Updates on HPV-Related Head and Neck Carcinomas

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Disclosures

- I have no relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *Commonalities and differences amongst individuals in this population.*
- *Factors that determine the type and level of care this population receives.*

Updates on HPV- Related Head and Neck Carcinomas

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Head and Neck Section

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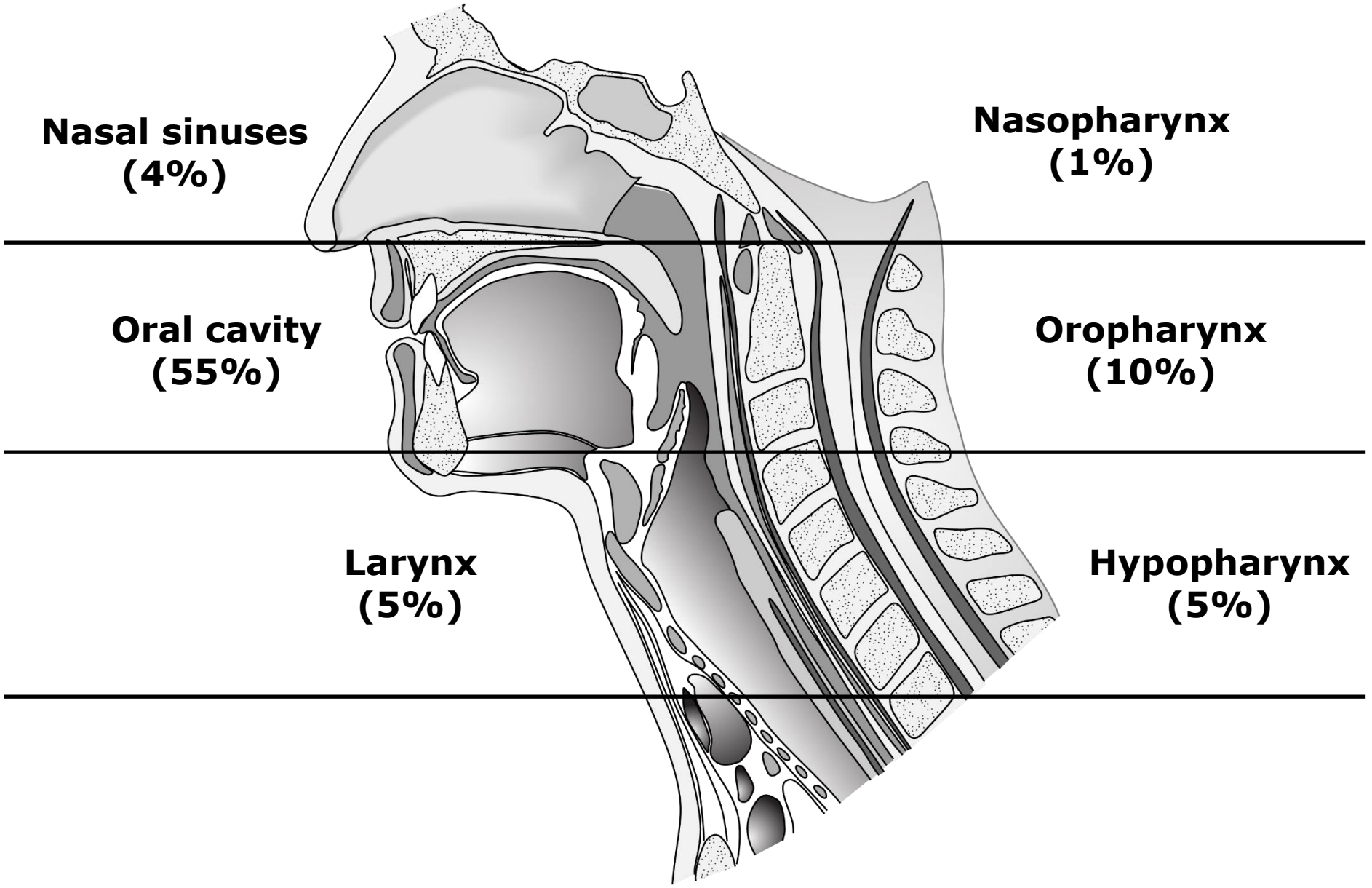
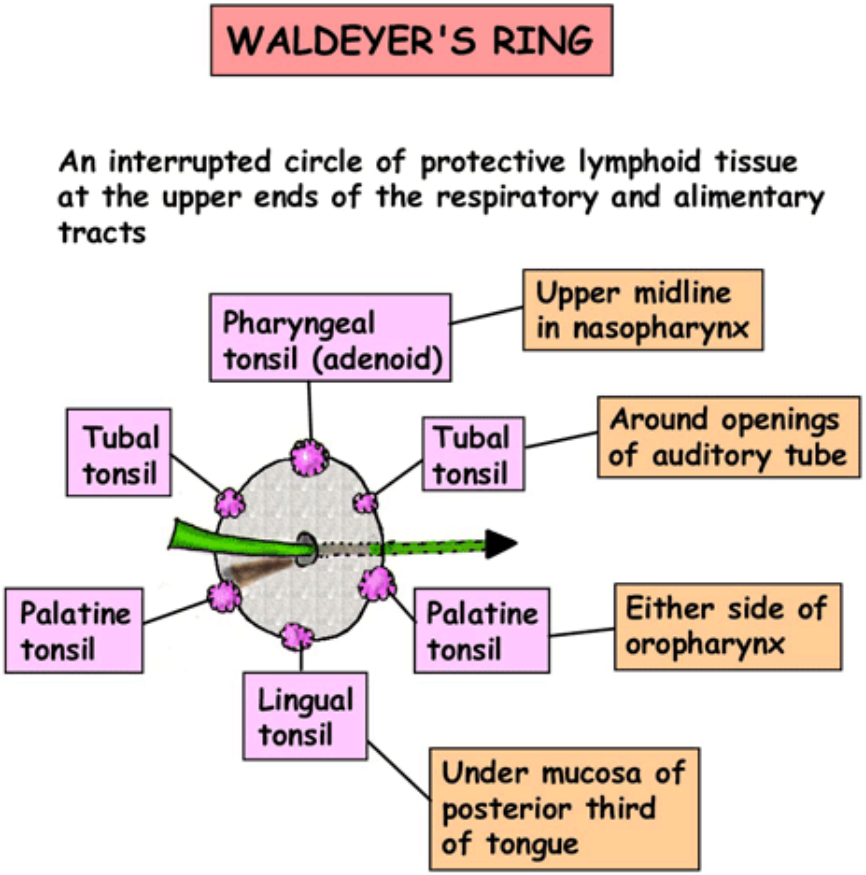

Nasal sinuses
(4%)
Nasopharynx
(1%)
Oral cavity
(55%)
Oropharynx
(10%)
Larynx
(5%)
Hypopharynx
(5%)

Oropharyngeal Mucosal Sites

- ## Pharyngeal tonsil :
  - In the middle on the roof of nasopharynx
  - Respiratory epithelium with patches of squamous epithelium
  - Numerous folds of pharyngeal epithelium, not true crypts

- ## Palatine tonsil:
  - Paired at oropharynx
  - Stratified squamous nonkeratinizing epithelium
  - 10-30 deep and sometimes branching crypts (polycryptic)

- ## Lingual tonsil:
  - Posterior third of tongue
  - Stratified squamous nonkeratinizing epithelium
  - Multiple monocryptic units with a single shallow crypt each



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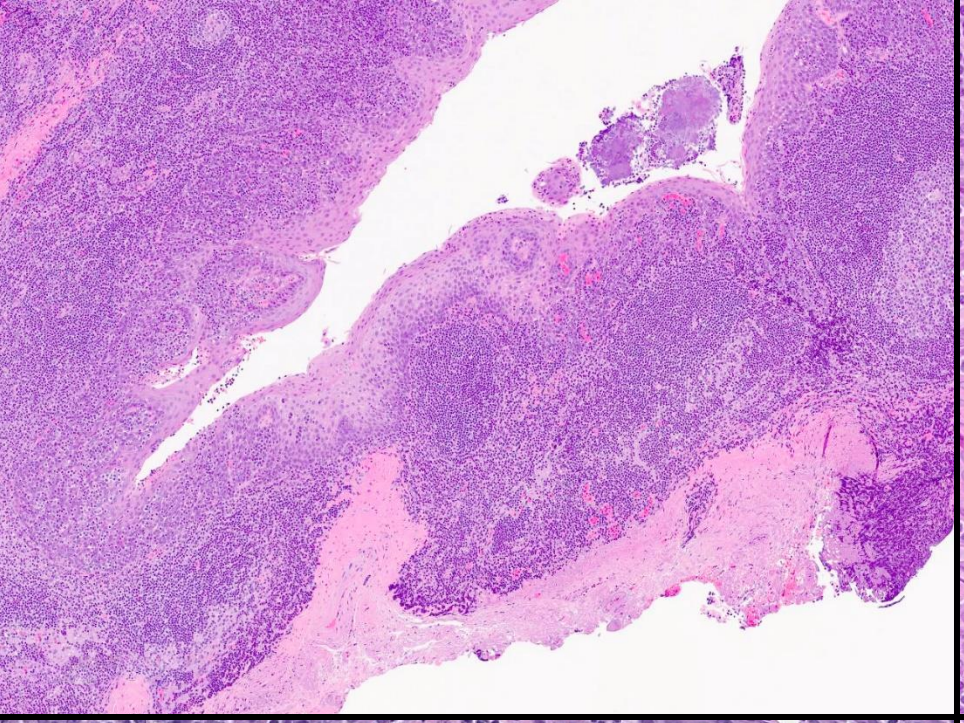
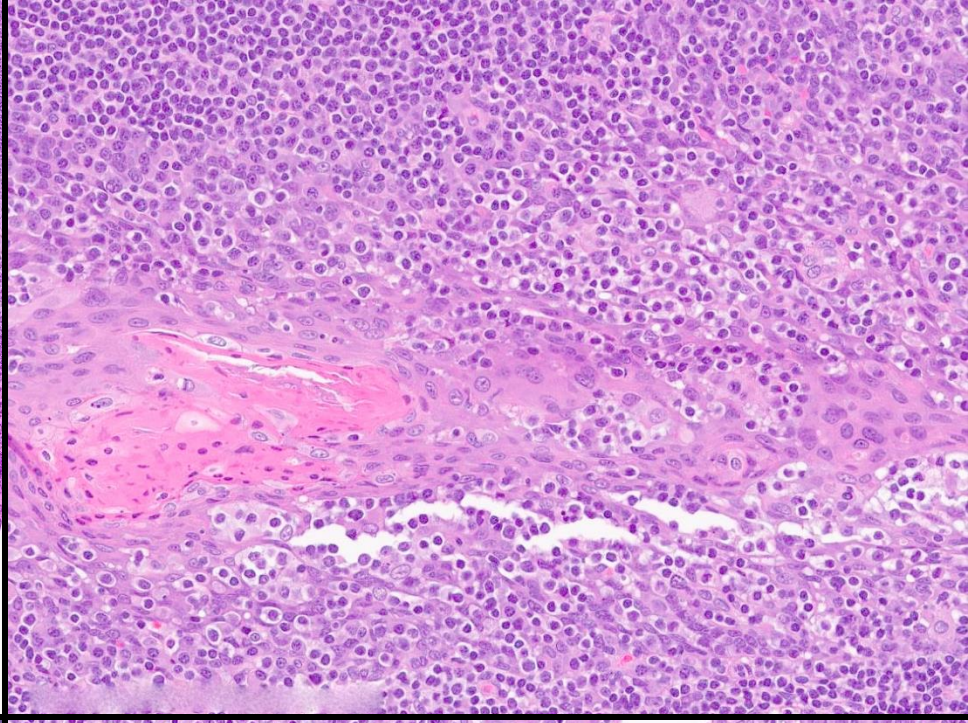
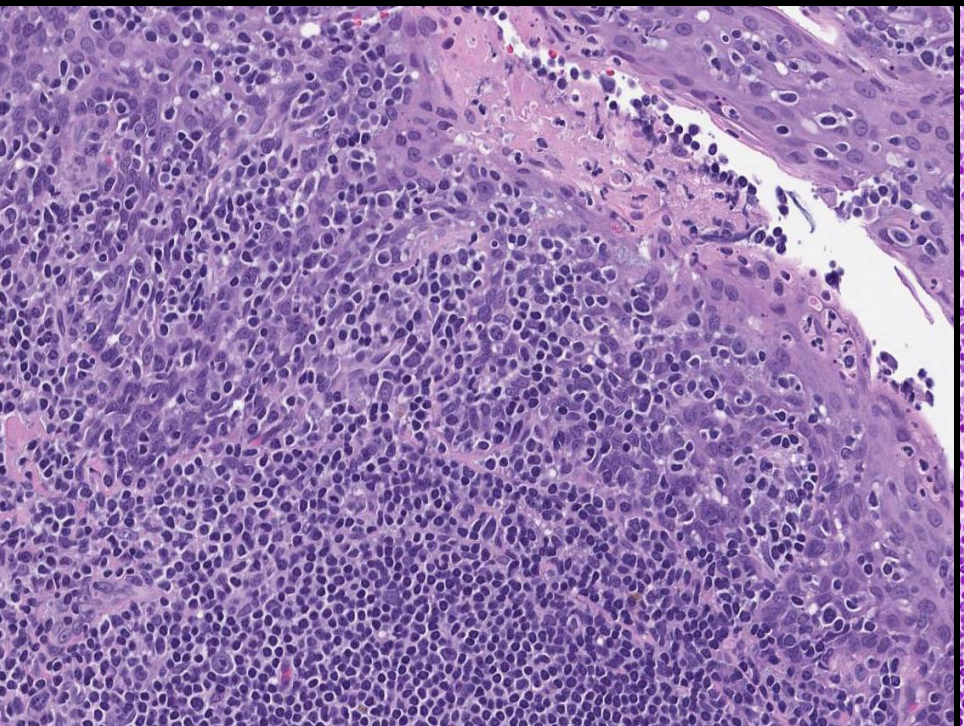
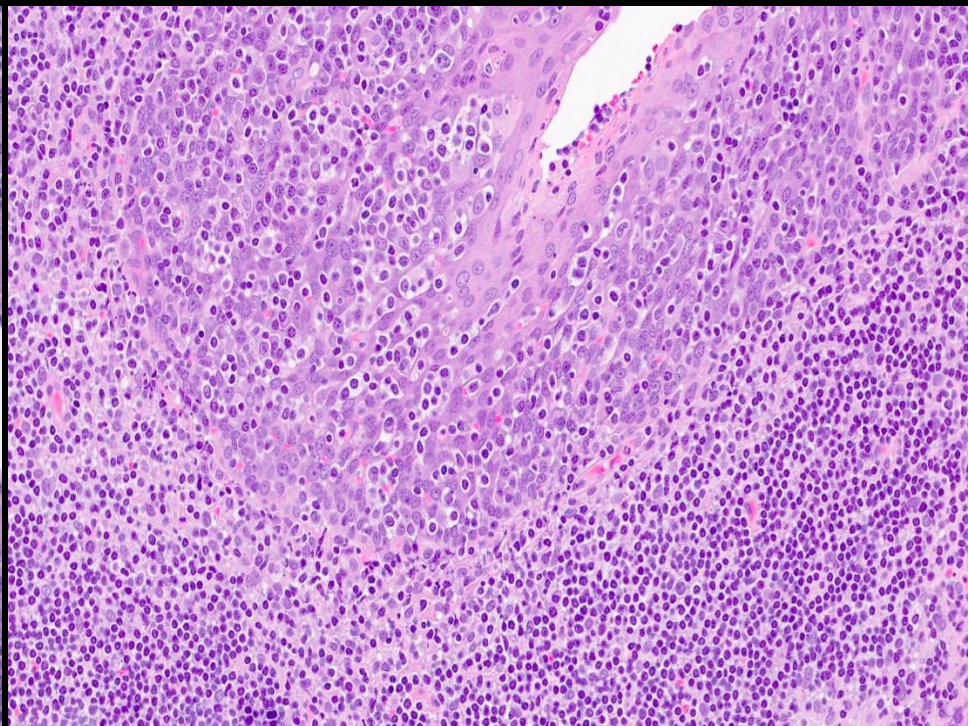
Microscopic Features of Lingual and Palatine Tonsils

- **Unique morphology with reticulated epithelium lining the tonsilar crypts**
- **Stratified squamous epithelium covering the surfaces extends into the recesses of tonsilar crypts**
- **A dense lymphoid infiltrate obscures the junction between the lymphoid and epithelial components, and splinters the epithelial sheath into irregular cords and nests**
- **These cords and nests no longer polarized, with basaloid appearance, and loss of distinctive cytoplasmic borders.**

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)

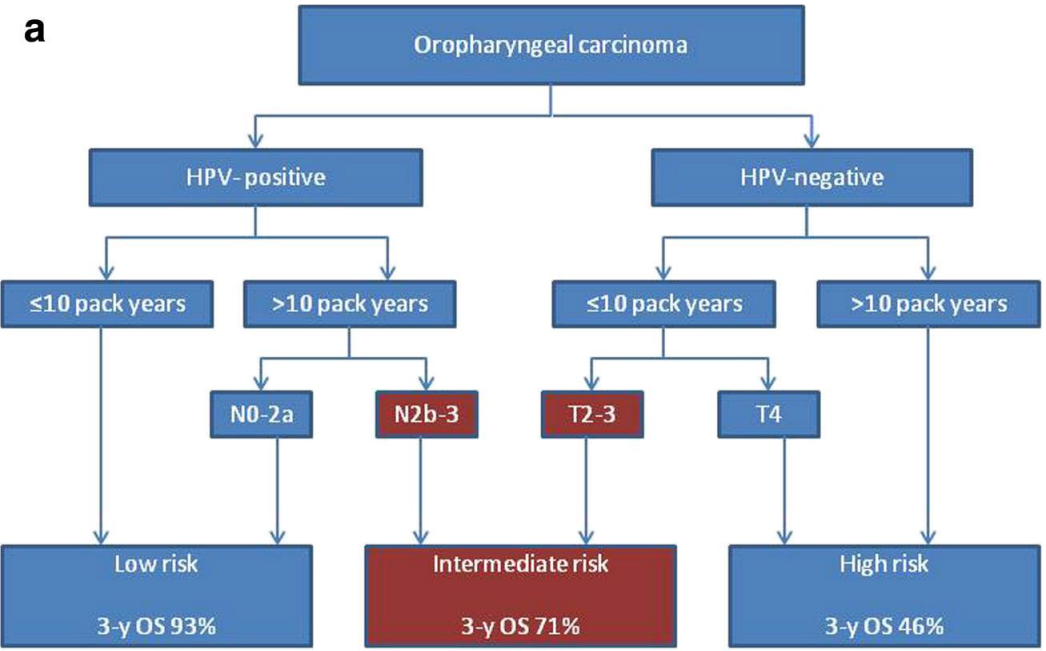
Recurrent or metastatic disease (IVC)- salvage re-XRT or surgery and combined chemo; palliative systemic therapy; EXTREME trial cetuximab+cisplatin+5FU

Patient selection for de-intensification for locally advanced HPV-OPC

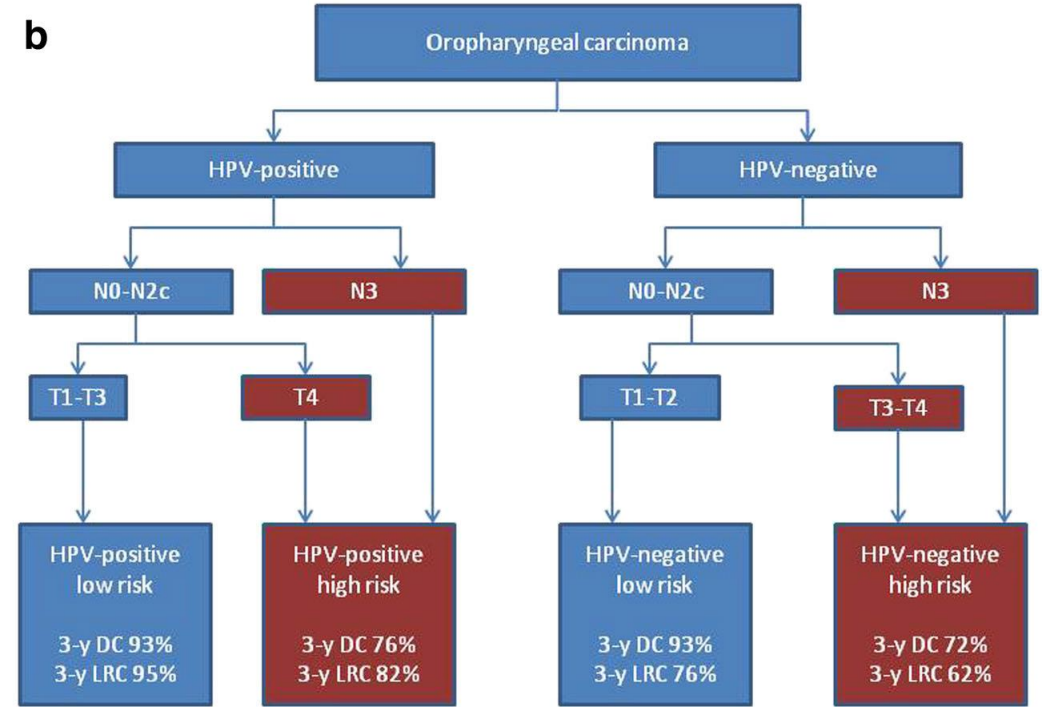
- **Reduction of XRT dose or reduction of cytotoxic chemo.**
- **Appropriate selection of patients.**
- **Ang et al (RTOG-0129) identified prognostic factors most influential on survival (HPV status, smoking history, tumor stage).**

Risk classification for oropharynx cancer according to HPV status (*Ang et al.* RTOG-0129) :

a. Overall survival (OS)



b. Distant and locoregional control



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**

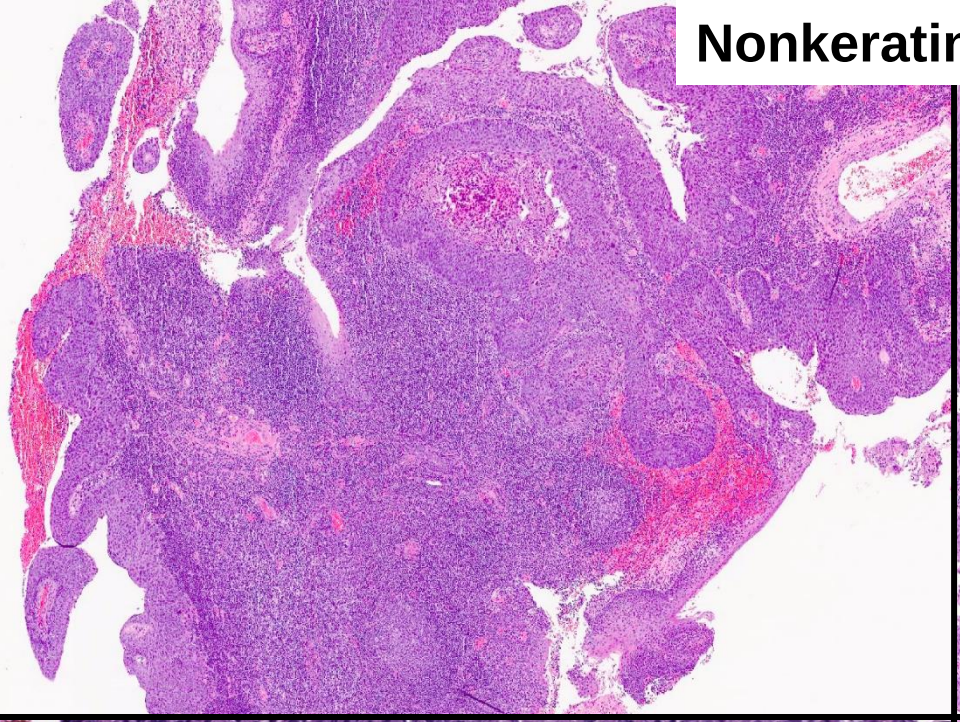
Microscopic Features of HPV-HNSCC

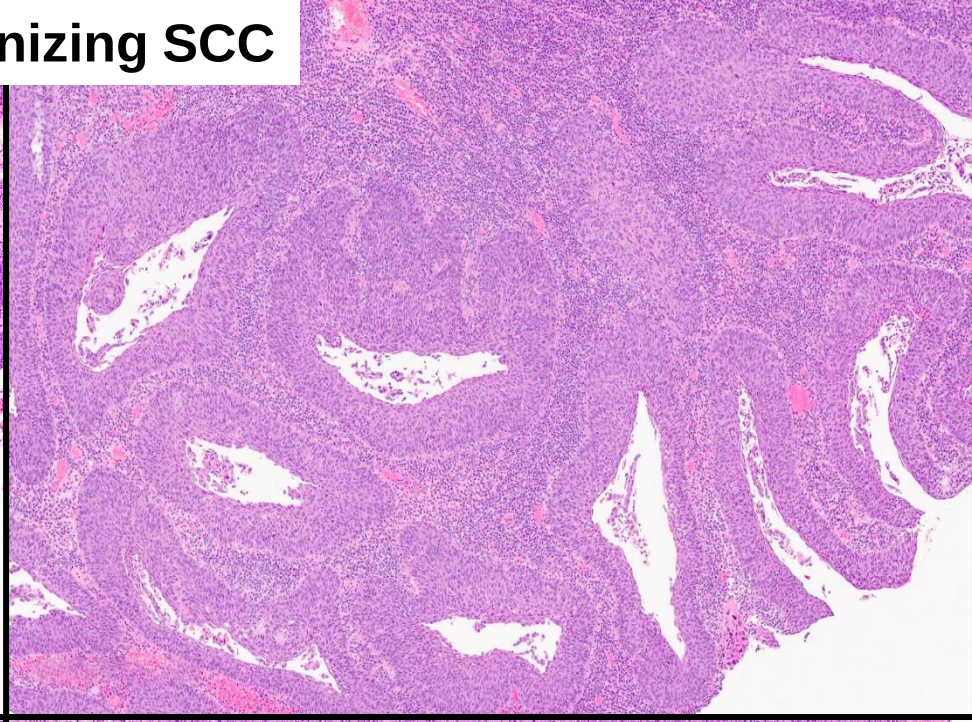
- **The histologic features of reticulated epithelium are retained, to varying degrees.**
- **Involvement of tonsilar surface (when occurs) is a secondary spillover from the tonsilar cypts.**
- **The transition between HPV-HNSCC and adjacent surface epithelium is abrupt, without precursor lesions.**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

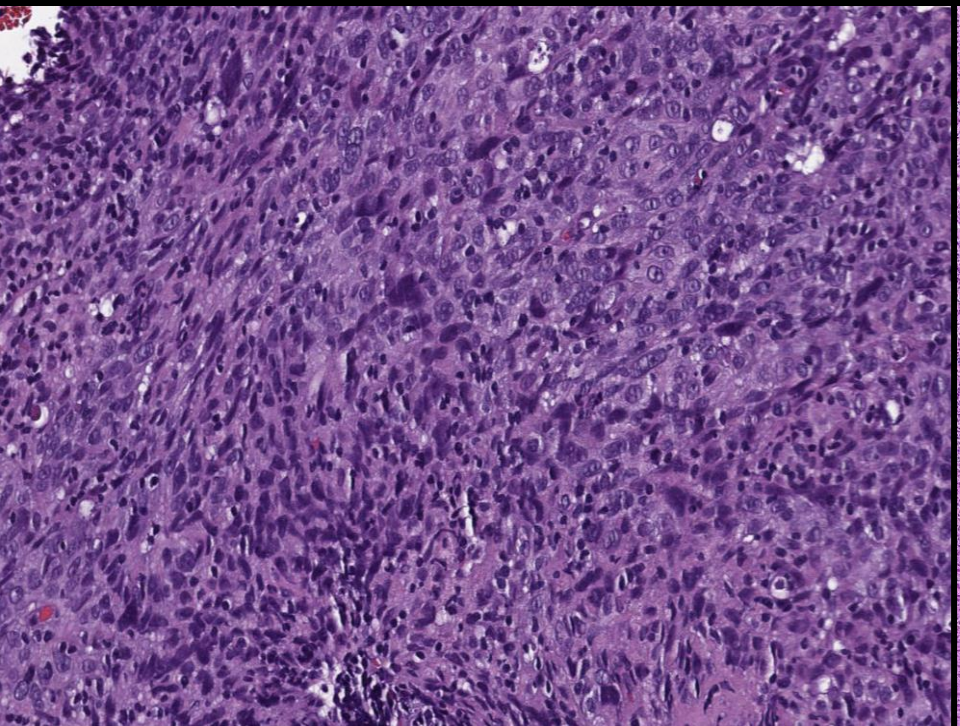
Microscopic Features of HPV-HNSCC (cont)

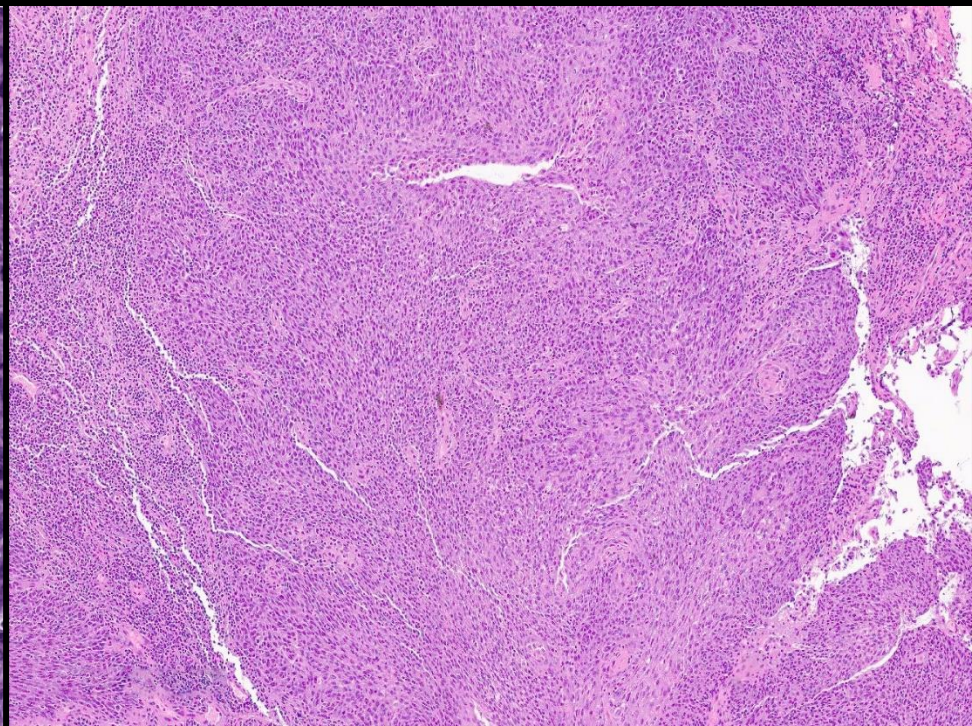
- Tumor nests associated with lymphoid cells (TILS)
- "Lymphoepithelial appearance"
- Cytology: syncytial, basaloid appearance
- LN metastasis: cystic degeneration, mistaken for branchial cleft cysts

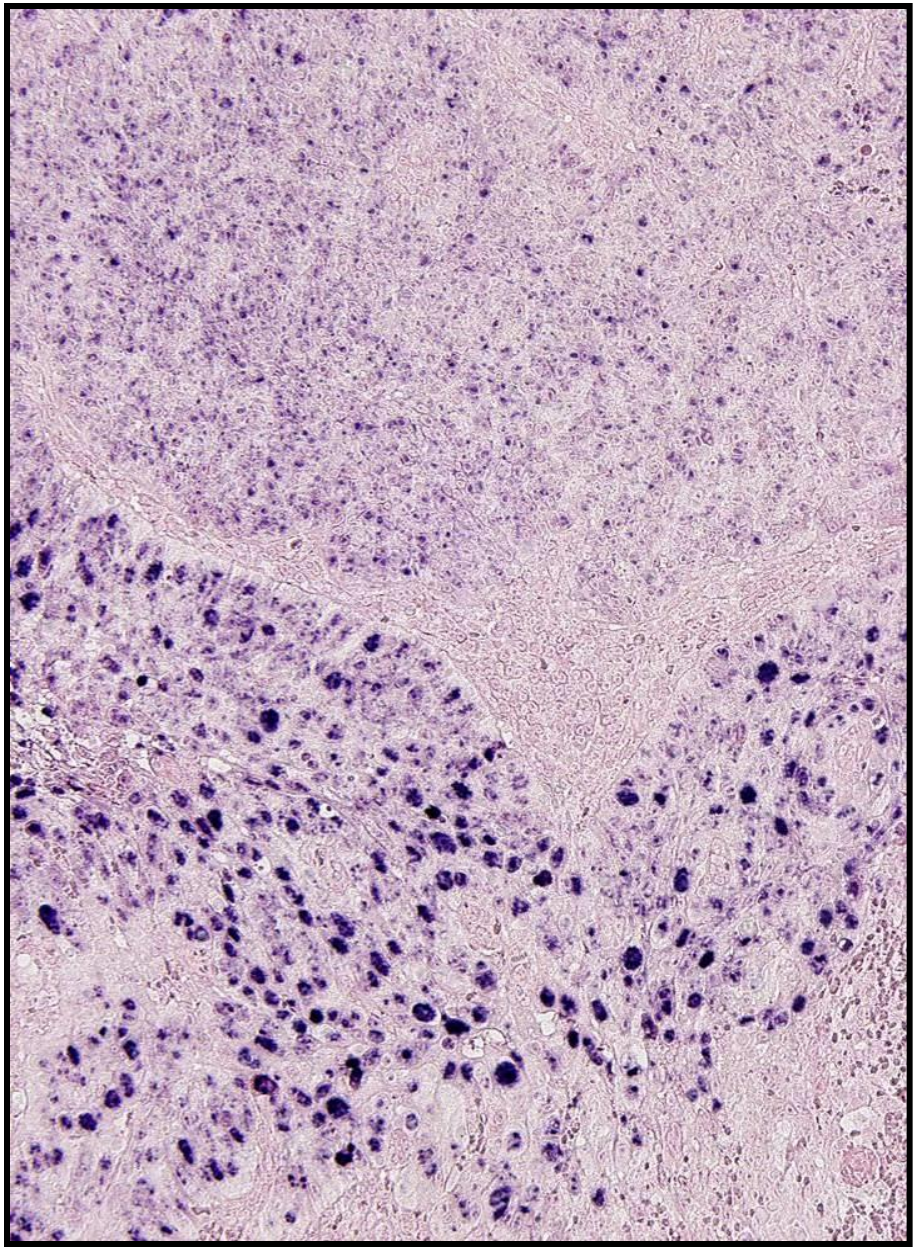
Nonkeratinizing SCC



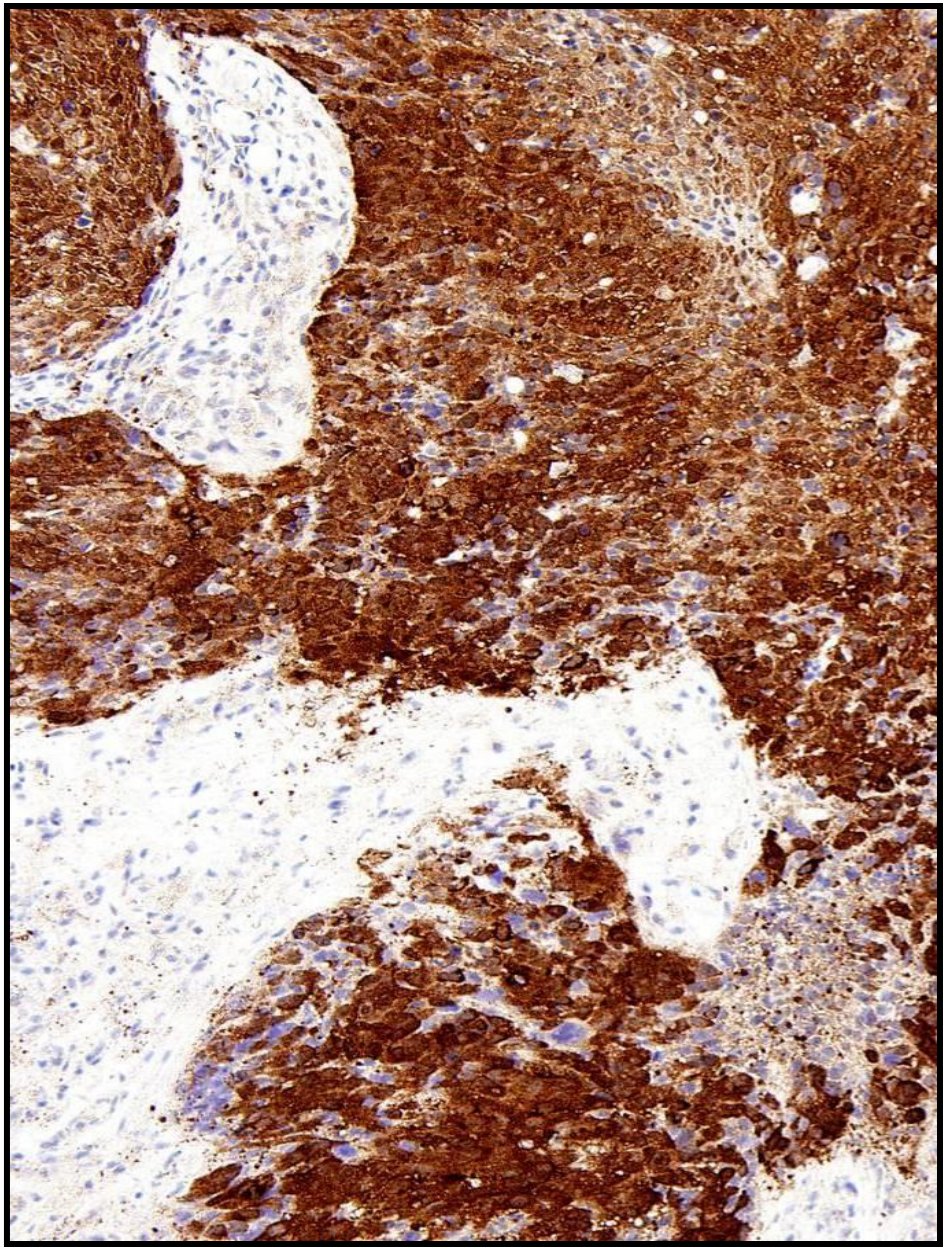






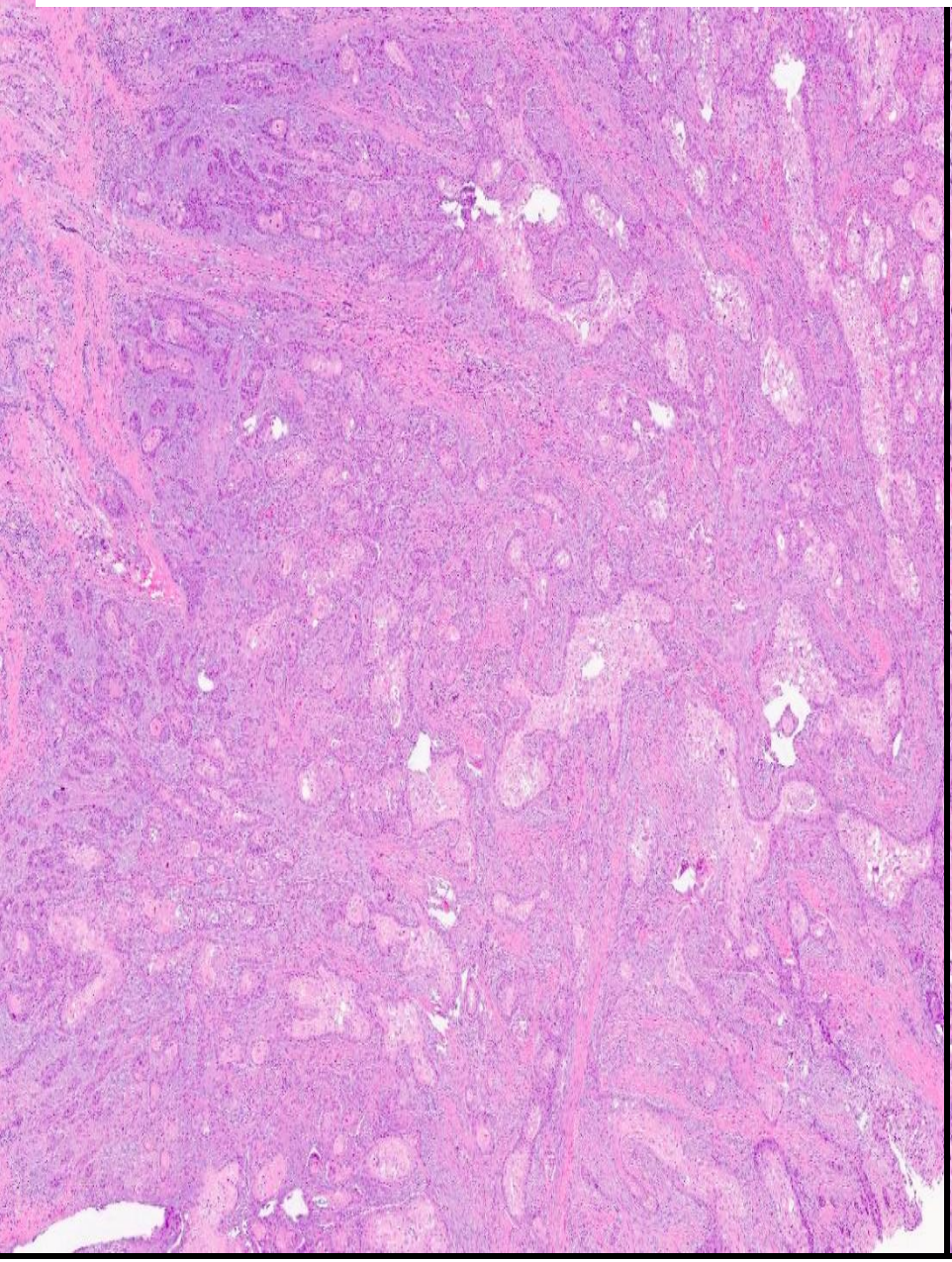


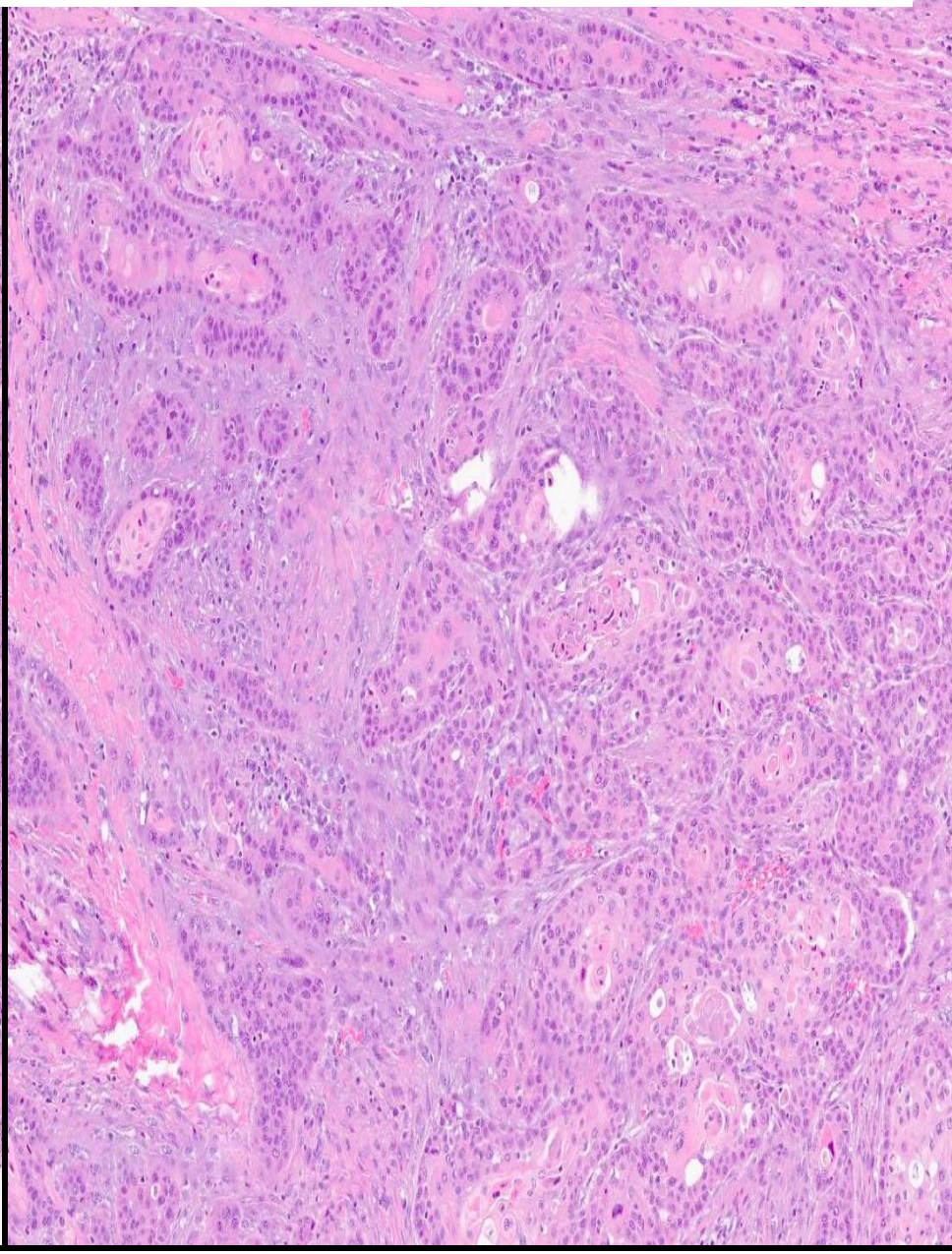
HR-HPV



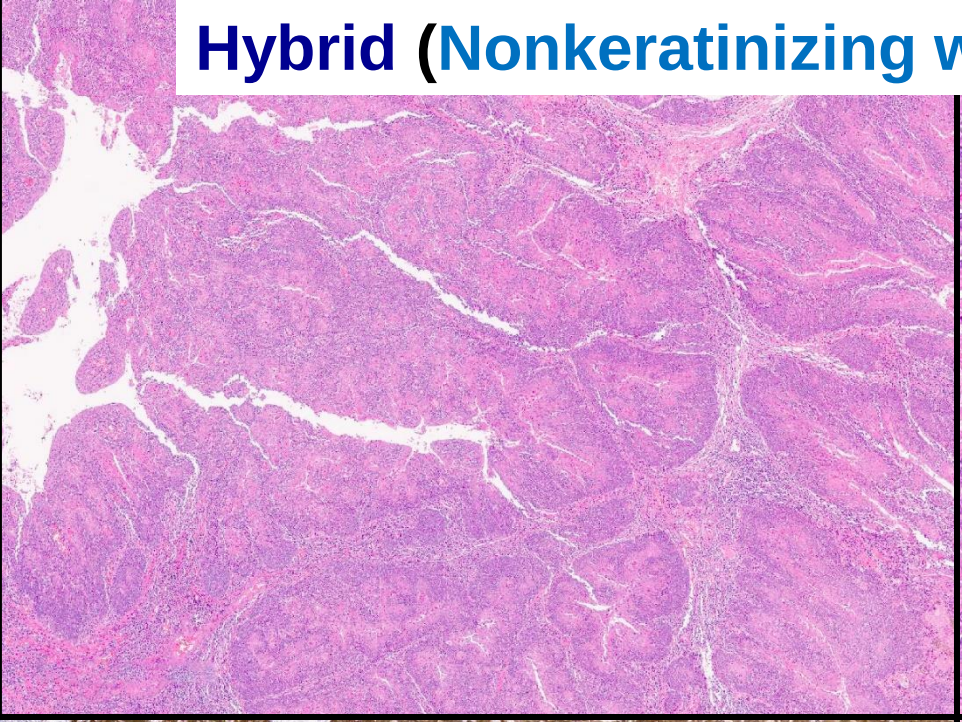
p16

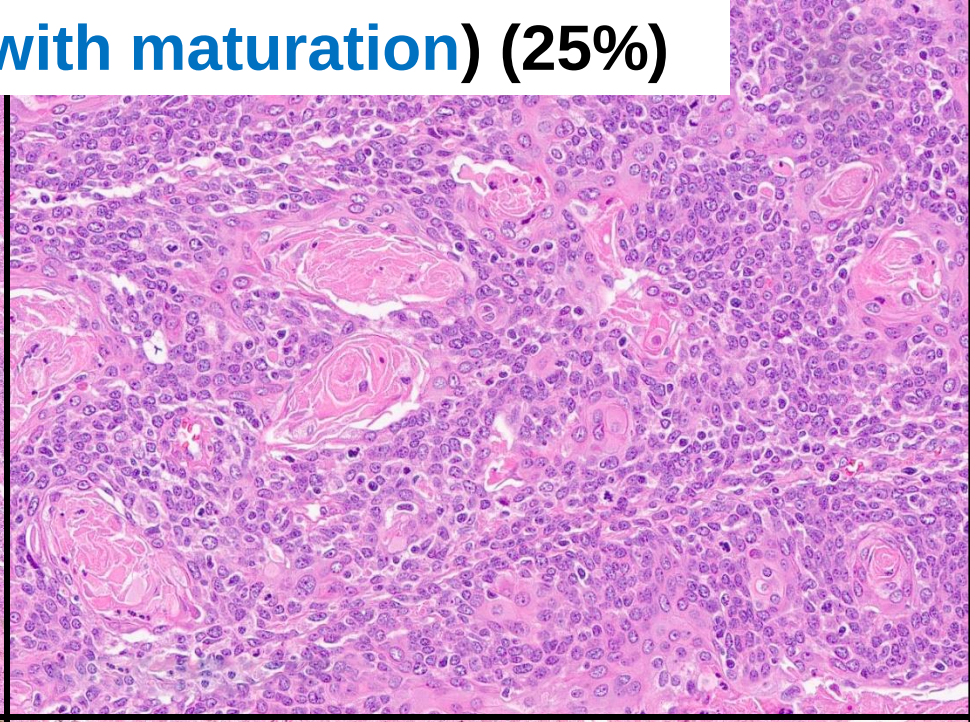
Non-HPV oropharyngeal SCC- keratinizing, with desmoplasia (25%)

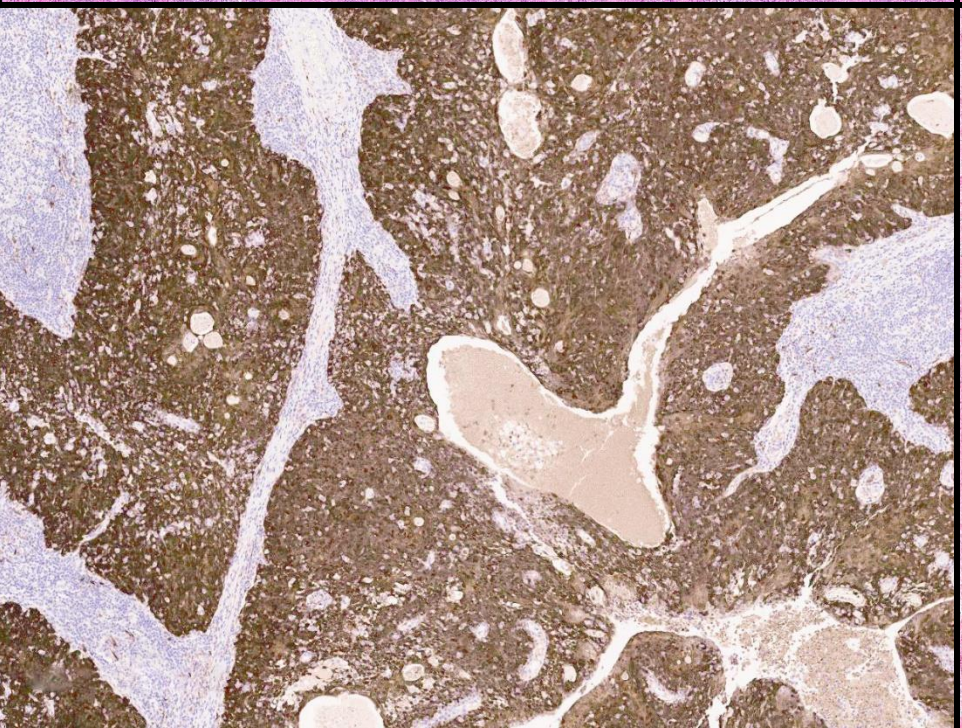


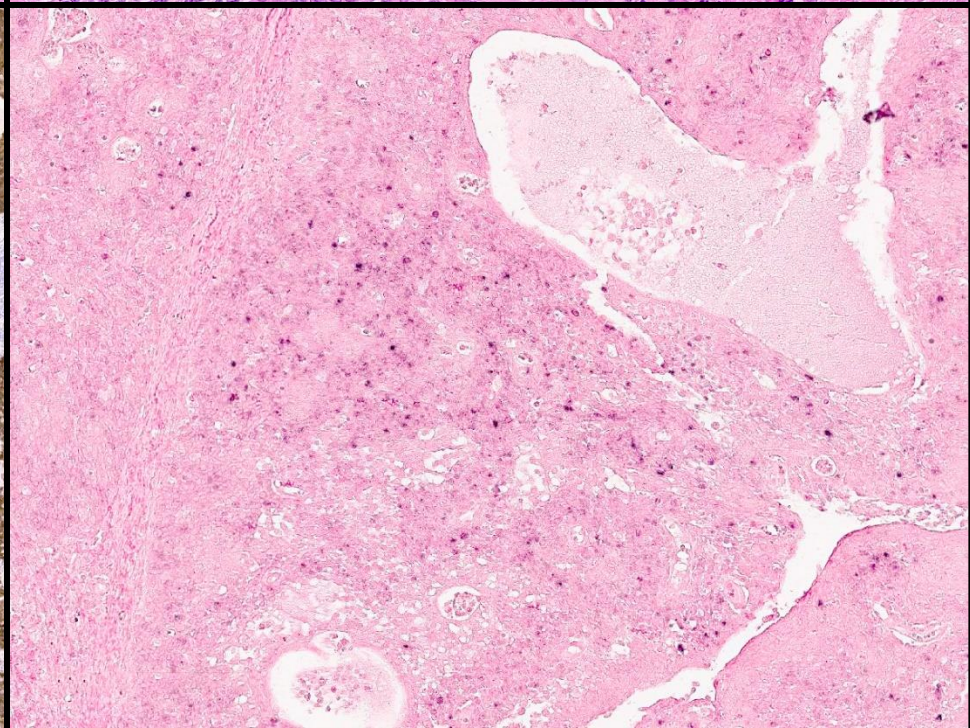


Hybrid (Nonkeratinizing with maturation) (25%)

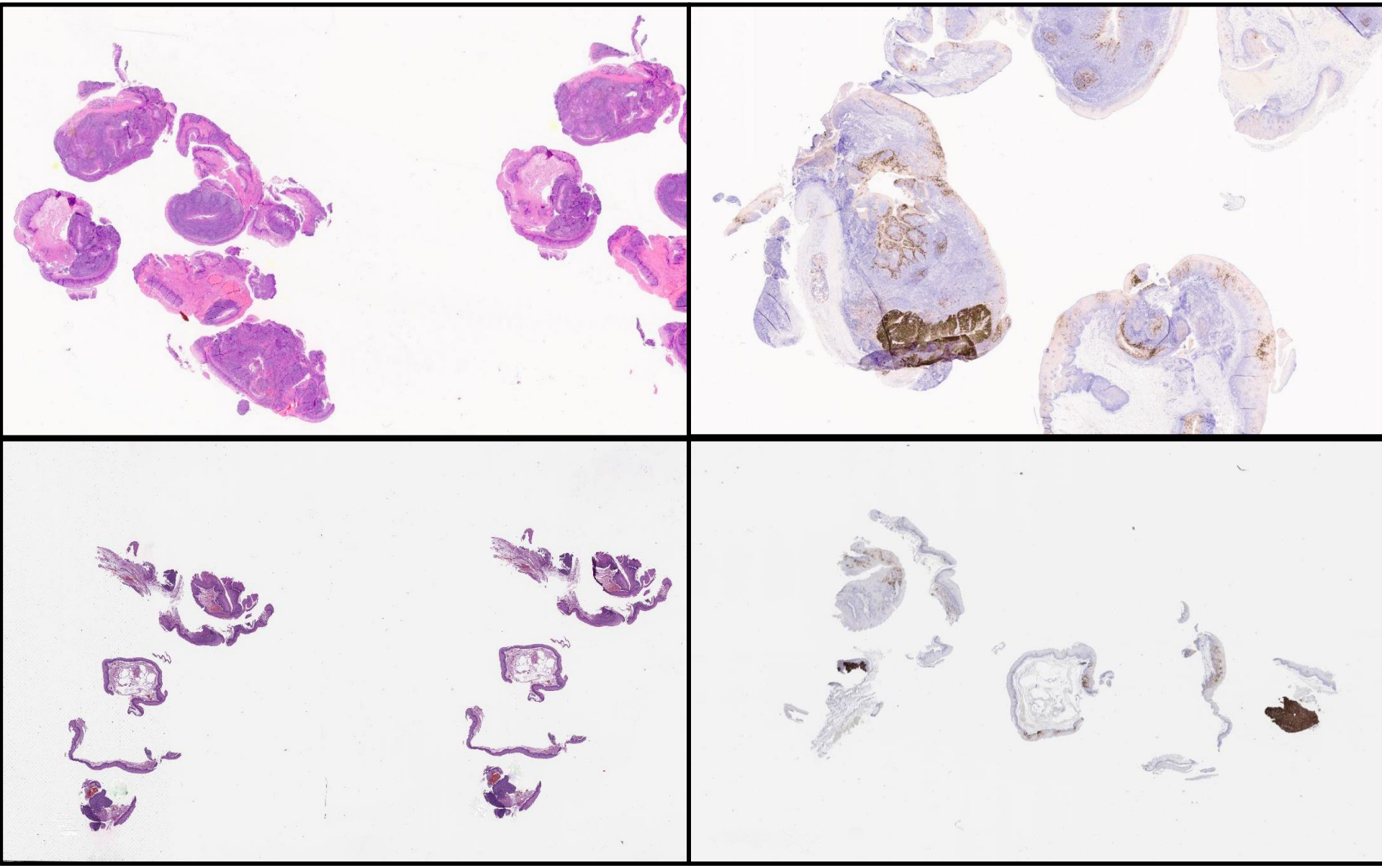


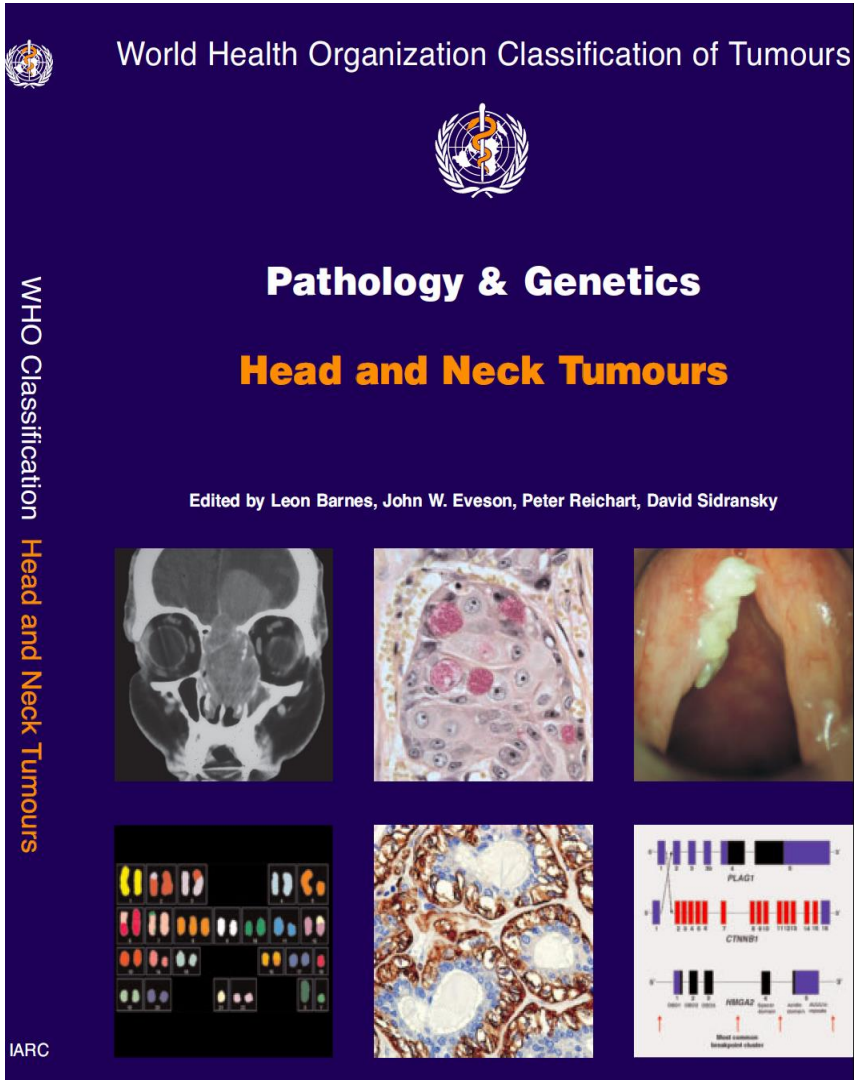




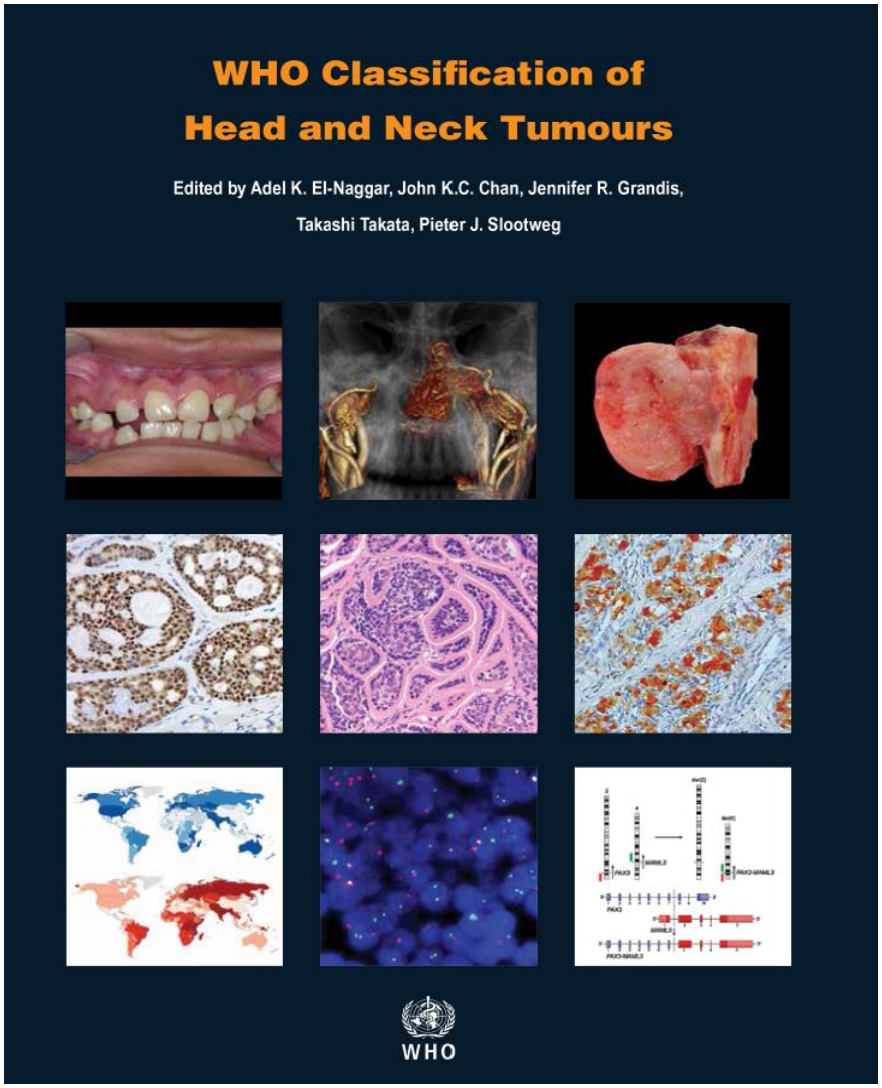


HPV-OPC: Small T1, Bulky LN mets (N2b,c)





2005 WHO 3



2016 WHO 4

2005

WHO classification of tumours of the oral cavity and oropharynx

Malignant epithelial tumours	
Squamous cell carcinoma	8070/3
Verrucous carcinoma	8051/3
Basaloid squamous cell carcinoma	8083/3
Papillary squamous cell carcinoma	8052/3
Spindle cell carcinoma	8074/3
Acantholytic squamous cell carcinoma	8075/3
Adenosquamous carcinoma	8560/3
Carcinoma cuniculatum	8051/3
Lymphoepithelial carcinoma	8082/3
Epithelial precursor lesions	
Benign epithelial tumours	
Papillomas	8050/0
Squamous cell papilloma and verruca vulgaris	
Condyloma acuminatum	
Focal epithelial hyperplasia	
Granular cell tumour	9580/0
Keratoacanthoma	8071/1
Salivary gland tumours	
Salivary gland carcinomas	
Acinic cell carcinoma	8550/3
Mucoepidermoid carcinoma	8430/3
Adenoid cystic carcinoma	8200/3
Polymorphous low-grade adenocarcinoma	8525/3
Basal cell adenocarcinoma	8147/3
Epithelial–myoepithelial carcinoma	8562/3
Clear cell carcinoma, not otherwise specified	8310/3
Cystadenocarcinoma	8450/3
Mucinous adenocarcinoma	8480/3
Oncocytic carcinoma	8290/3
Salivary duct carcinoma	8500/3
Myoepithelial carcinoma	8982/3
Carcinoma ex pleomorphic adenoma	8941/3
Salivary gland adenomas	
Pleomorphic adenoma	8940/0
Myoepithelioma	8982/0
Basal cell adenoma	8147/0
Canalicular adenoma	8146/0
Duct papilloma	8503/0
Cystadenoma	9440/0
Soft tissue tumours	
Kaposi sarcoma	
Lymphangioma	
Ectomesenchymal chondromyxoid tumour	
Focal oral mucinosis	
Congenital granular cell epulis	
Haematolymphoid tumours	
Diffuse large B-cell lymphoma (DLBCL)	9680/3
Mantle cell lymphoma	9673/3
Follicular lymphoma	9690/3
Extranodal marginal zone B-cell lymphoma of MALT type	9699/3
Burkitt lymphoma	9687/3
T-cell lymphoma (including anaplastic large cell lymphoma	9714/3
Extramedullary plasmacytoma	9[illegible]
Langerhans cell histiocytosis	9[illegible]
Extramedullary myeloid sarcoma	
Follicular dendritic cell sarcoma / tumour	9[illegible]
Mucosal malignant melanoma	8720/3
Secondary tumours	

[1] Morphology code of the International Classification of Diseases for Oncology (ICD-O) (WHO) and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.

2016

WHO classification of tumours of the oropharynx (base of tongue, tonsils, adenoids)

Squamous cell carcinoma, HPV positive	8085/3
Squamous cell carcinoma, HPV negative	8070/3
Squamous cell carcinoma, (non-keratinizing)	8072/3
Pleomorphic adenoma	8940/0
Adenoid cystic carcinoma	8200/3
Polymorphous adenocarcinoma	8525/3
Haematolymphoid neoplasms	
Hodgkin lymphoma, nodular lymphocyte predominant	9659/3
Classical Hodgkin lymphoma	
Nodular sclerosis classical Hodgkin lymphoma	9663/3
Mixed cellularity classical Hodgkin lymphoma	9652/3
Lymphocyte-rich classical Hodgkin lymphoma	9651/3
Lymphocyte-depleted classical Hodgkin lymphoma	9653/3
Burkitt lymphoma	9687/3
Follicular lymphoma	9690/3
Mantle cell lymphoma	9673/3
T-lymphoblastic lymphoma / leukaemia	9837/3
Follicular dendritic sarcoma	9758/3

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) (742A). Behaviour is coded /0 for benign tumours, /1 for unspecified, borderline, or uncertain behaviour, /2 for carcinoma in situ and grade III intraepithelial neoplasia, and /3 for malignant tumours. The classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions. *These new codes were approved by the IARC/WHO Committee for ICD-O. *Italics*: Provisional tumour entities. **Grading according to the 2013 *WHO Classification of Tumours of Soft Tissue and Bone*.

WHO classification of the tumours of the oral cavity and mobile tongue

Squamous cell carcinoma	8070/3
Oral epithelial dysplasia	
Low grade	8077/0
High grade	8077/2
Proliferative verrucous leukoplakia	
Condyloma acuminatum	
Verruca vulgaris	
Focal epithelial hyperplasia	
Congenital granular cell epulis	
Soft tissue myoepithelioma	8982/0
Granular cell tumour	9580/0
Rhabdomyoma	8900/0
Lymphangioma	9170/0
Haemangioma	9120/0
Schwannoma	9560/0
Neurofibroma	9540/0
Kaposi sarcoma	9140/3
Oral mucosal melanoma	8720/3
Mucoepidermoid carcinoma	8430/3
Pleomorphic adenoma	8940/0
Haematolymphoid tumours	
CD30 positive T-cell lymphoproliferative disorder	9718/3
Plasmablastic lymphoma	9735/3
Langerhans cell histiocytosis	9751/3

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Oropharynx is a separate chapter in the WHO 4

2016

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Oropharyngeal SCCs are sub-classified by HPV status in the WHO 4 edition

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**
- **Adenocarcinoma**
- **Sarcomatoid**

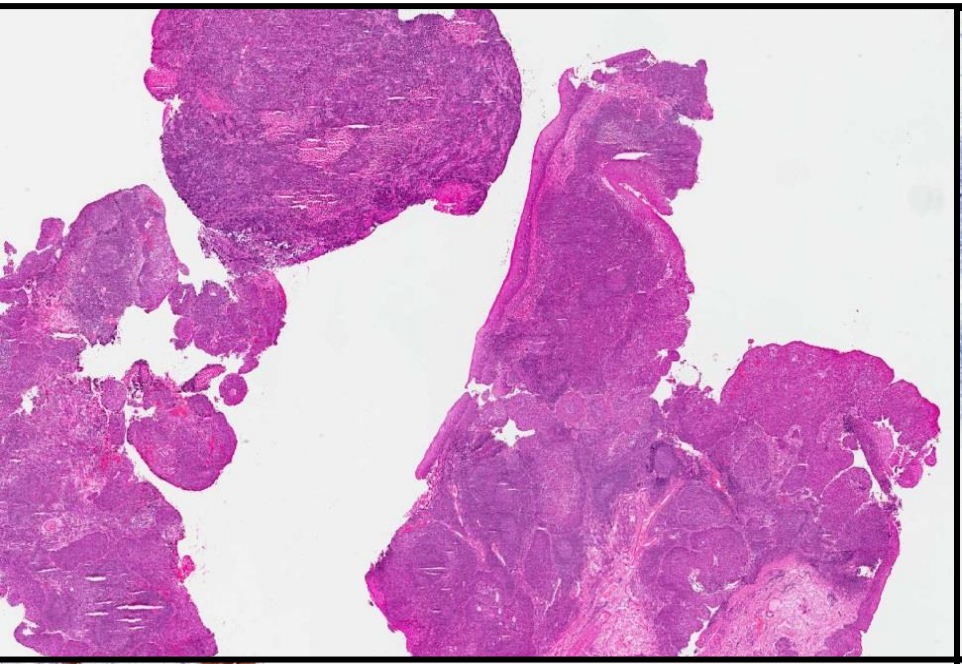
- **Neuroendocrine carcinoma- NEC variants of OPC HPV+ are aggressive**

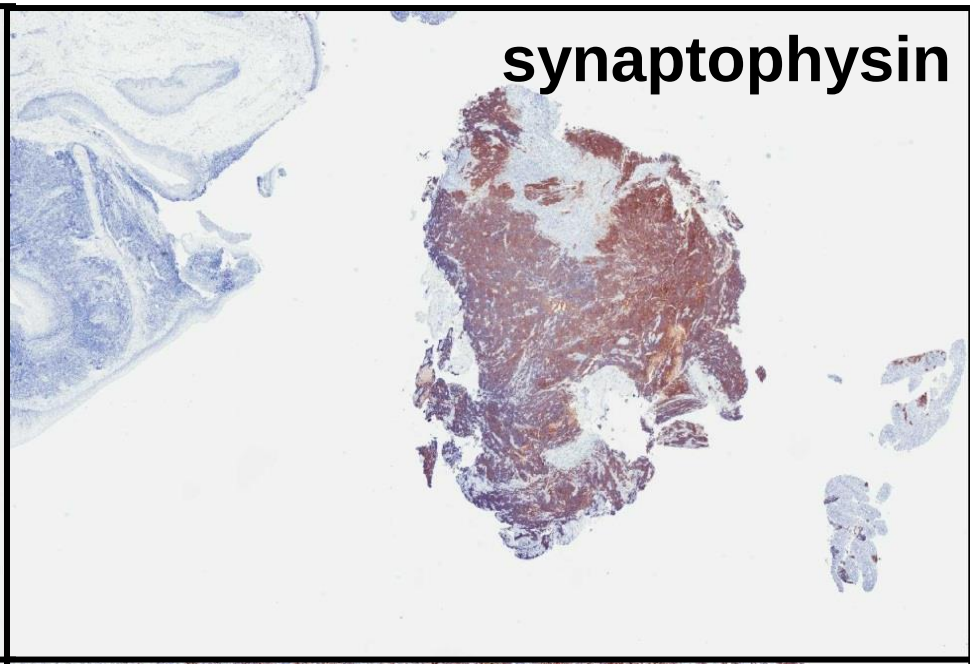
  Small cell NEC
  Large cell NEC

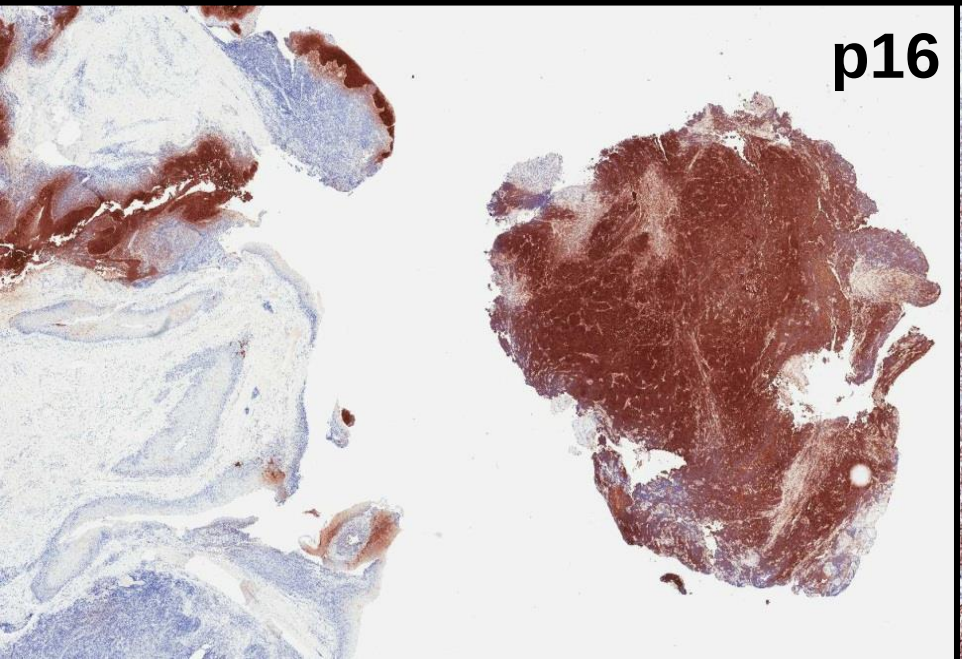
HPV and Small Cell Phenotype

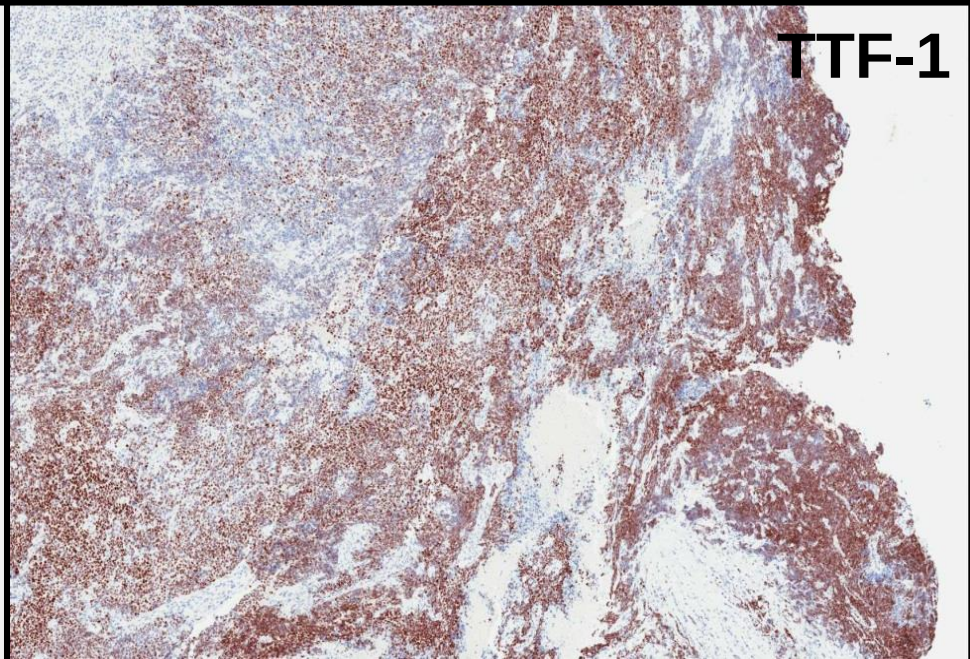
- **Exception from the subset of HPV related carcinomas with favorable prognosis**
- **Small cell carcinoma histology, associated with more conventional squamous carcinoma**
- **HPV detected in both components**
- **Share the same aggressive clinical course (like gyn, lung) with distant metastasis and poor outcome**

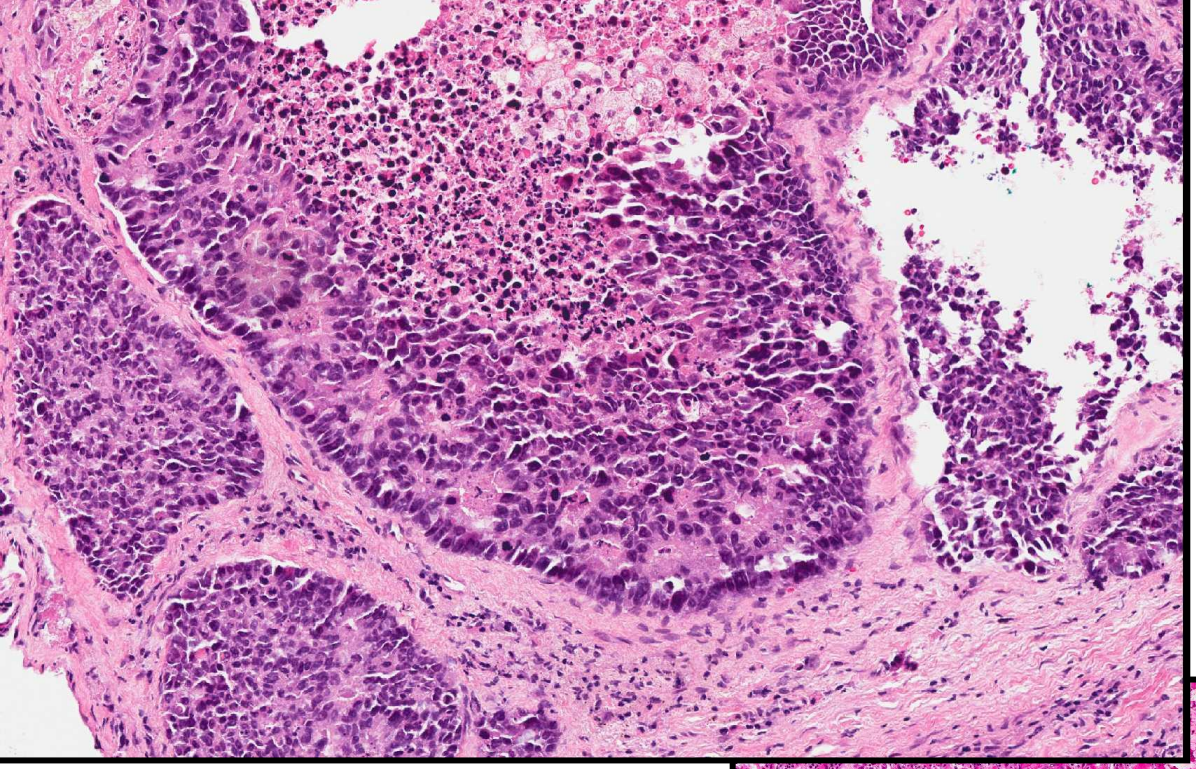
Tonsil with a squamous and neuroendocrine component



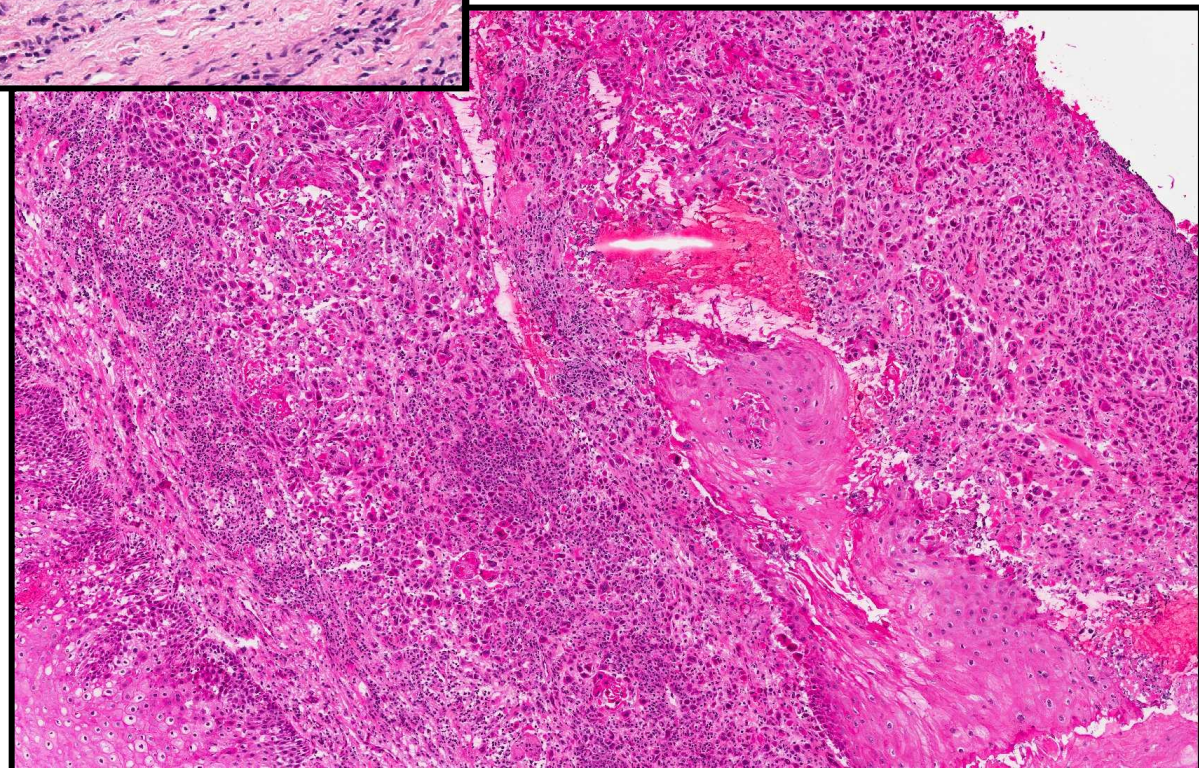








NEC (L BOT)



SCC (epiglottis)

HPV Testing

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

When to test for HPV

- **ALL oropharyngeal SCC and variants**
- **Cervical LN mets of unknown primary**
- **NOT non-oropharyngeal ENT sites (routinely)**

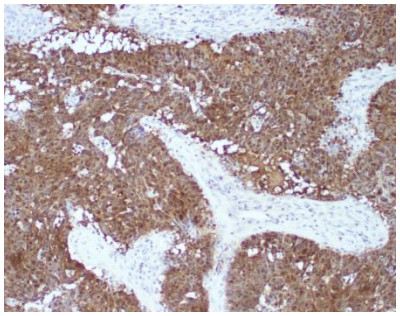
How to test for HPV?

- **High-risk types only**

- **Methods:**
  - **P16 IHC**
  - **PCR for HPV DNA**
  - **PCR for HPV E6/E7 mRNA**
  - **DNA ISH**
  - **RNA ISH**
  - **Combinations/ algorithms**

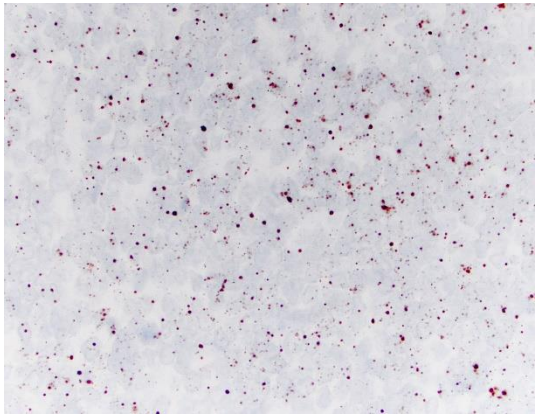
p16 IHC

widely available, easy to perform and interpret
highly sensititive
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**

World Health Organization

Head and Neck tumours

2022 WHO 5

5.0: Oral cavity and mobile tongue

5.0.0.1: Introduction

5.1.0: Non-neoplastic lesions

5.1.0.0: Necrotising sialometaplasia
5.1.1.4: Multifocal epithelial hyperplasia
5.2.0.4: Oral melanoacanthoma

5.1: Epithelial tumours

5.1.1: Papillomas
- 5.1.1.1: Squamous papillomas

5.1.2: Oral potentially malignant disorders & oral epithelial dysplasia
- 5.1.2.0: Oral potentially malignant disorders
- 5.1.2.3: Oral epithelial dysplasia
- 5.1.2.1: Proliferative verrucous leukoplakia
- 5.1.2.2: Submucous fibrosis
- 5.1.2.4: HPV-associated oral epithelial dysplasia

5.1.3: Squamous cell carcinomas
- 5.1.3.1: Oral squamous cell carcinoma
- 5.1.3.2: Verrucous carcinoma
- 5.1.3.3: Carcinoma cuniculatum

5.2: Tumours of uncertain histogenesis

- 5.2.0.1: Congenital granular cell epulis
- 8.0.8.3: Granular cell tumour
- 5.2.0.2: Ectomesenchymal chondromyxoid tumour
- 7.5.1.3: Melanotic neuroectodermal tumour of infancy

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

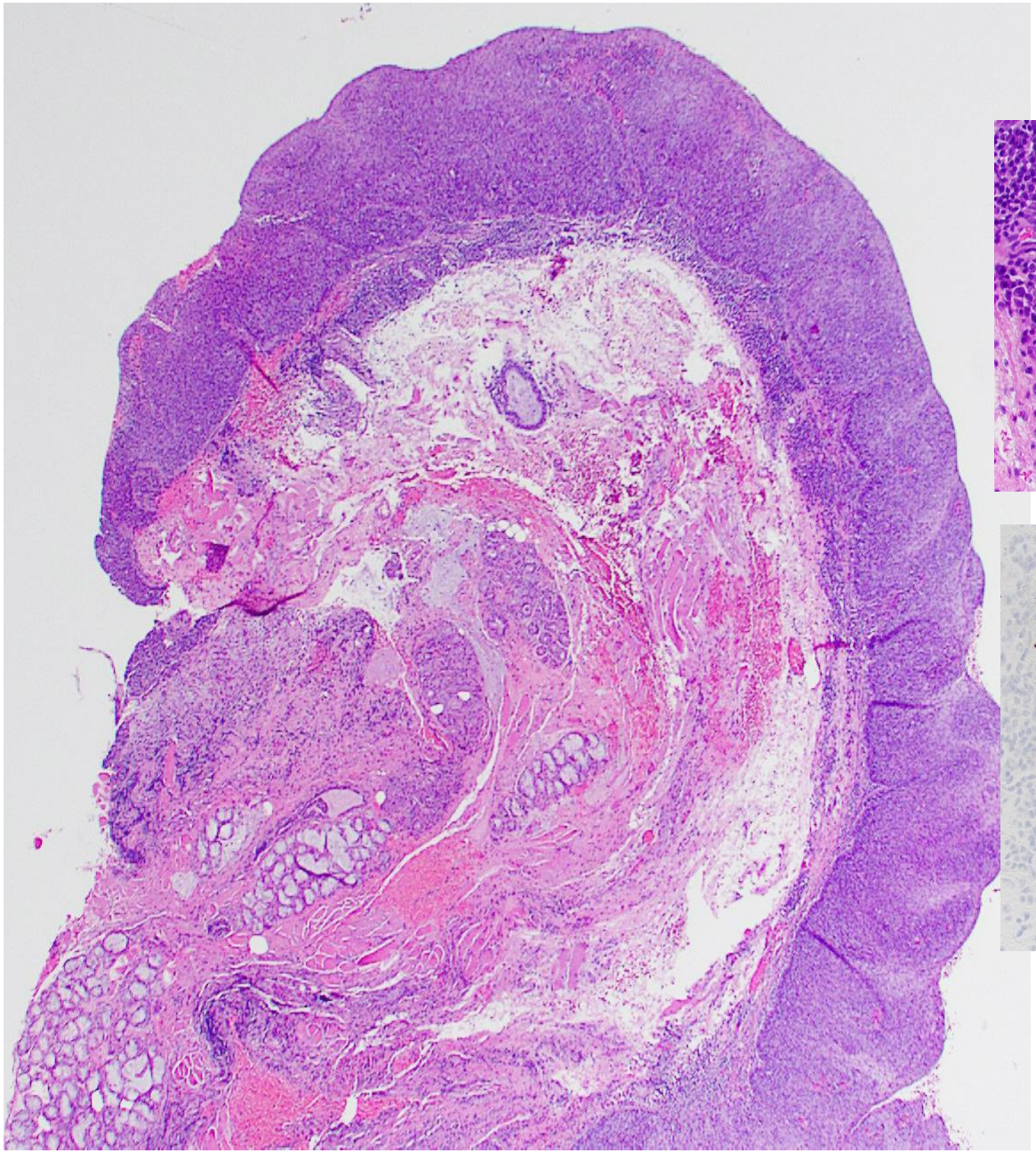
- Most commonest sites: ventral/ lateral tongue and FOM; buccal mucosa.

Diagnostic molecular pathology

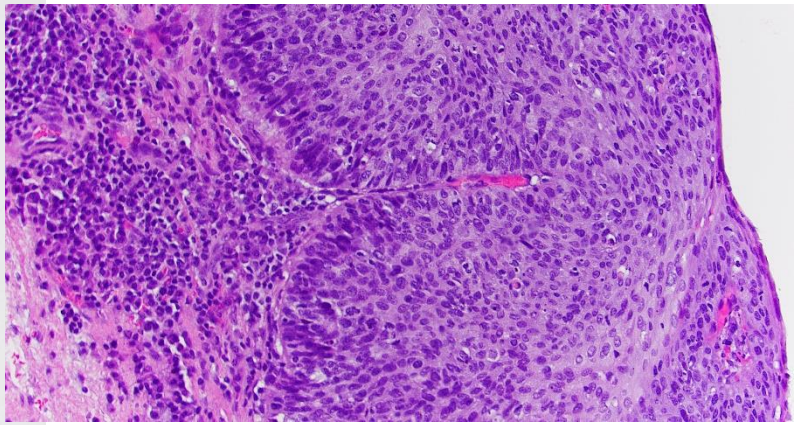
- p16 IHC expression in the presence of OED with viral cytopathic changes should be supported by testing for high-risk HPV by RNA ISH.

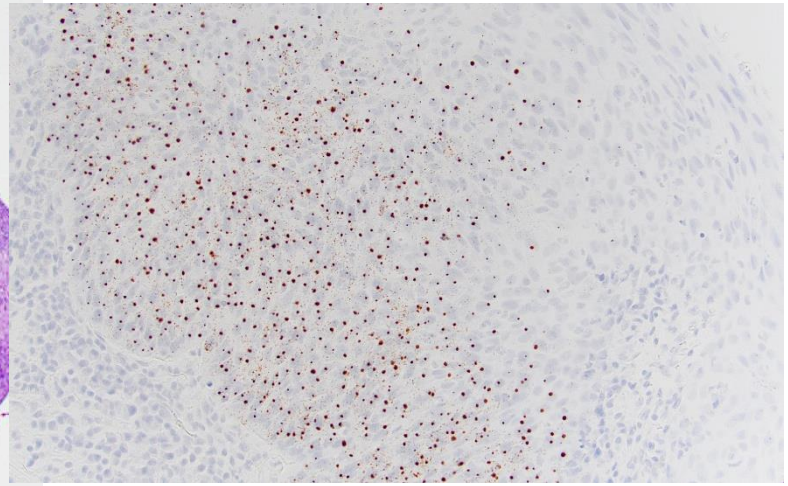
Prognosis and prediction

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



FOM





HR-HPV RNA Scope

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

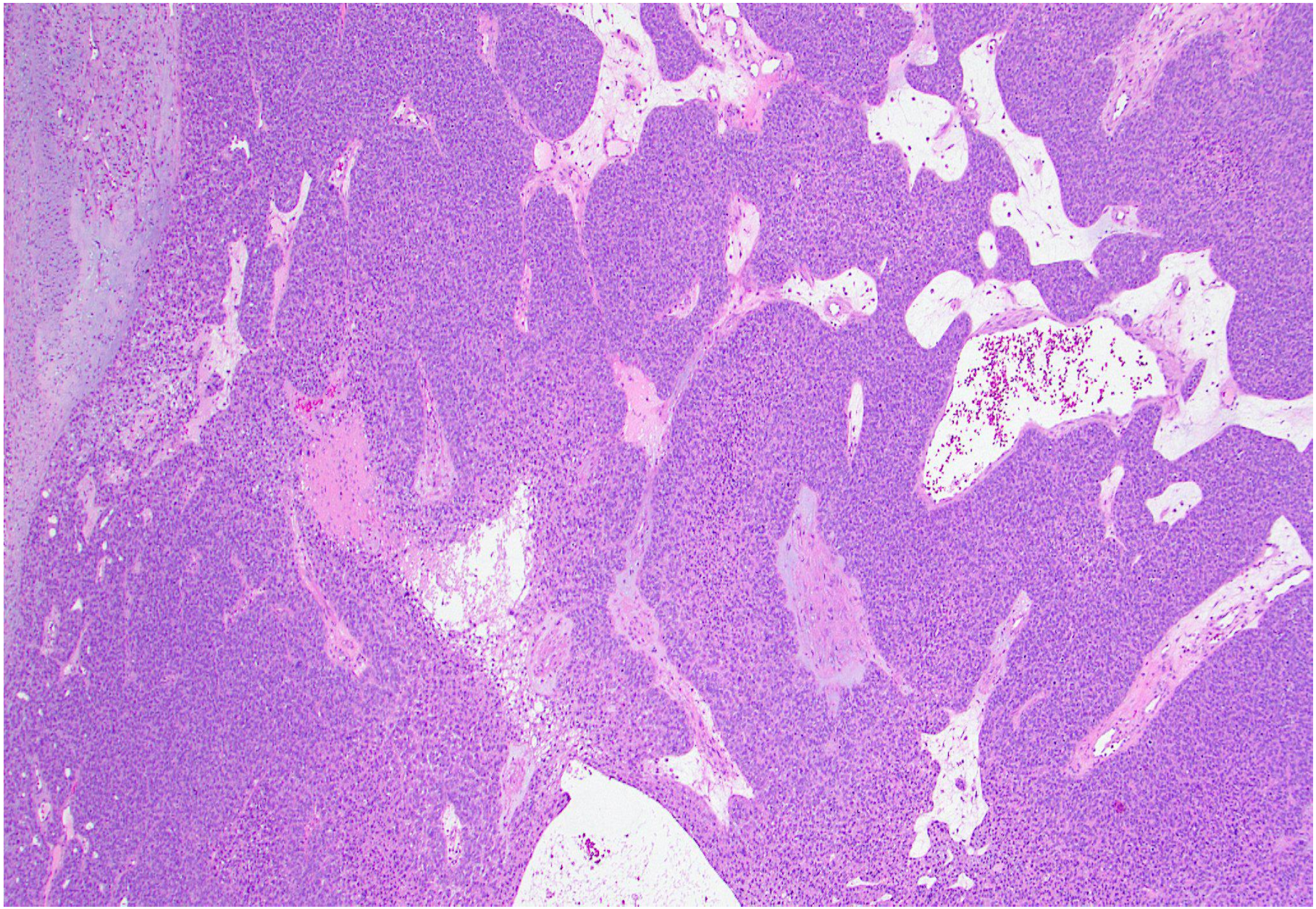
A distinctive HPV-related carcinoma of the sinonasal tract with histologic and immunophenotypic features of both surface-derived and salivary gland carcinoma.

Etiology:

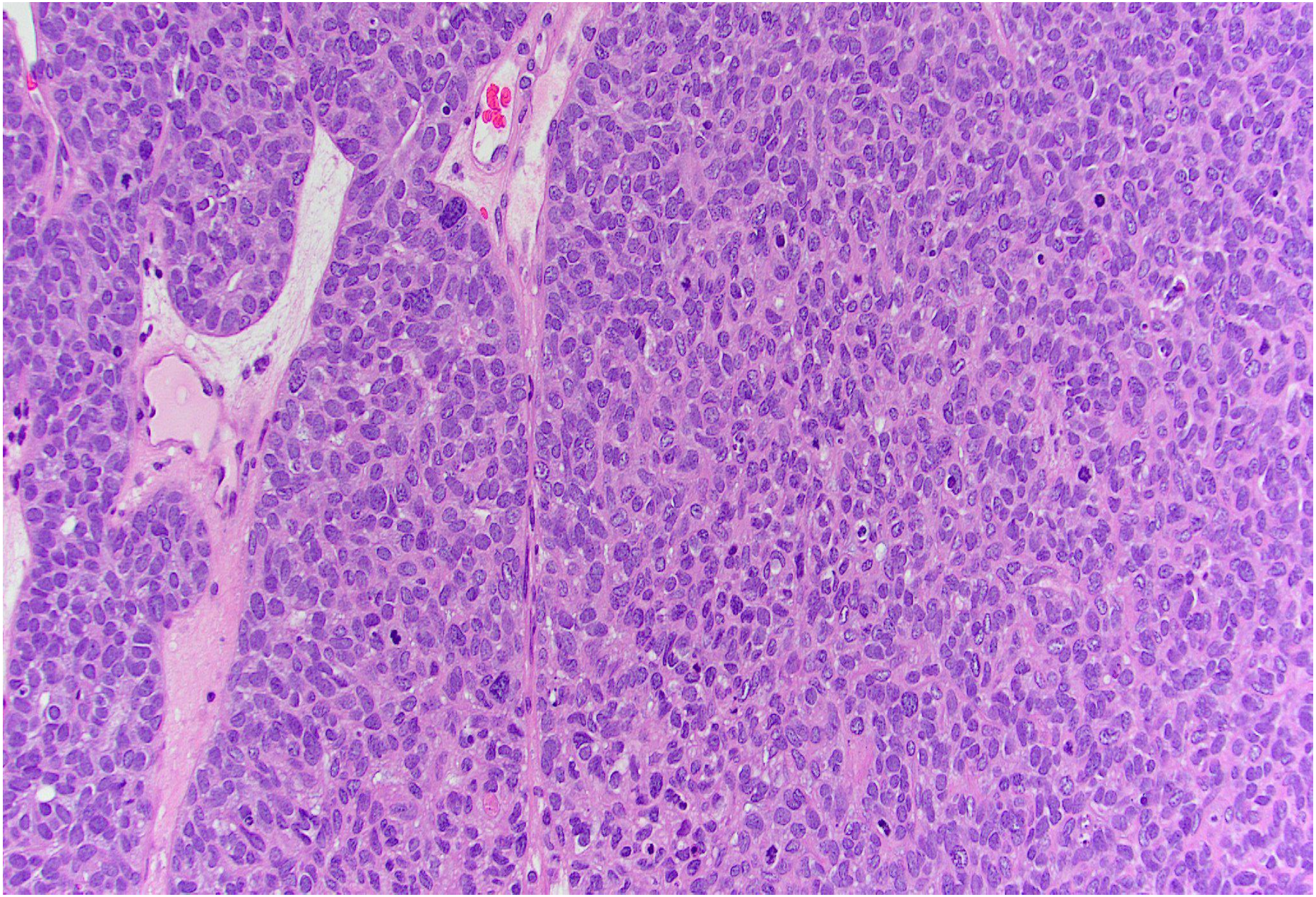
- **HPV type 33; and occasionally types 35, 16, 52, 56, or 82**

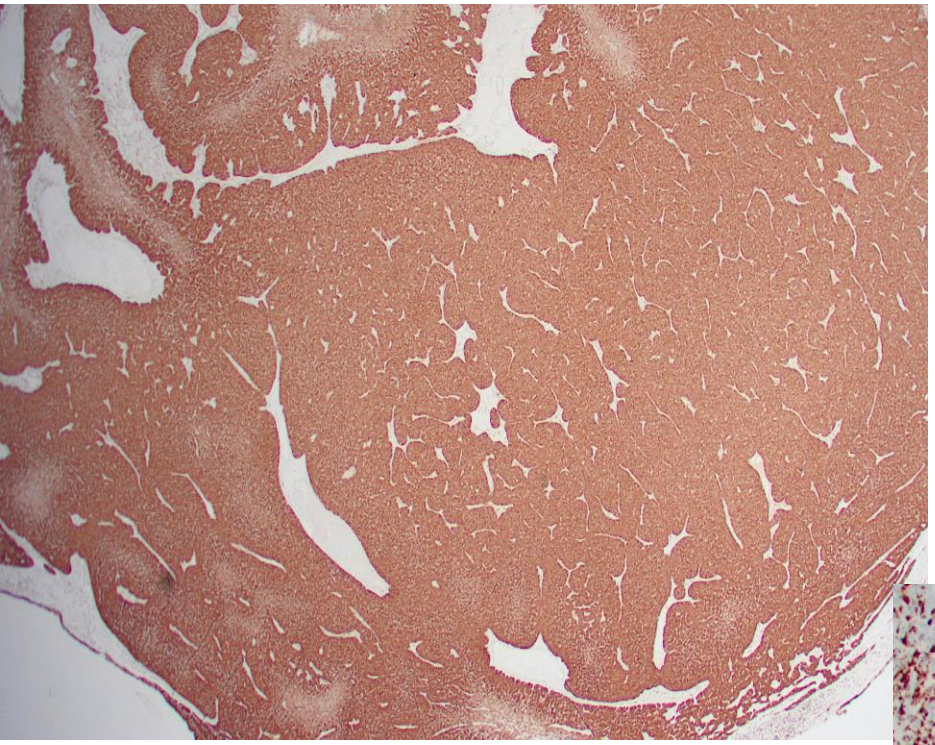
Localization:

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

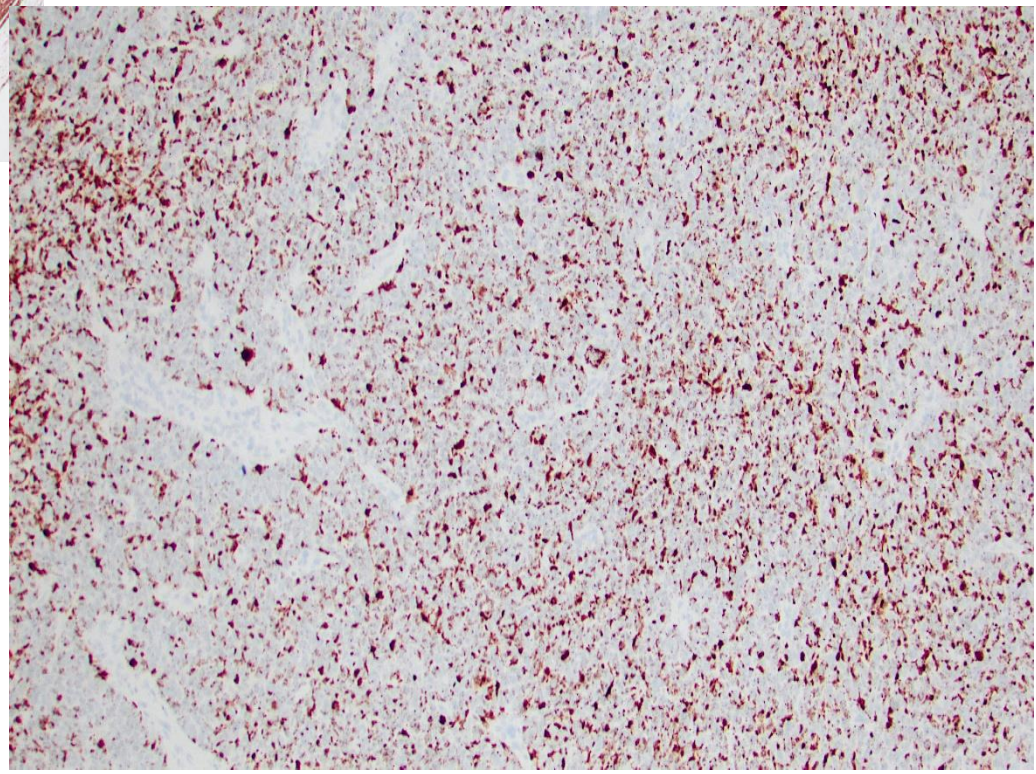


“Nasal Polyp”





P16 (IHC)



HR- HPV (mRNA ISH)

Squamous phenotype

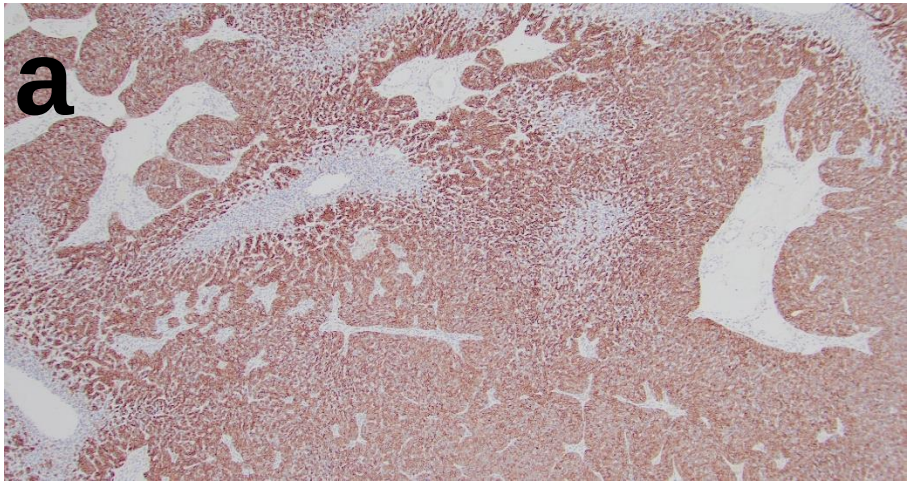
a. CK5/6

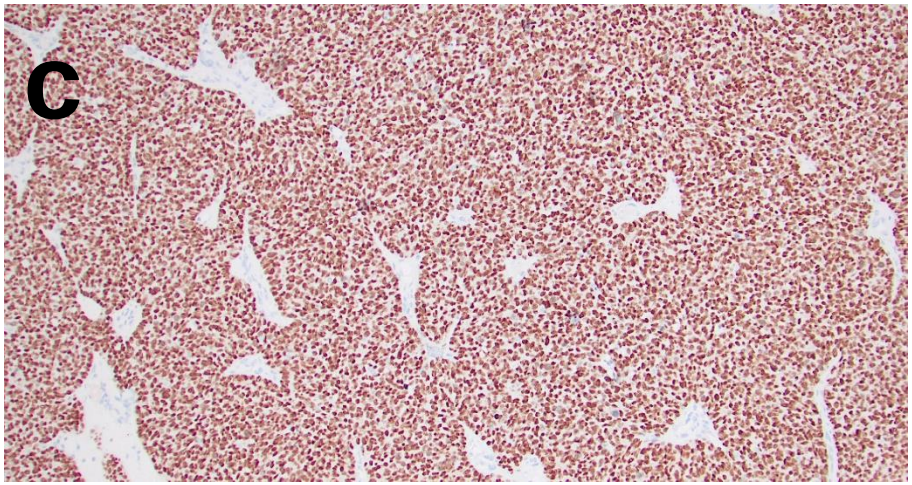
b. p40

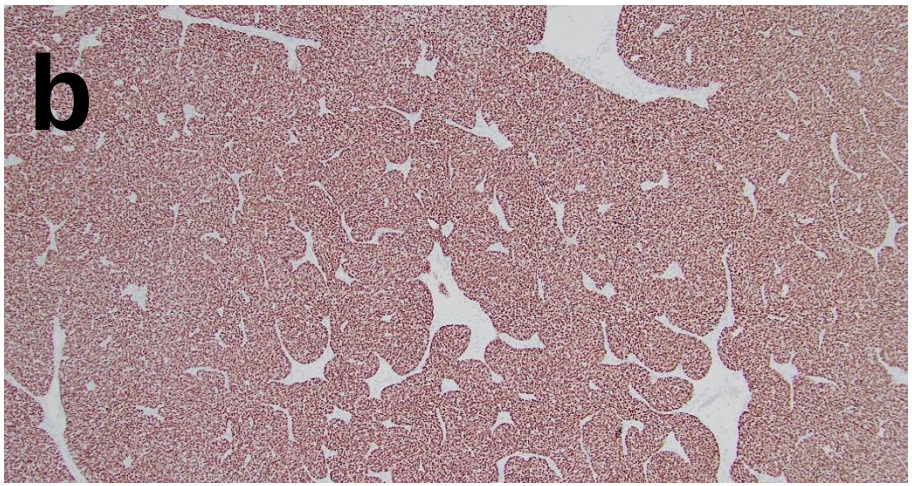
Myoepithelial phenotype

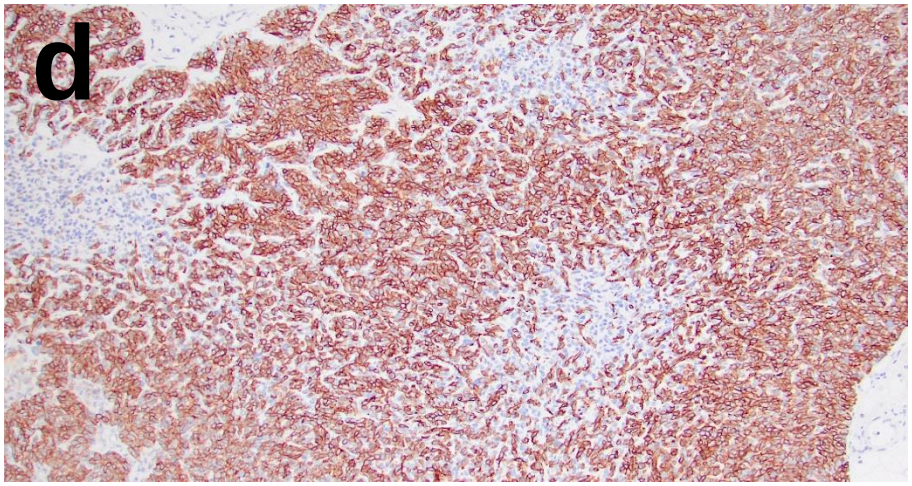
c. SOX10

d. Calponin



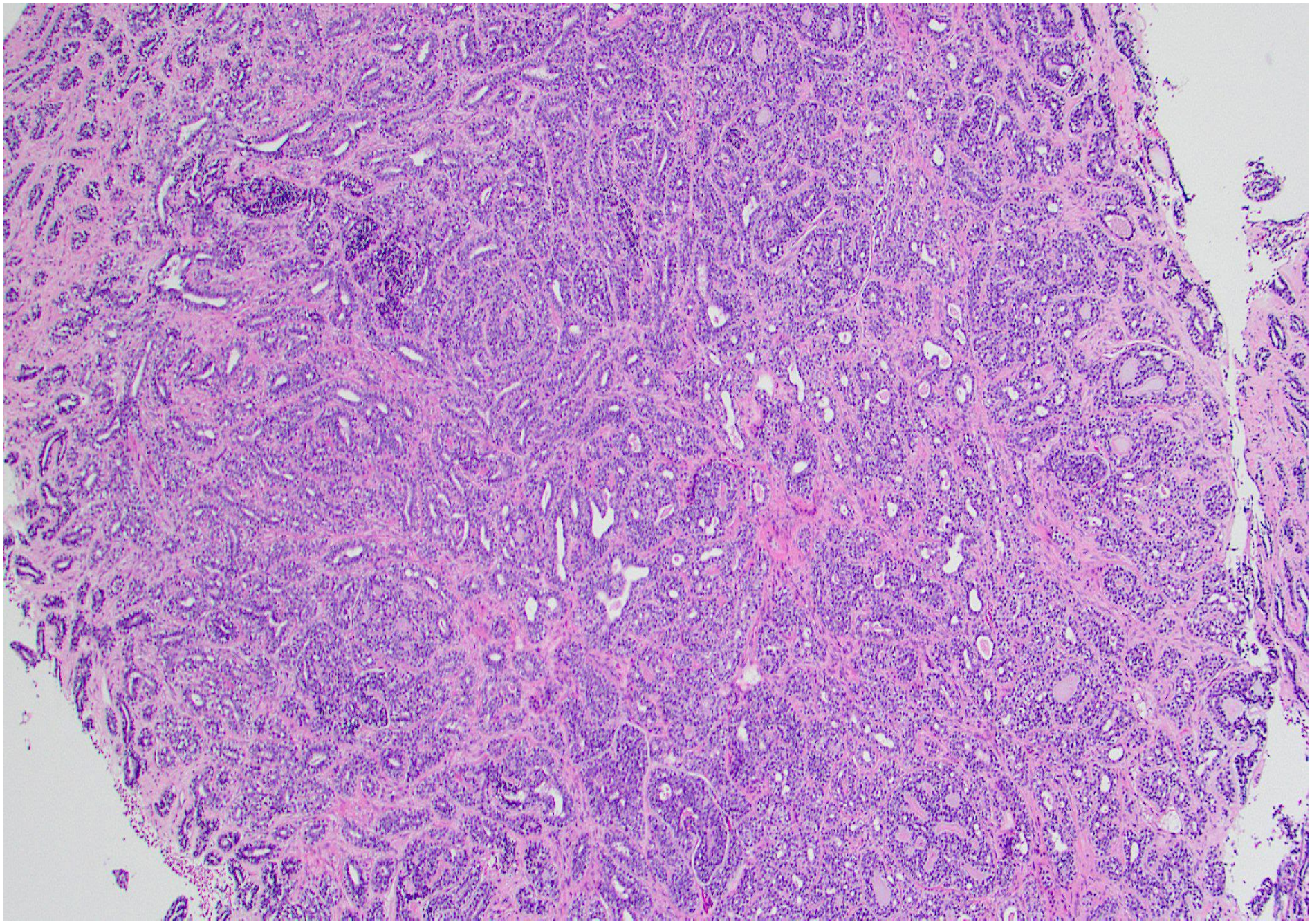




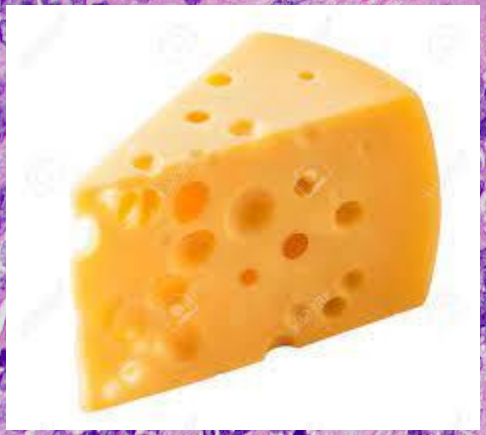


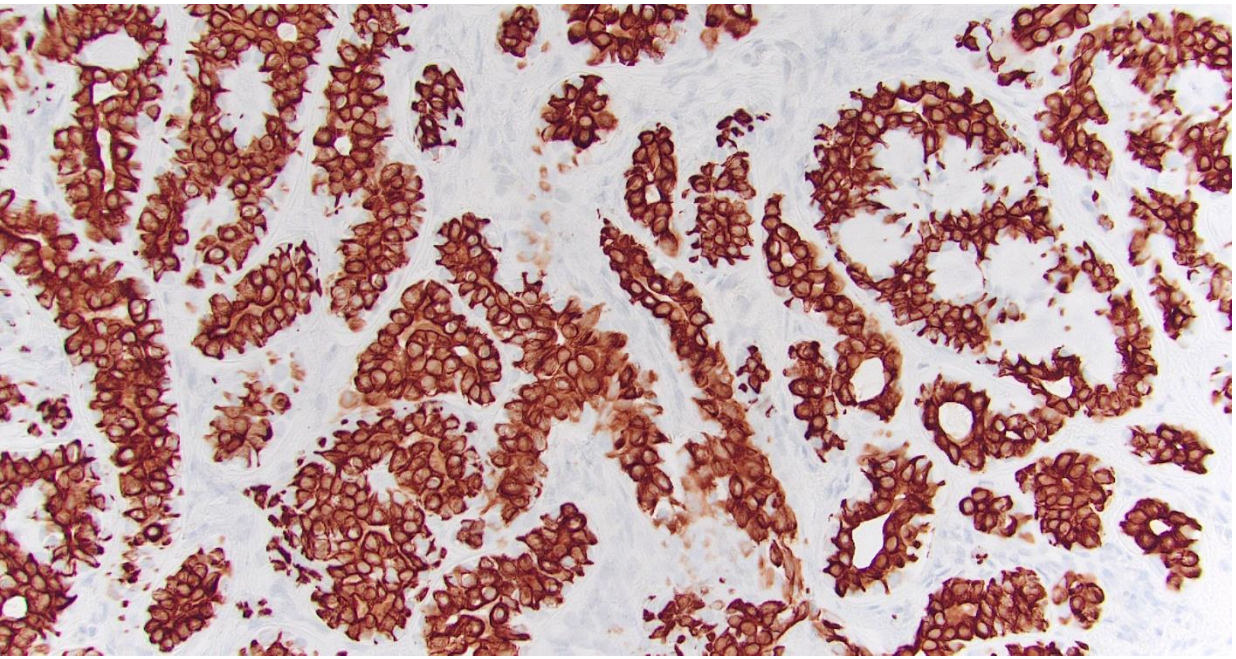
NGS: no MYB, MYBL1, NFIB events

Dgn: HMSC



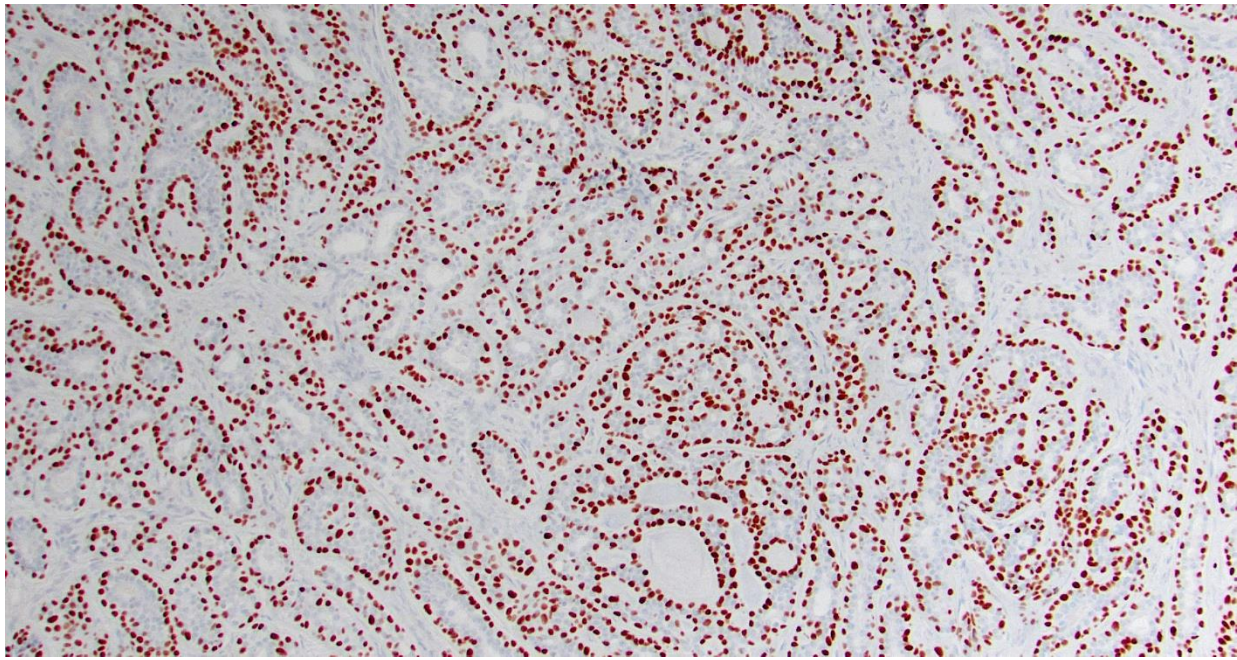
“Nasopharynx, mass”



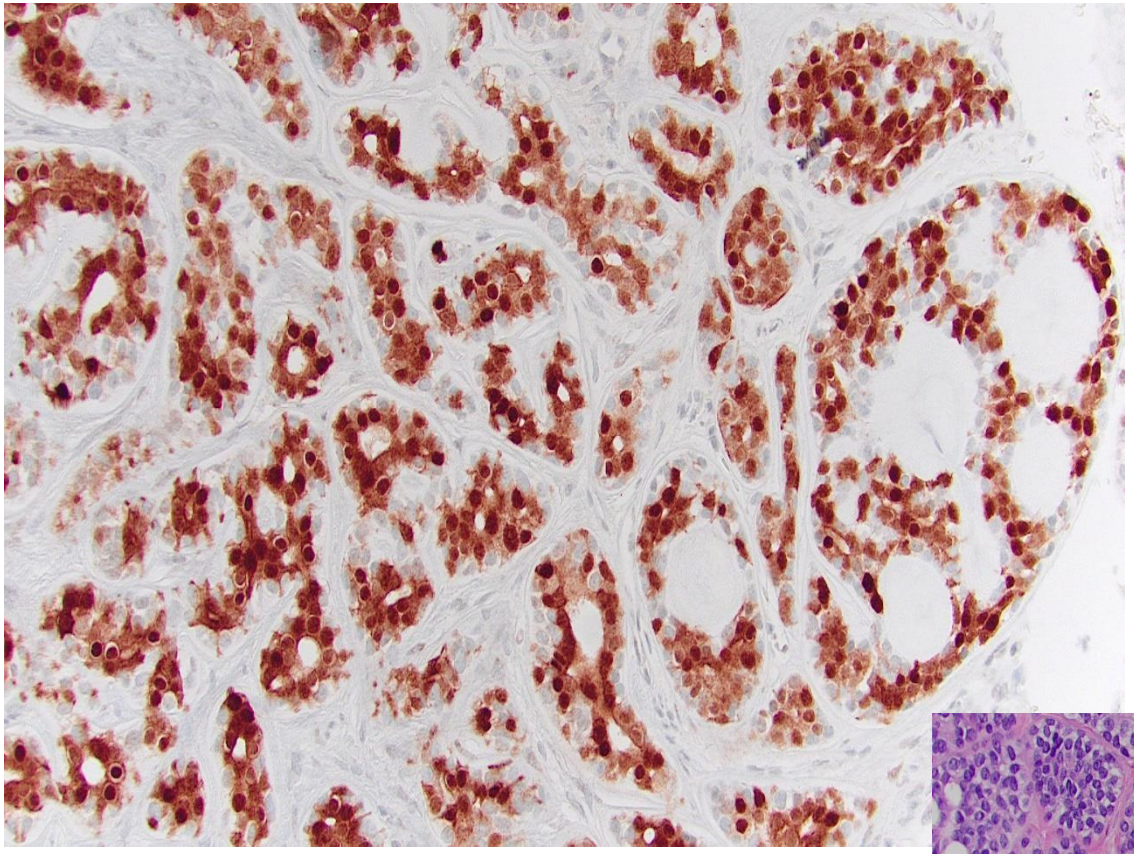


CK7 (luminal/ epithelial)

P63 (abluminal, myoepithelial

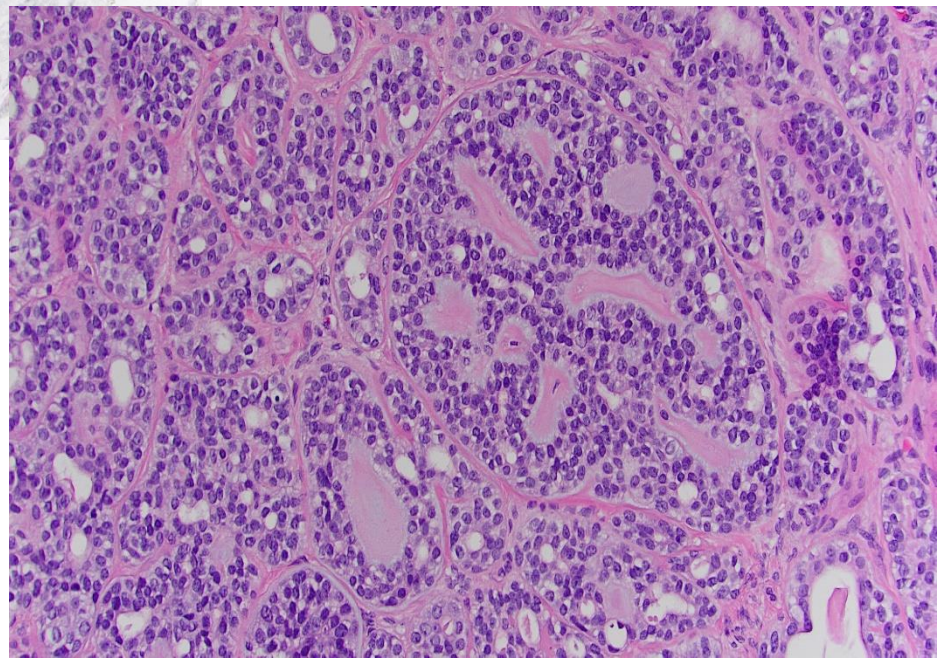


“Bicellular”:
epithelial and myoepithelial cells



p16

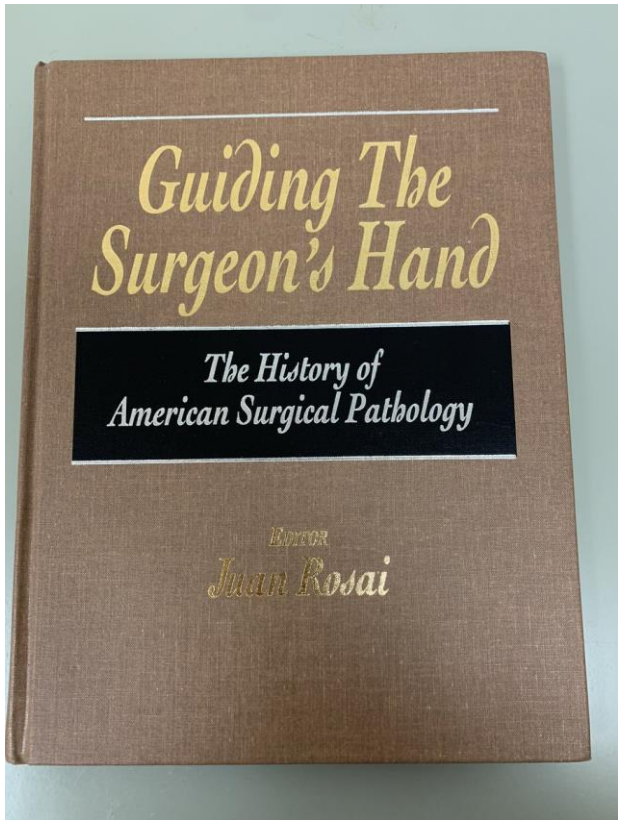
NGS: no MYB, MYBL1, NFIB events



Dgn: Salivary epithelial-myoepithelial carcinoma

Otto Dix (1891-1969)
Dr. Wilhelm Mayer-Hermann, Berlin 1926
MoMa 1932

“Trust your eyes.”
Otto Dix



Thank you!