibility for clinical trials

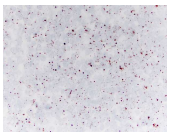
p16 IHC

widely available, easy to perform and interpret
highly sensitive
diffuse (>70%), strong, nuclear and cytoplasmic
80% specific in the oropharynx
<u>poor surrogate outside of oropharynx</u>



HPV- HR (RNA ISH)

highly sensitive/ highly specific
detects transcriptionally active virus
widely available on automated platforms



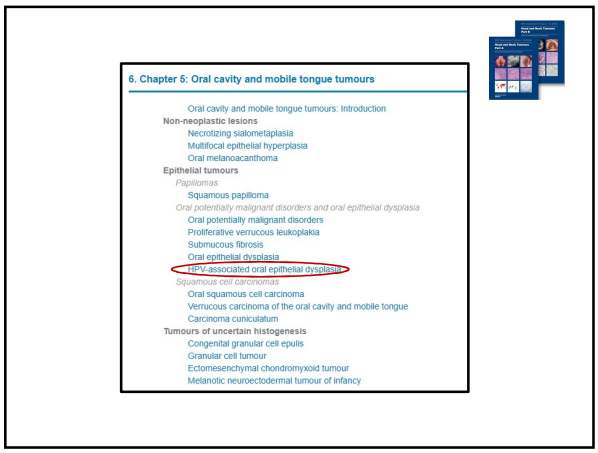
"Tumor cells are POSITIVE for High Risk Human Papilloma Virus (HPV subtypes 16,18,26,31,33,35,39,45,51,52,53,56,58,59,66,68,73 and 82) by RNAScope HPV HR18 assay. "

The assay was performed on formalin-fixed paraffin-embedded tissue using Leica BOND III System utilizing the Bond RNAscope Detection Kit at City of Hope. RNAscope® 2.5 LS Probe-HPV-HR18 includes HPV 16,18,26,31,33,35,39,45,51,52,53,56,58,59,66,68,73 and 82, E6/E7 mRNA probes. Appropriate positive and negative controls were employed and are acceptable. In case of uncertainty, the results may be marked as equivocal, and the test may be repeated on the same or alternative specimen from the patient.

Transcriptionally active HPV in HN cancer

Outside the oropharynx:

- Rare (except sinonasal tract)
- Prognostic significance unclear
- Routine testing NOT recommended
- If done, p16 alone is NOT sufficient



WHO 2022 New Entity

HPV-associated oral epithelial dysplasia (HPVOED)

Definition

- characterized by distinctive viral cytopathic changes caused by transcriptionally active high-risk HPV with a risk of progression to SCC.

Localization

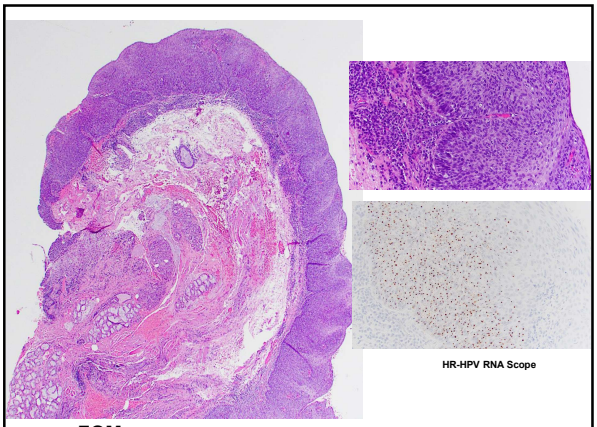
- Most commonest sites: ventral/ lateral tongue and FOM; buccal mucosa.

Diagnostic molecular pathology

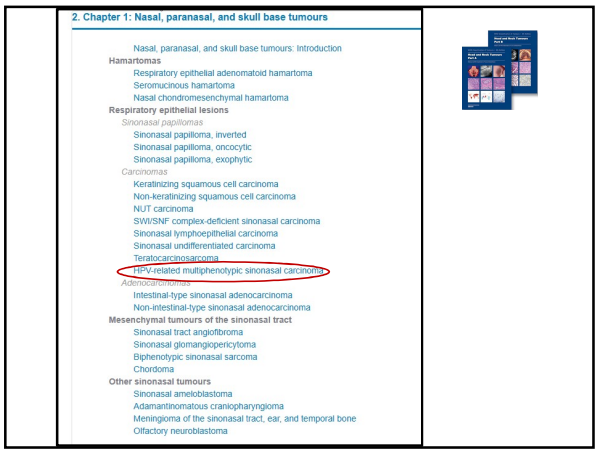
- p16 IHC expression in the presence of OED with viral cytopathic changes should be supported by testing for high-risk HPV by RNA ISH.

Prognosis and prediction

- development of invasive SCC occurs in 5% to 15% of cases.



FOM



HPV-related sinonasal carcinomas

- **Usually non-keratinizing**
- **One variant encounter only in the sinonasal tract:**
  HPV-related Multiphenotypic Sinonasal Carcinoma

WHO 2022 New Entity

HPV-related Multiphenotypic Sinonasal Carcinoma (HMSC)

~~Basaloid Squamous~~ Carcinoma with Adenoid-like Cystic Features

aka

HPV-related carcinoma with adenoid cystic-like features

Definition

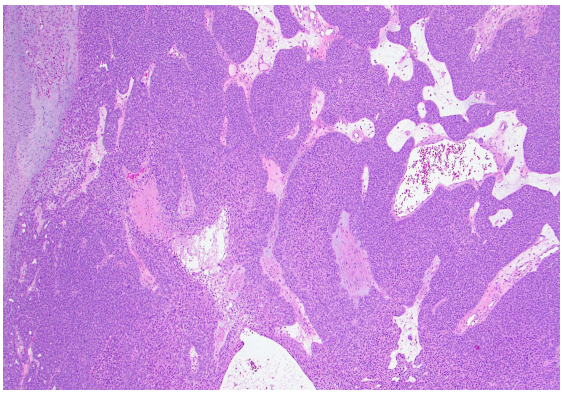
A distinctive HPV-related carcinoma of the sinonasal tract with histologic and immunophenotypic features of both surface-derived and salivary gland carcinoma.

Etiology:

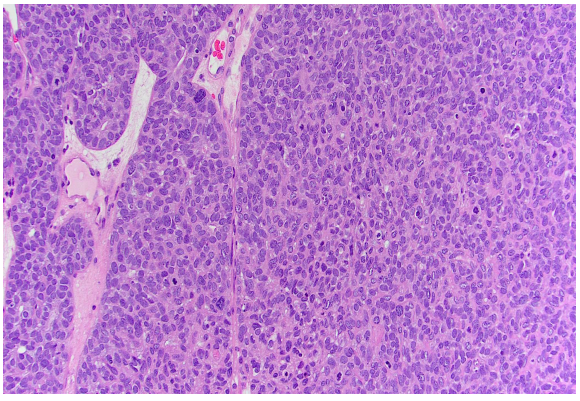
- **HPV type 33; and occasionally types 35, 16, 52, 56, or 82**

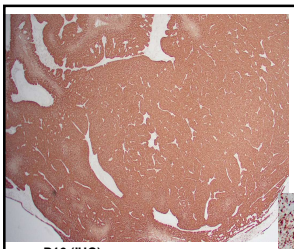
Localization:

- **in the nasal cavity and/or paranasal sinuses (ethmoid, maxillary sinus, sphenoid) with occasional secondary extension into the orbit.**

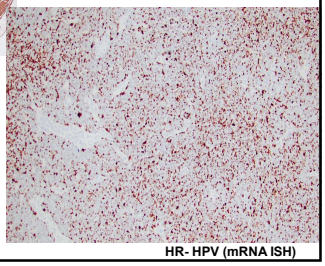


"Nasal Polyp"





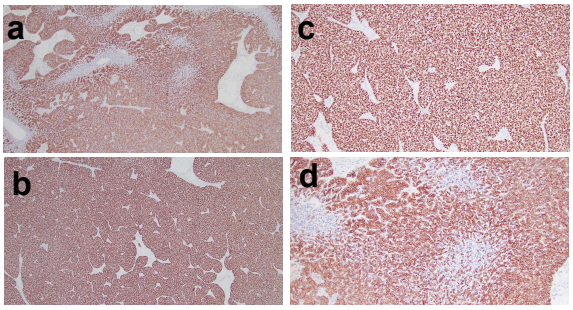
P16 (IHC)



HR- HPV (mRNA ISH)

Squamous phenotype
a. CK5/6
b. p40

Myoepithelial phenotype
c. SOX10
d. Calponin



NGS: no MYB, MYBL1, NFIB events

Dgn: HMSC

Morphologic Spectrum of HPV-associated Sinonasal Carcinomas (HPV E6/7 ISH assay)

- Nonkeratinizing squamous cell carcinoma
- Multiphenotypic sinonasal carcinoma
- Sinonasal adenocarcinoma/ adenosquamous carcinoma