Viral-Associated Carcinomas of the Head and Neck

NY Pathological Society
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Viral-Associated Neoplasms of the H&N

- **Human papillomavirus (HPV):**
  - **Papilloma (Low-risk)**
  - **Oropharyngeal carcinoma (High-risk)**
- **Epstein-Barr virus (EBV):**
  - **Nasopharyngeal carcinoma**
  - **Hematolymphoid tumors**
  - **Smooth muscle tumors**
- **Merkel cell polyoma virus:**
  - **Merkel cell carcinoma**
- **Human herpes virus 8:**
  - **Kaposi sarcoma**
- **Human immunodeficiency virus (HIV)**
  - **HNSCC**

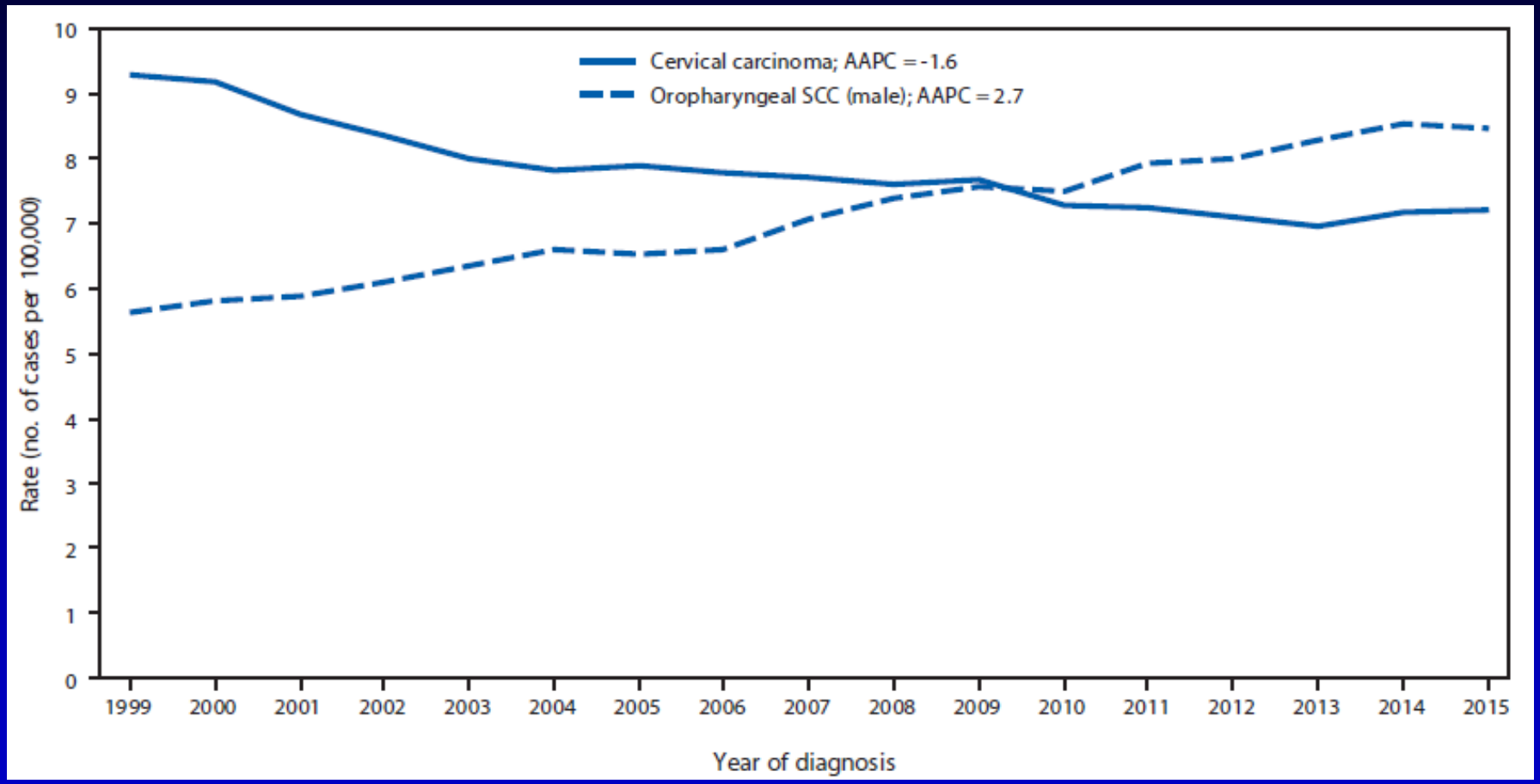
Viral-Associated Carcinomas of the Head and Neck
Outline

- Oropharyngeal HPV-associated squamous cell carcinoma (WHO 2017 – SCC, HPV-positive):
  - Clinicopathologic features
  - Morphologic variants
  - Ancillary testing & CAP Recommendations
- Nasopharyngeal EBV-associated squamous cell carcinoma
- Metastatic cervical (neck) carcinoma with unknown primary tumor

HPV-positive SCC vs HPV-negative SCC

	HPV-positive SCC	HPV-negative SCC
Incidence	Increasing	Stable to decreasing
Age/Gender	Younger; M>F	Older; M>F
Race	Caucasian >>>> African American	African American > Caucasian
Risk factors	HPV	Smoking, alcohol
Primary location	Oropharynx (BOT; tonsil)	All UADT mucosal sites
Histology	Nonkeratinizing SCC	Keratinizing SCC
p16	Positive	Negative
AJCC staging	Lower T, higher N	Higher T, lower N
ChemoXRT response	Good with low rate of recurrence	Good with high rate recurrence
Prognosis	Better disease-free & overall survival (worse if smokers)	Worse disease-free and overall survival

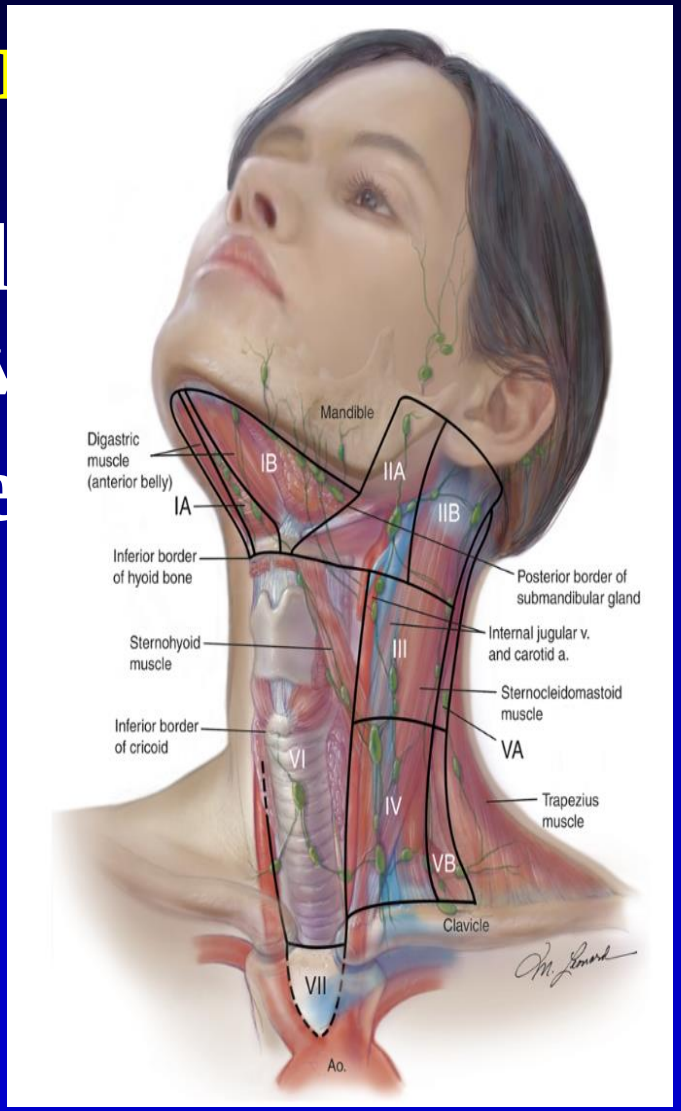
Trends in HPV-associated Cancers



Van Dyne EA, et al. MMWR 2018;67:918-924

Clinical Histor

- 41 year old male presented
  enlarging neck mass at Lev
- There was no past or curre
  malignancy
- No known risk factors



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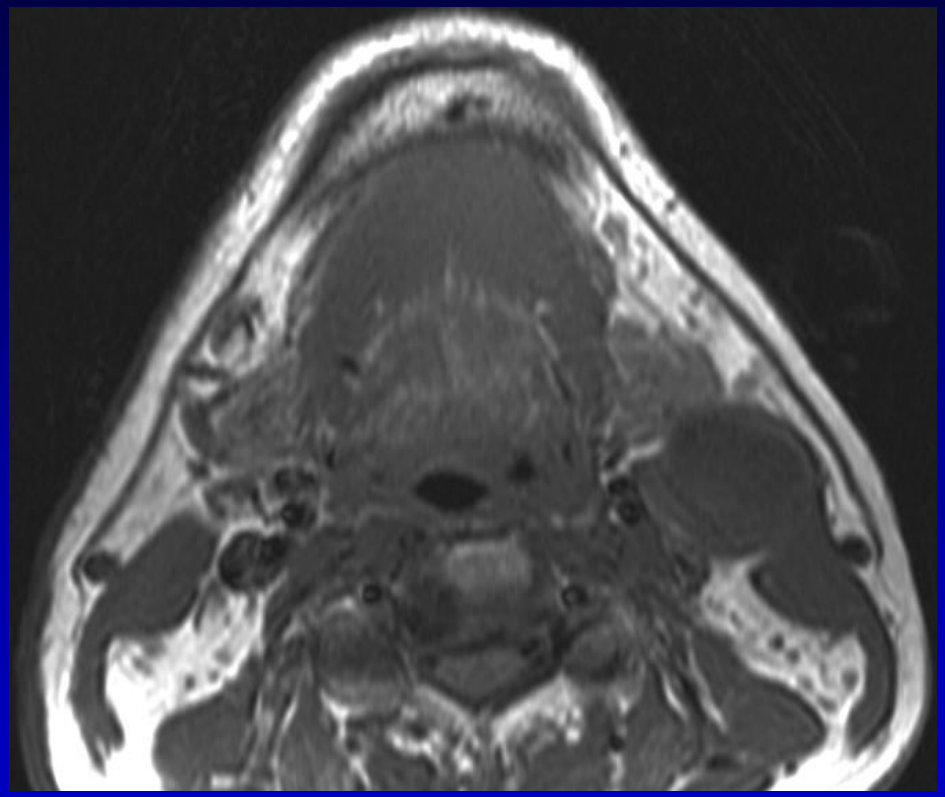
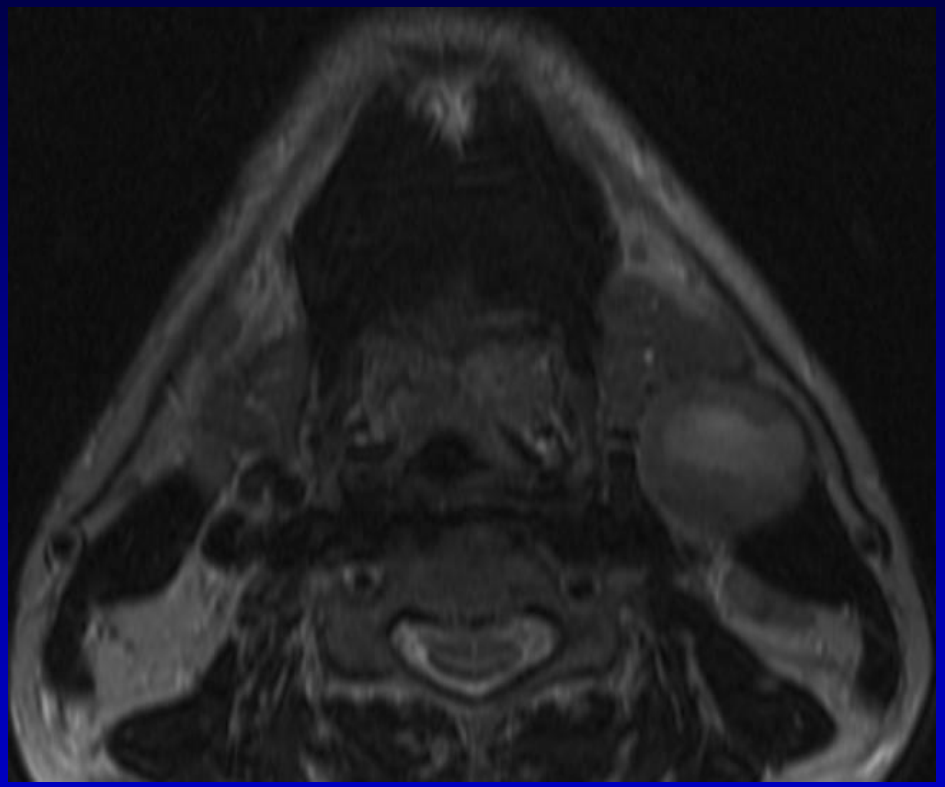


T1



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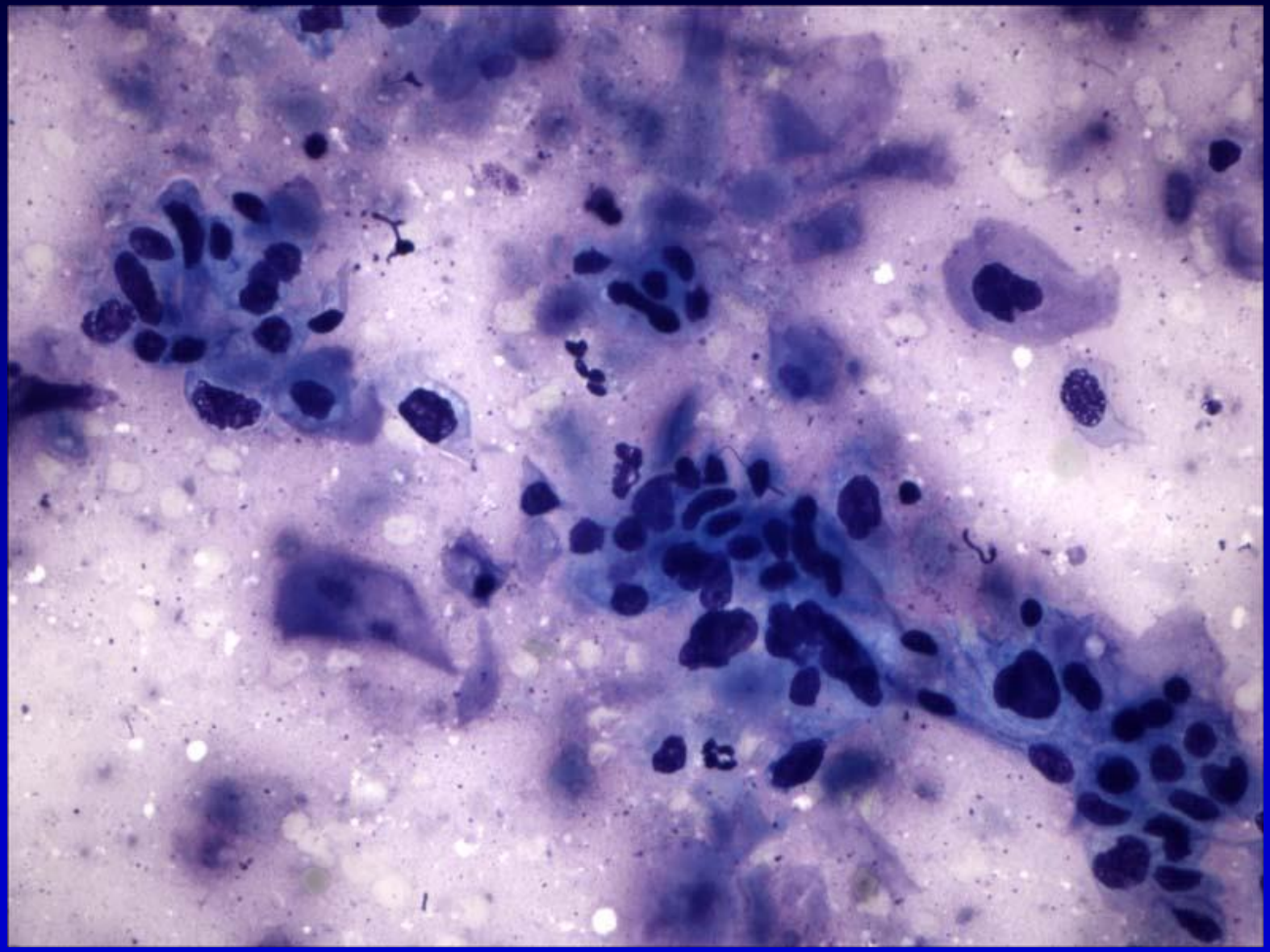
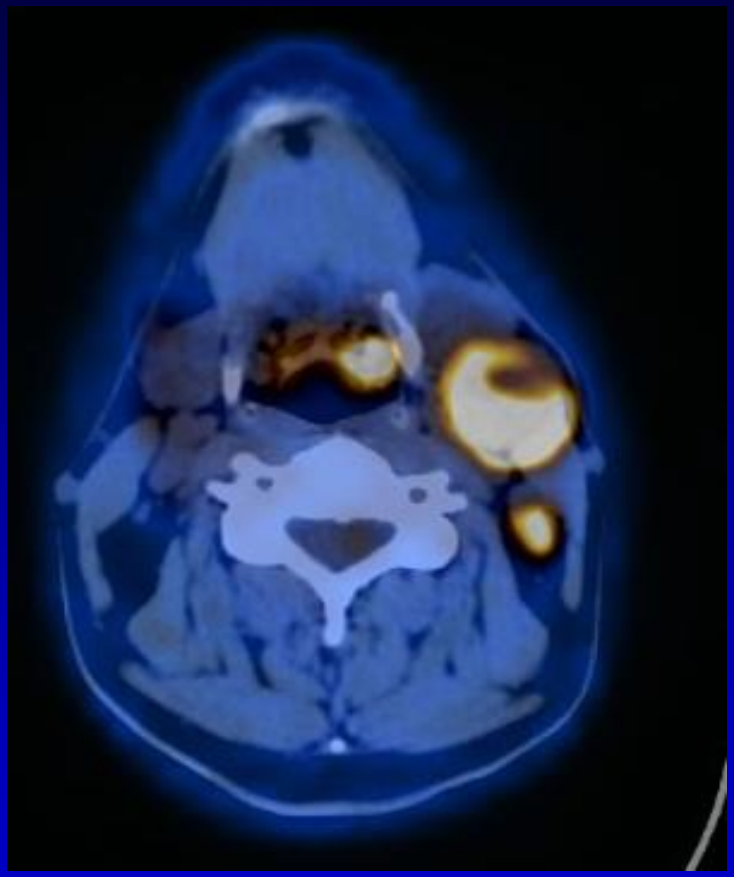
FNAB



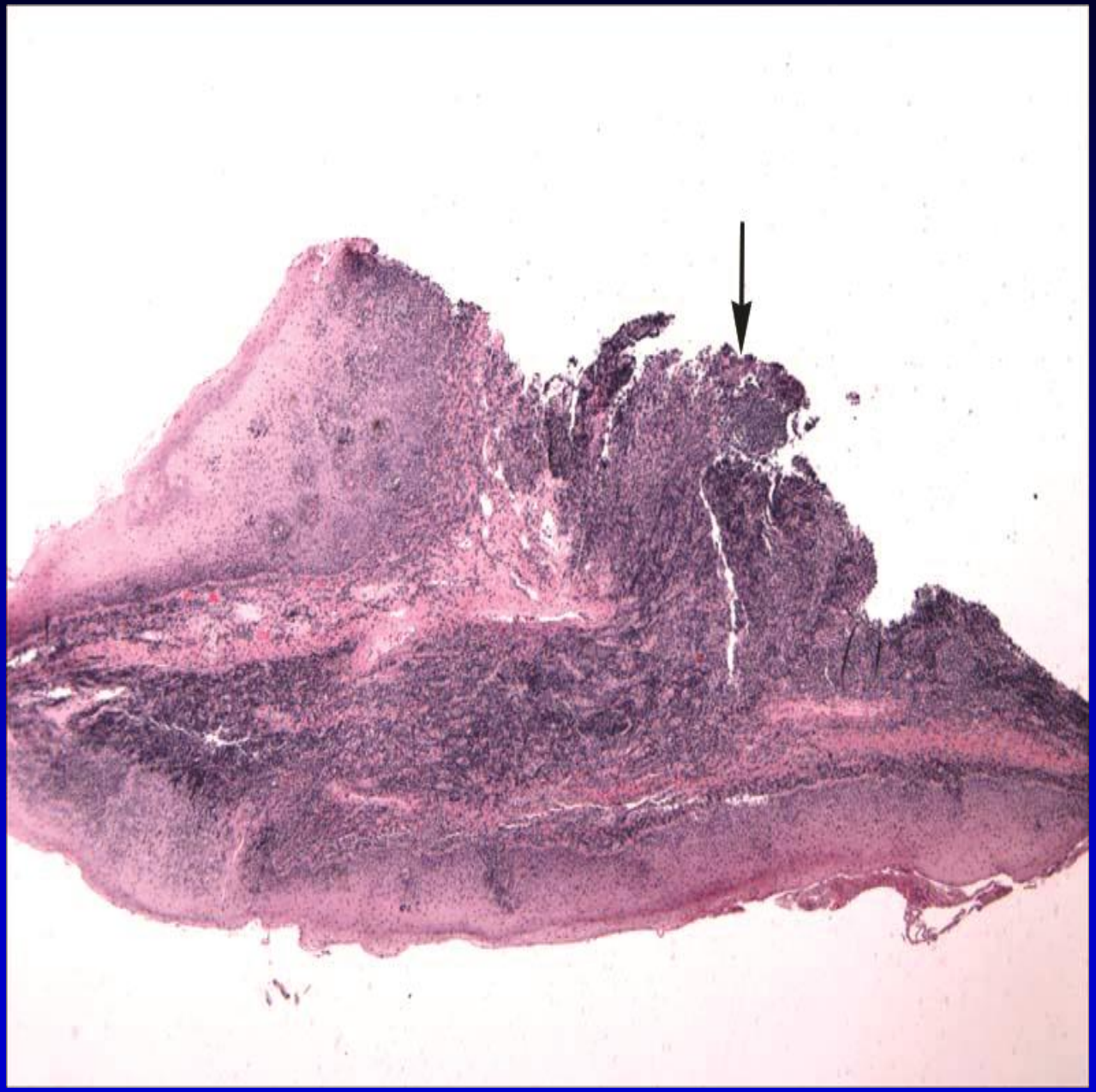
FNAB Diagnosis

- Metastatic poorly-differentiated carcinoma favor squamous cell carcinoma

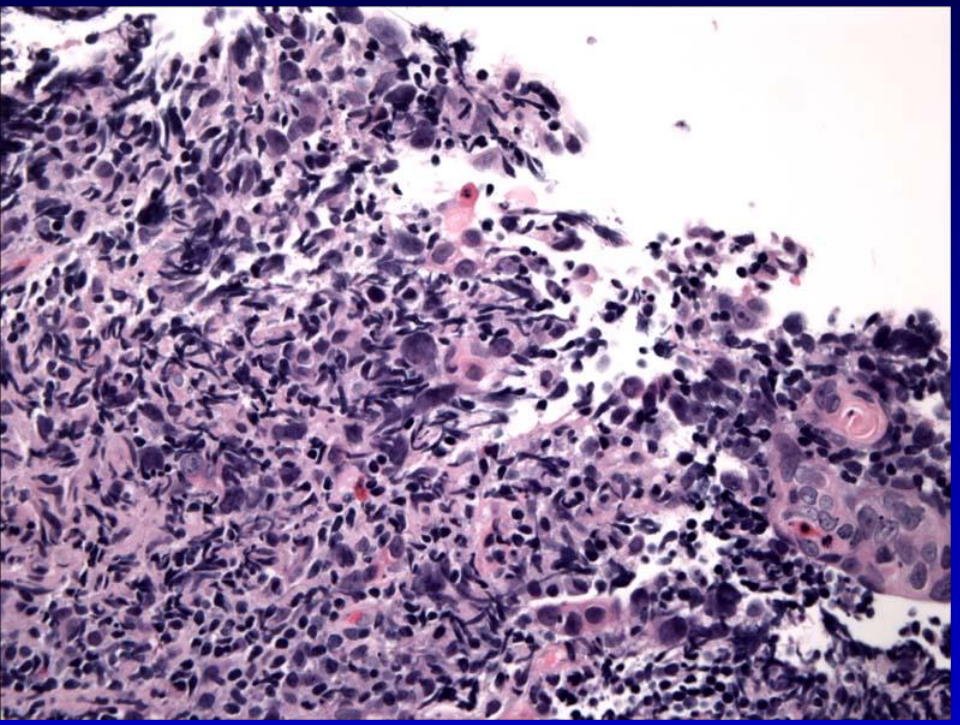
PET/CT

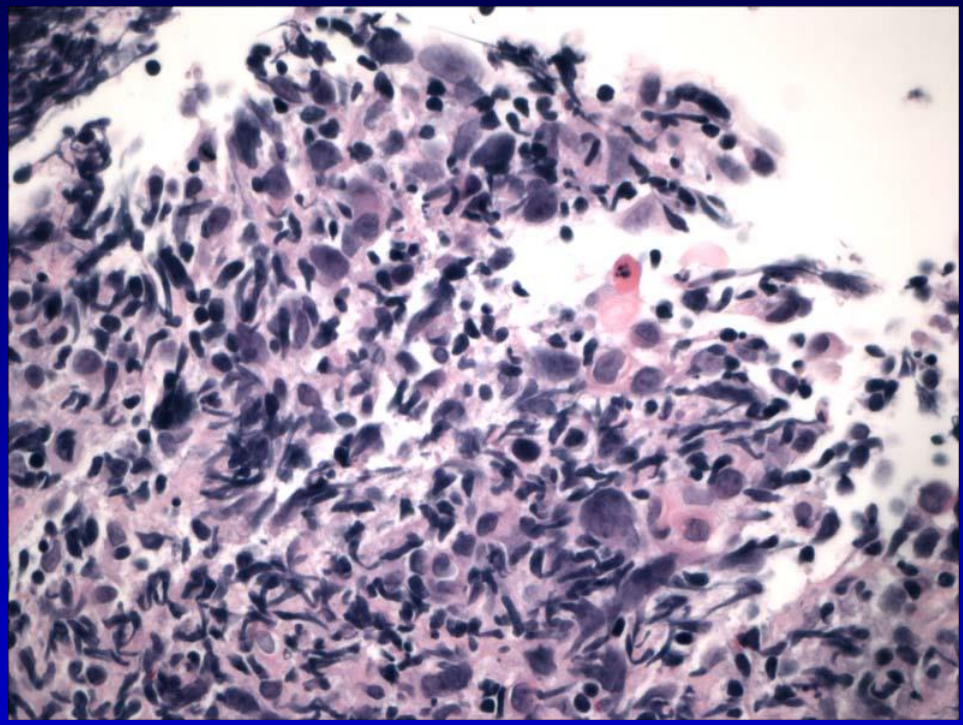


BOT

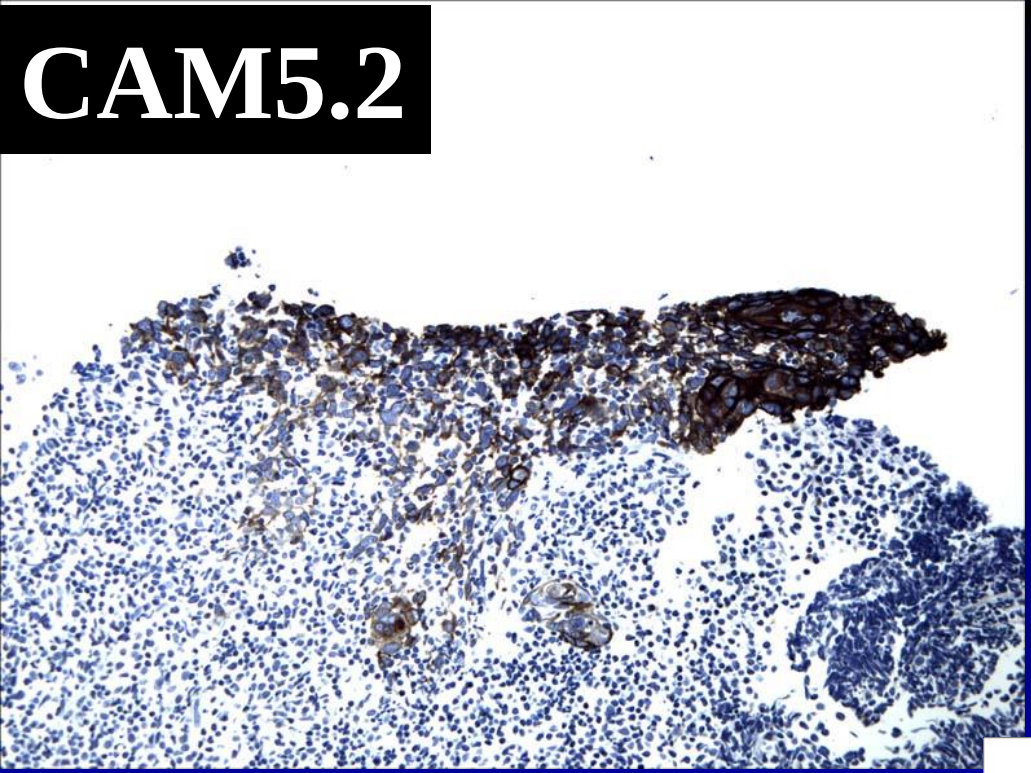


BOT
Biopsy





CAM5.2



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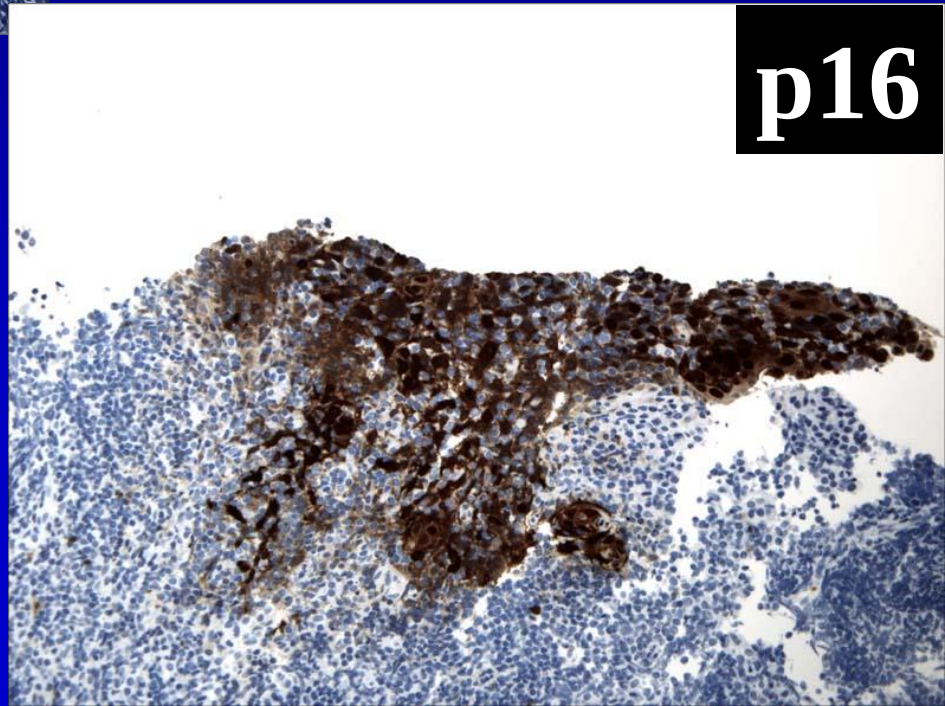

Diagnosis

- **Oropharyngeal (Tonsillar) Carcinoma:**

  - Poorly-differentiated squamous cell carcinoma

  - Squamous cell carcinoma with basaloid features

  - Nonkeratinizing carcinoma - recapitulate tonsillar crypt epithelium so in fact are differentiated and NOT poorly-differentiated cancers and should not be graded as such

Nonkeratinizing Carcinoma

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Human Papillomavirus (HPV)

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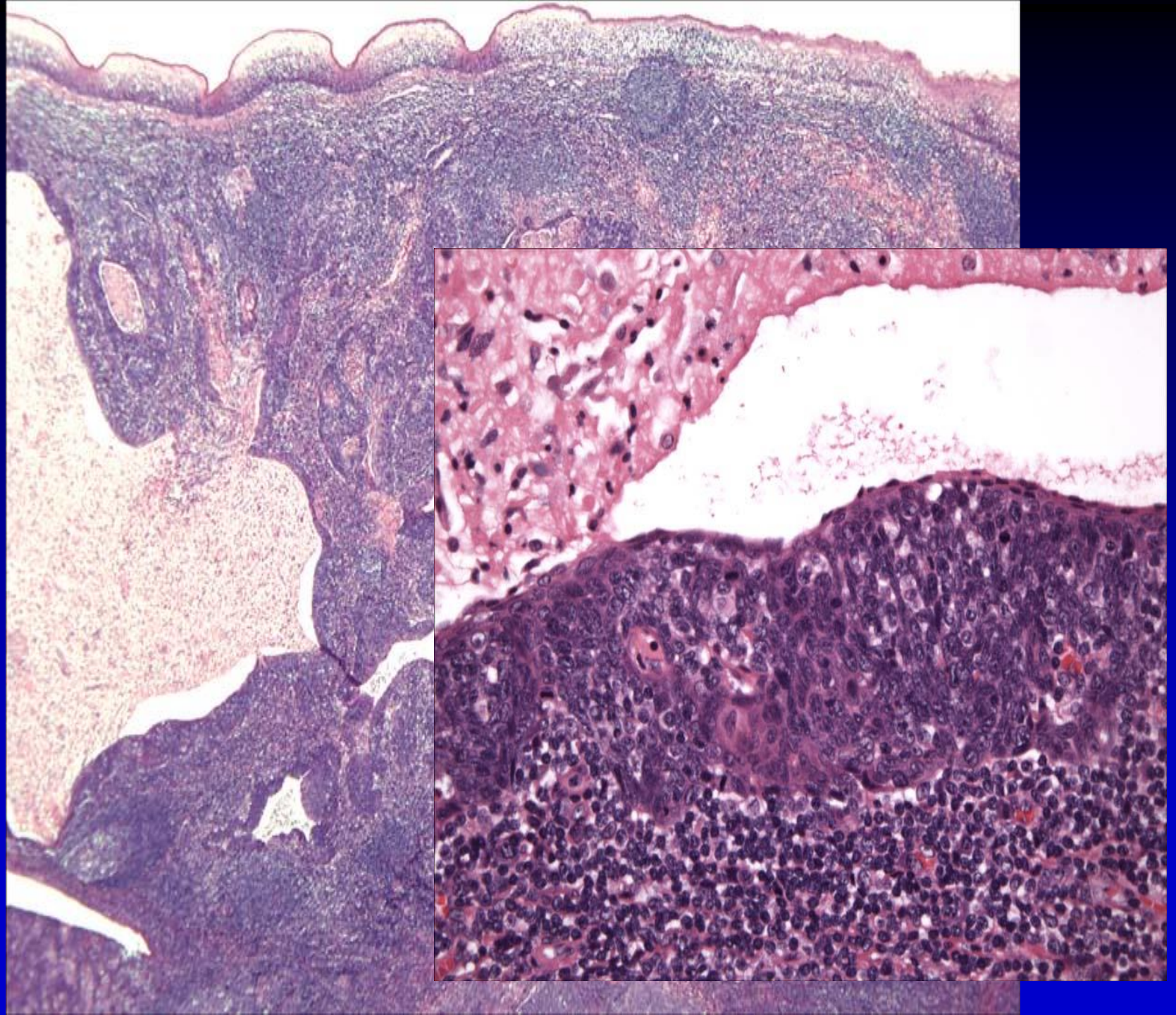
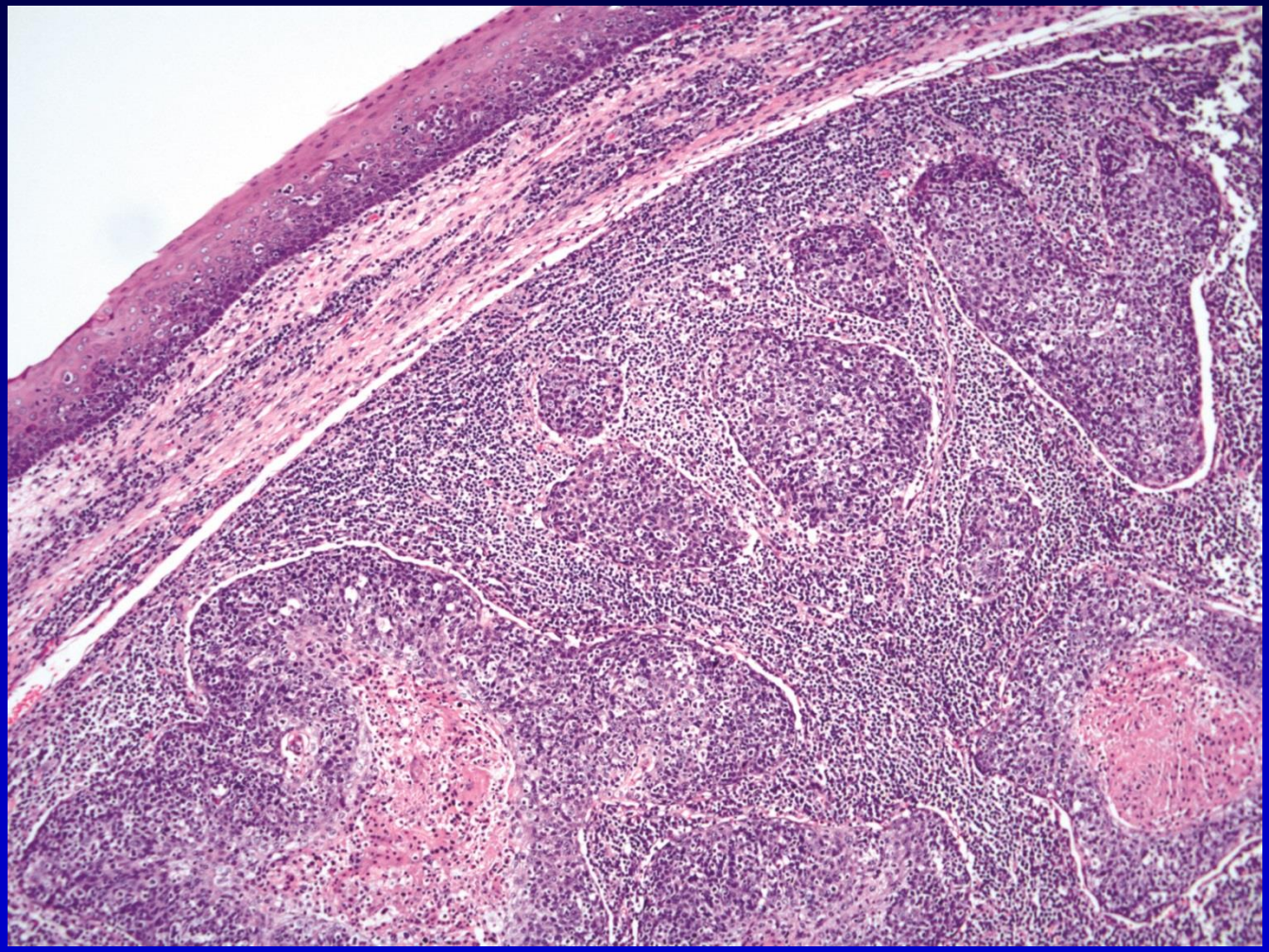
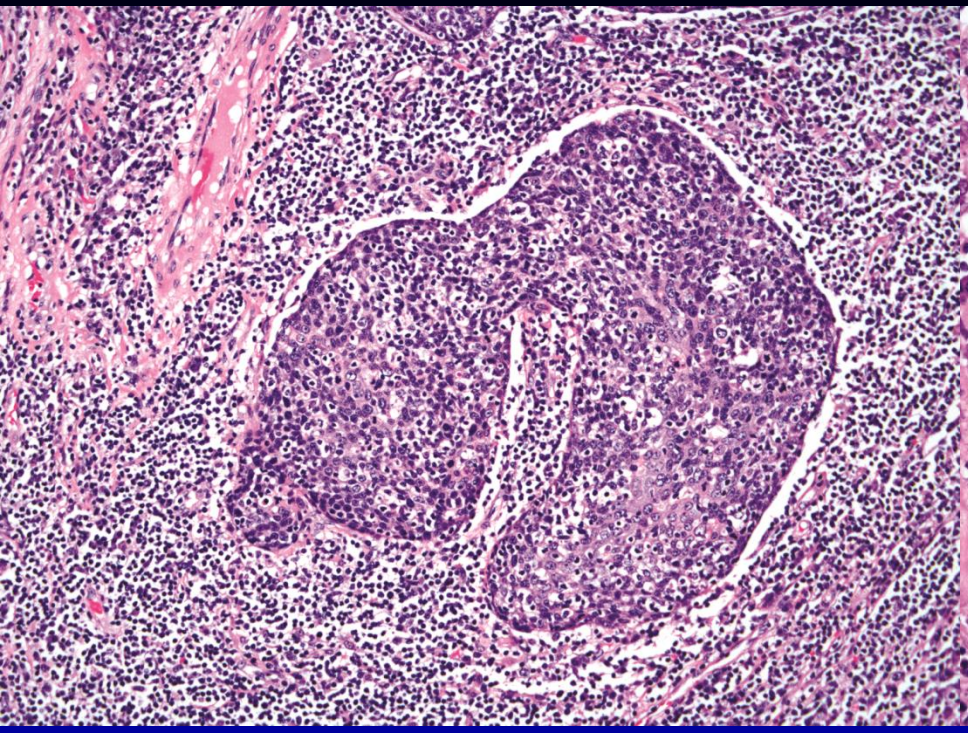
Oropharyngeal Carcinoma

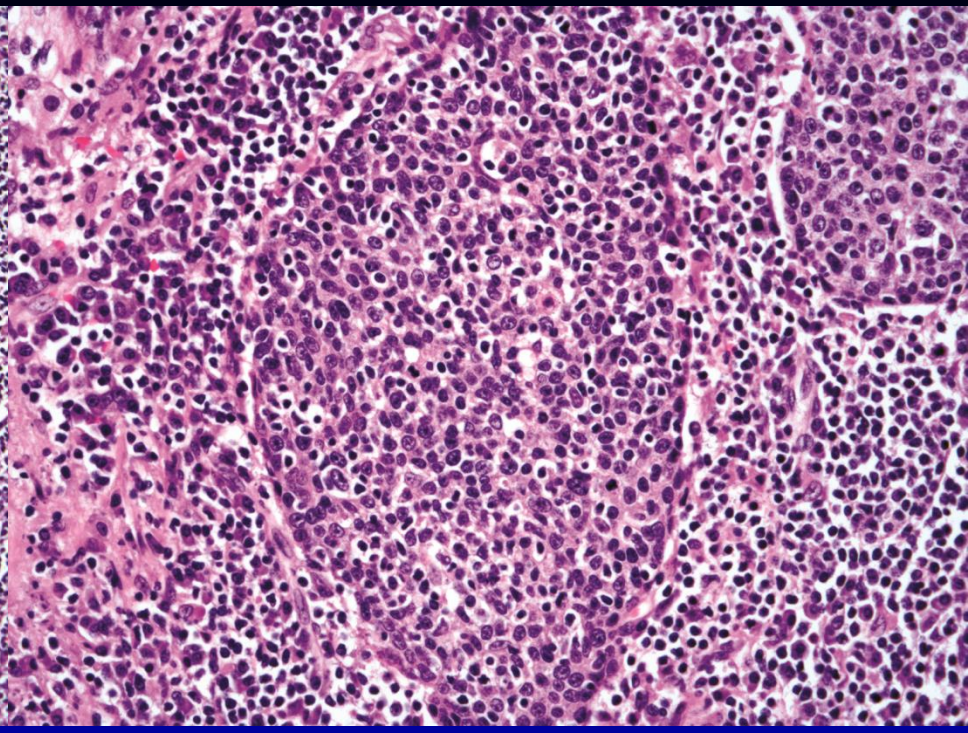
(SCC, HPV-positive WHO 2017)

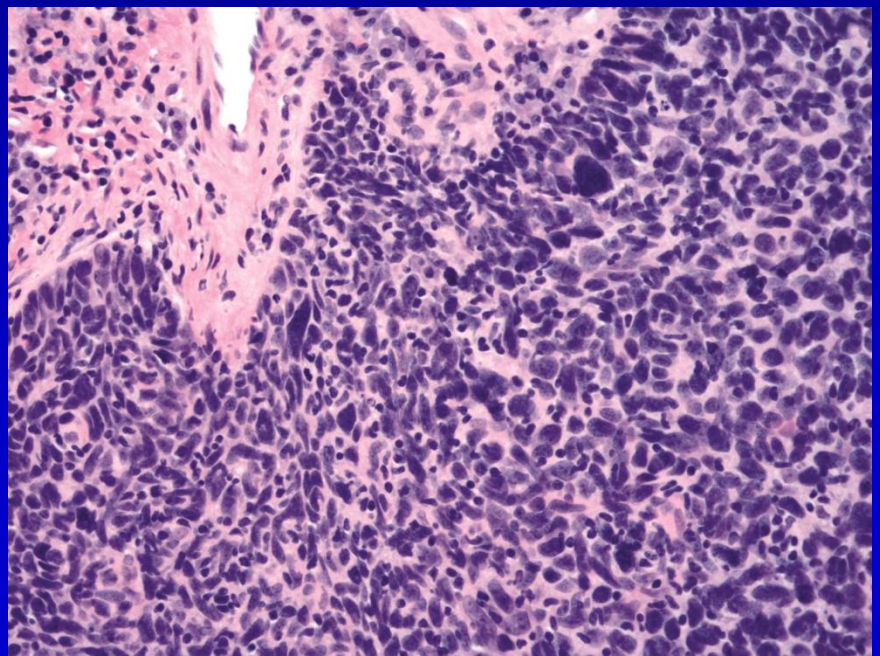


Invasive Oropharyngeal SCC, Predominantly Nonkeratinizing

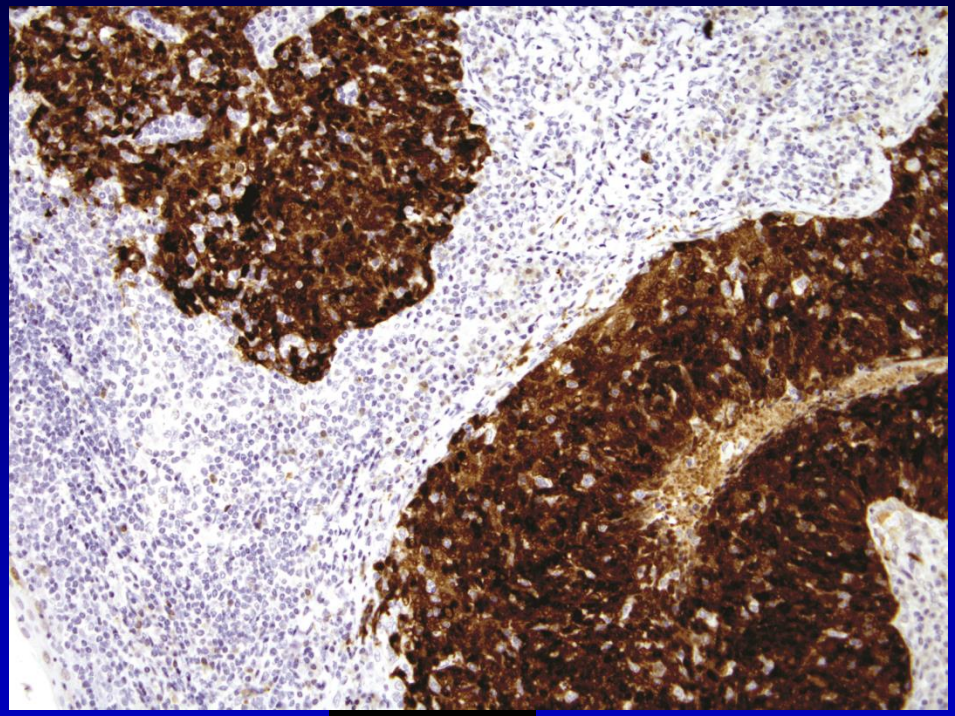








Oropharyngeal SCC, HPV-Positive



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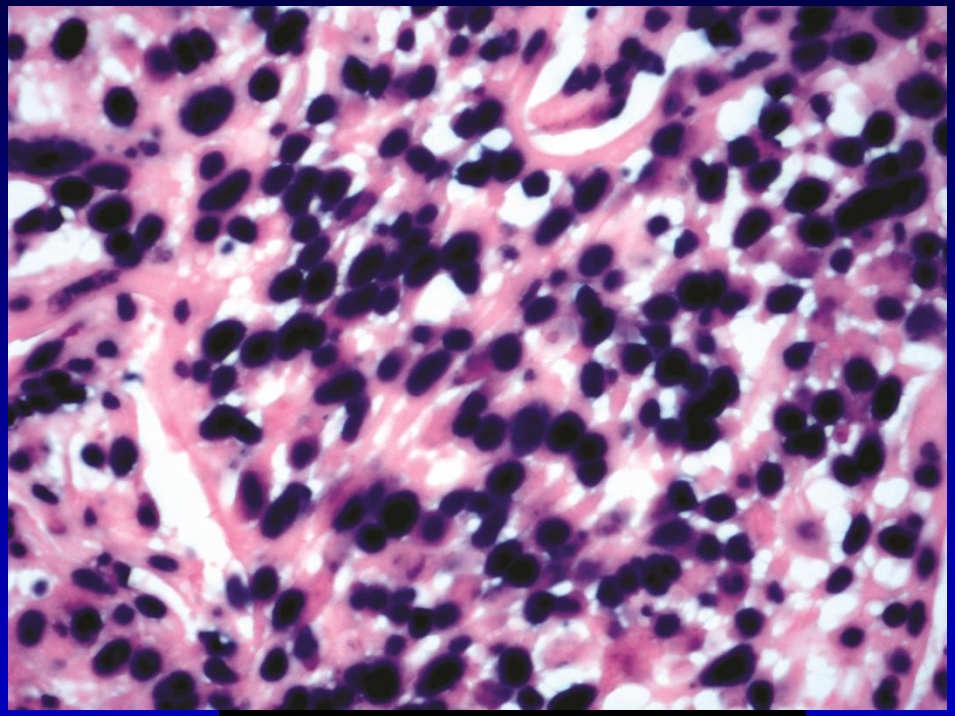
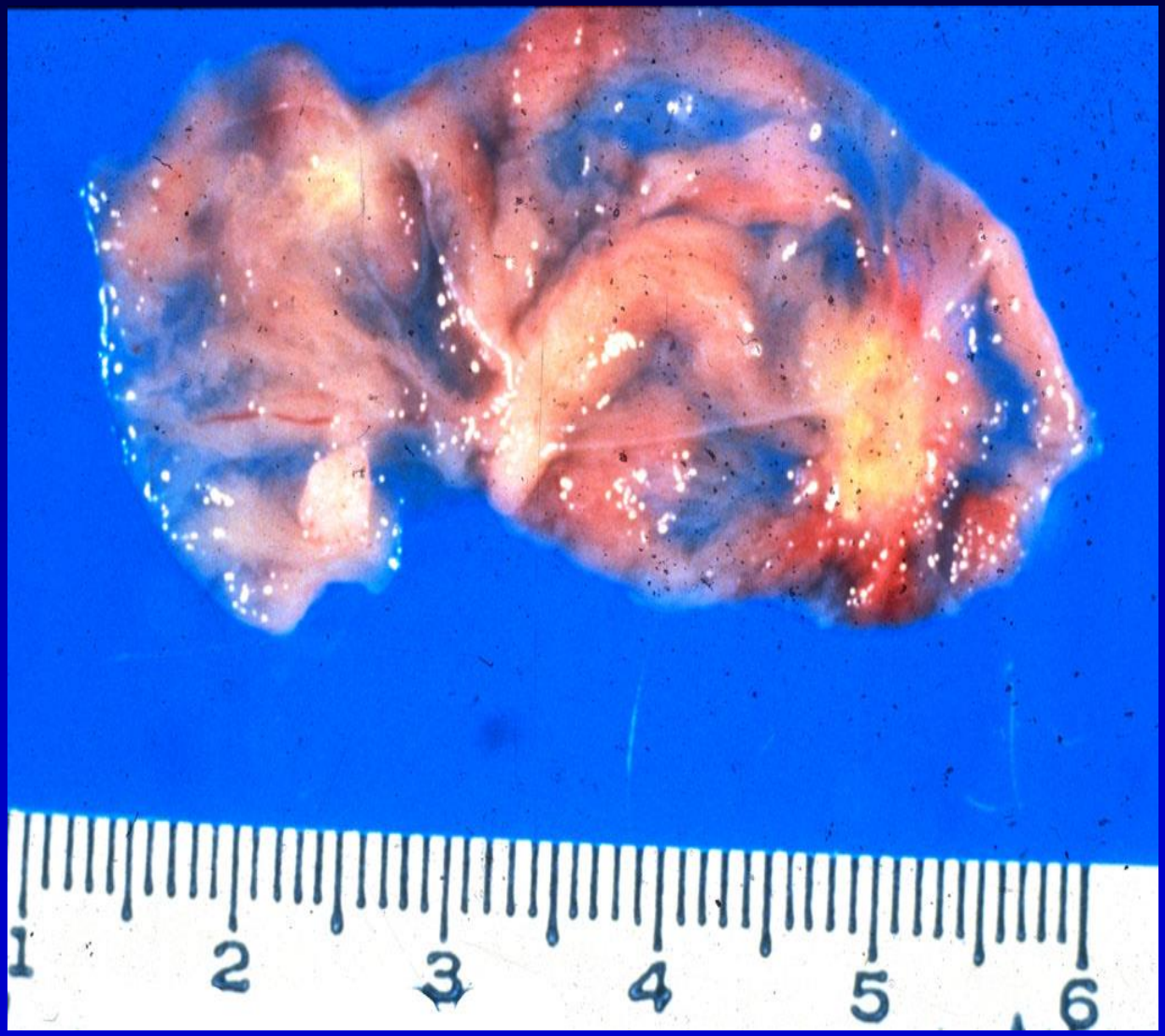
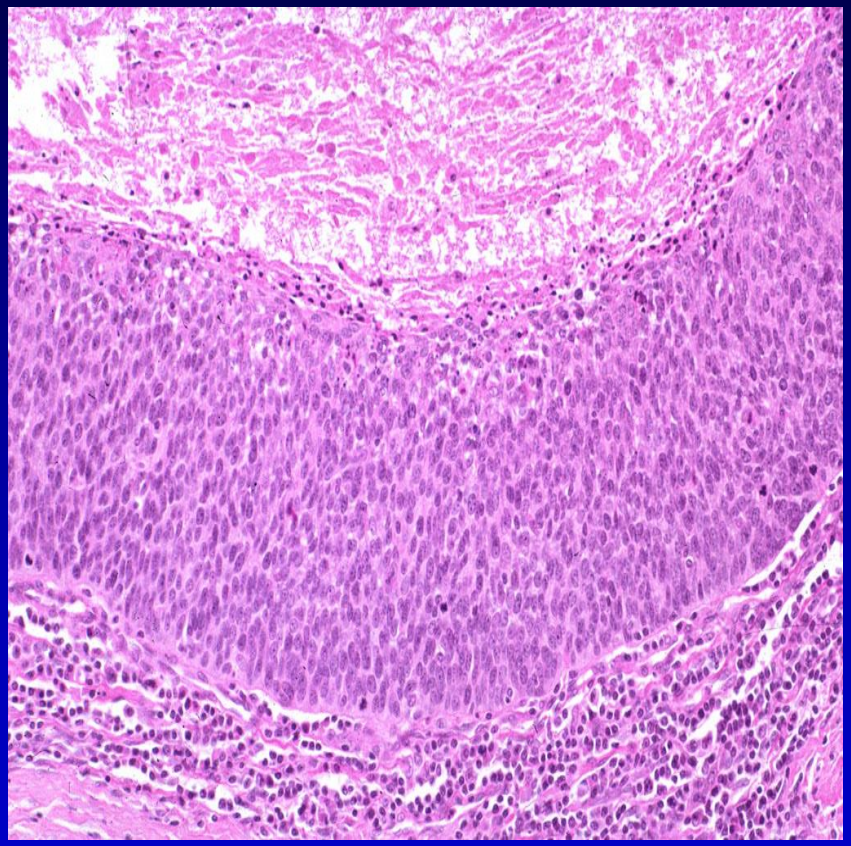


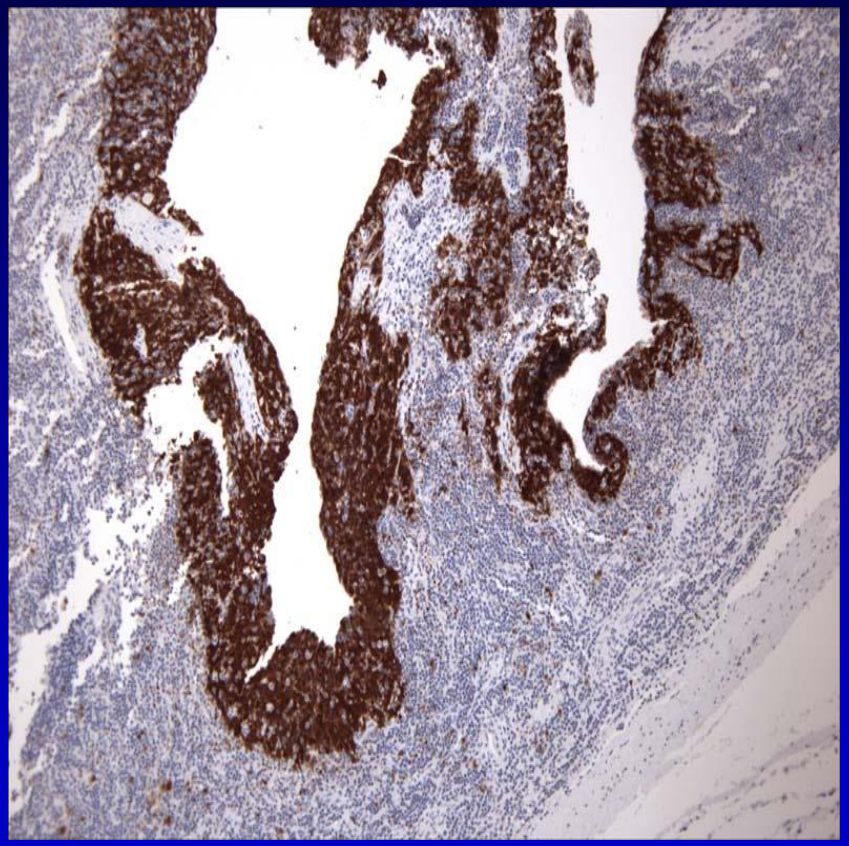
ISH HPV16

Metastatic SCC, HPV-positive c/w Oropharyngeal Origin



Metastatic SCC, HPV-positive c/w Oropharyngeal Origin





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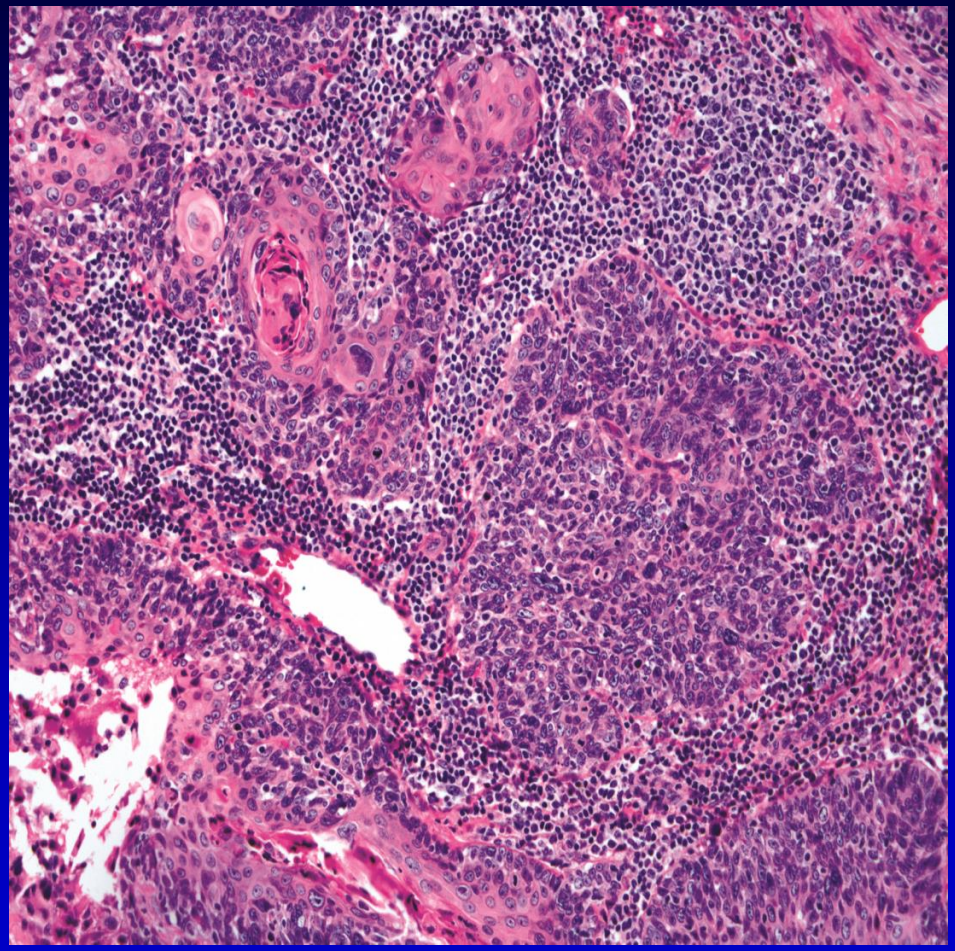
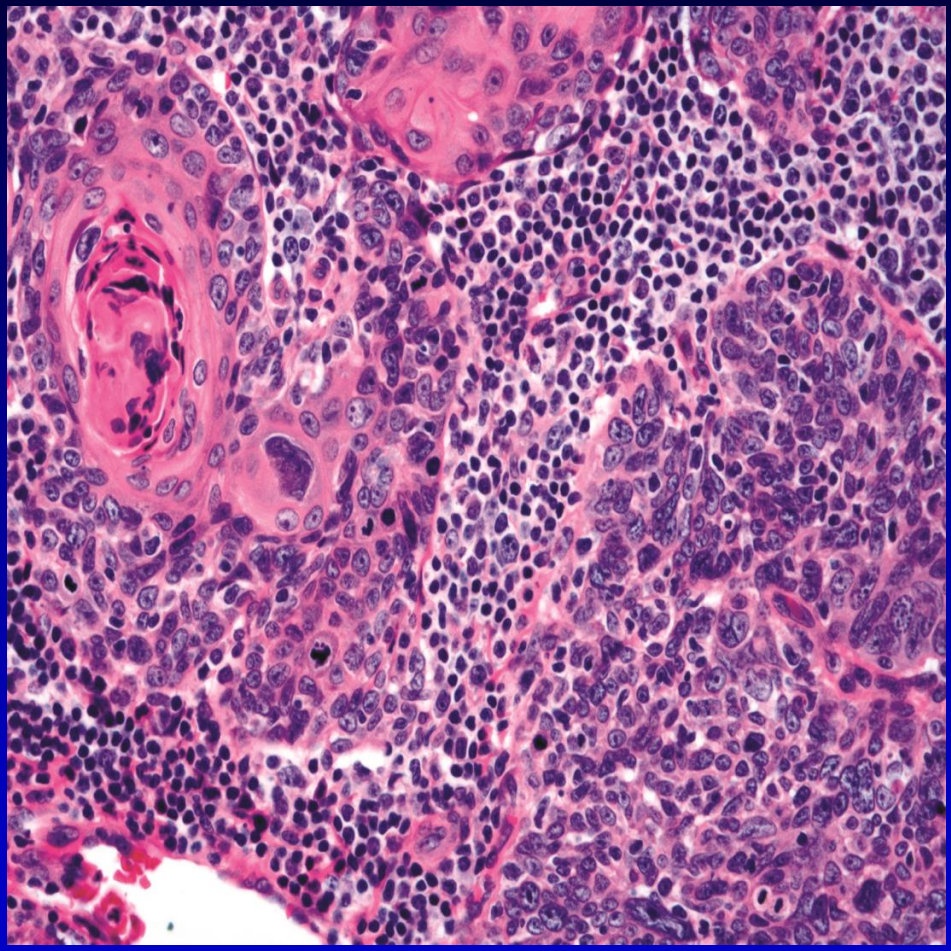
Oropharyngeal SCC, HPV-Positive Morphologic Spectrum

- Nonkeratinizing
- Hybrid
- Papillary SCC (PSCC)
- Basaloid SCC (BSCC)
- Lymphoepithelial-like
- Spindle cell SCC (sarcomatoid carcinoma)
- Adenosquamous (ciliated cell) carcinoma
- Sinonasal tract: HPV-related carcinoma with adenoid cystic-like features:

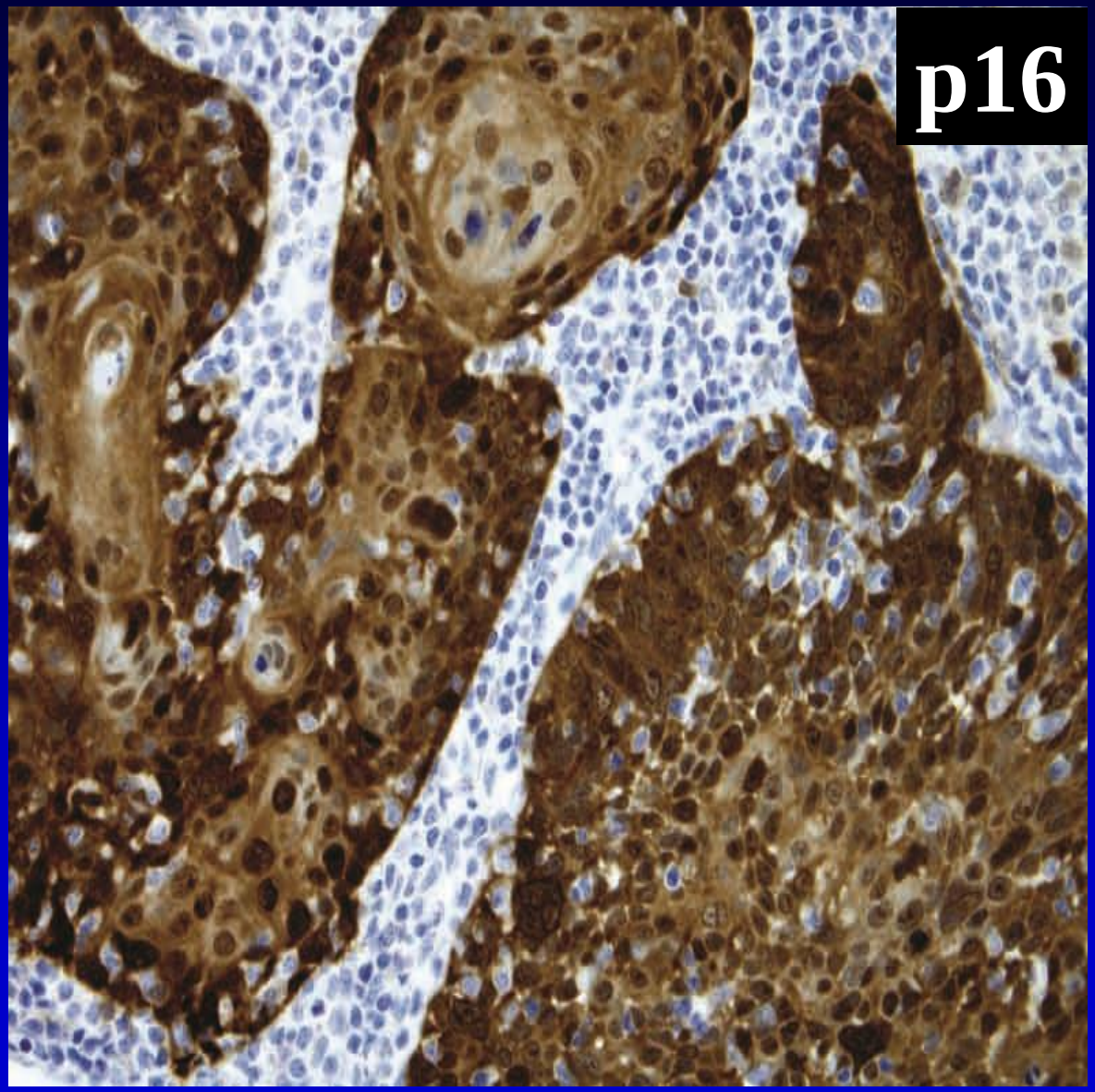
  → HPV-related multiphenotypic sinonasal carcinoma

Hybrid Oropharyngeal SCC

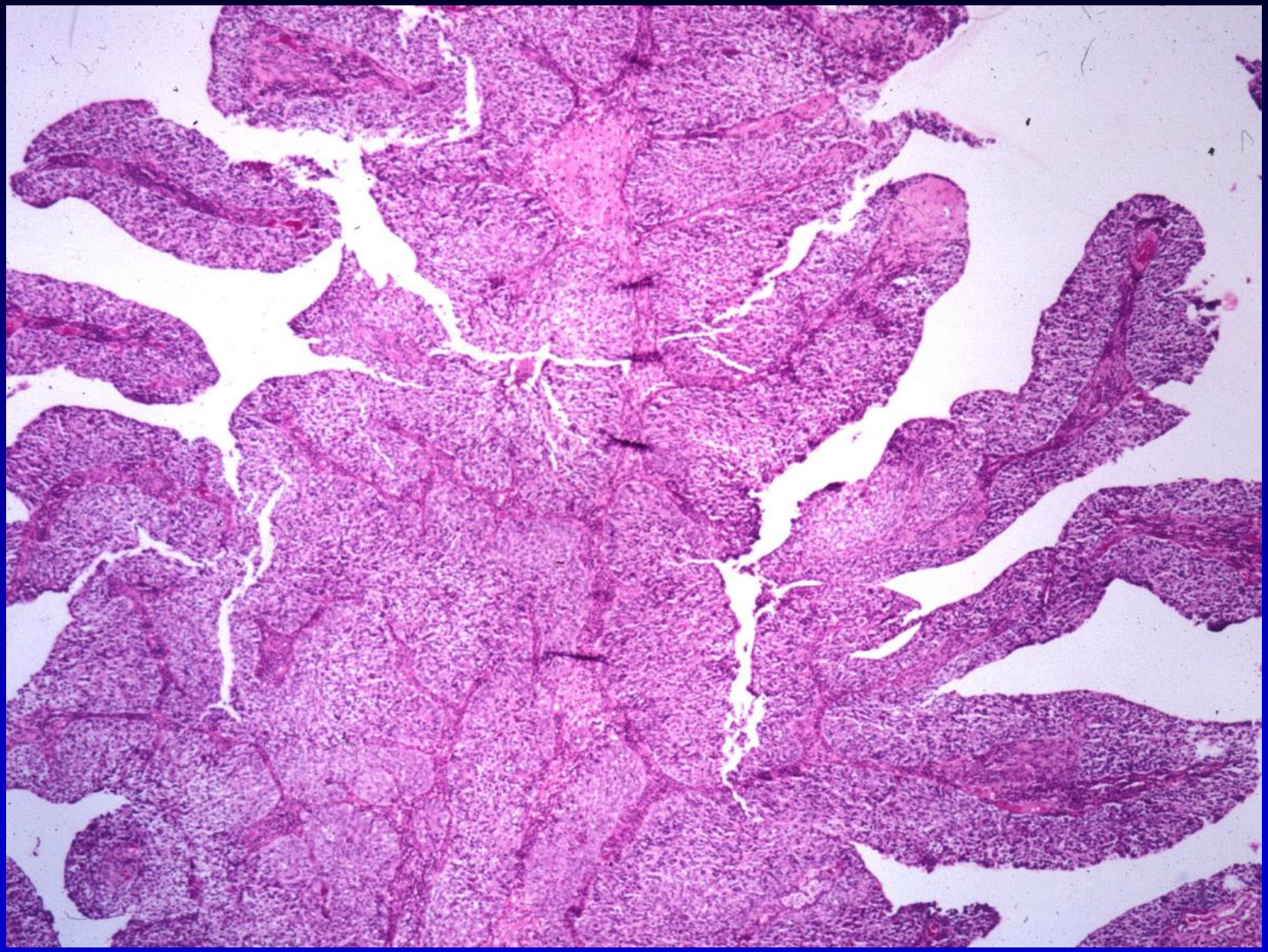




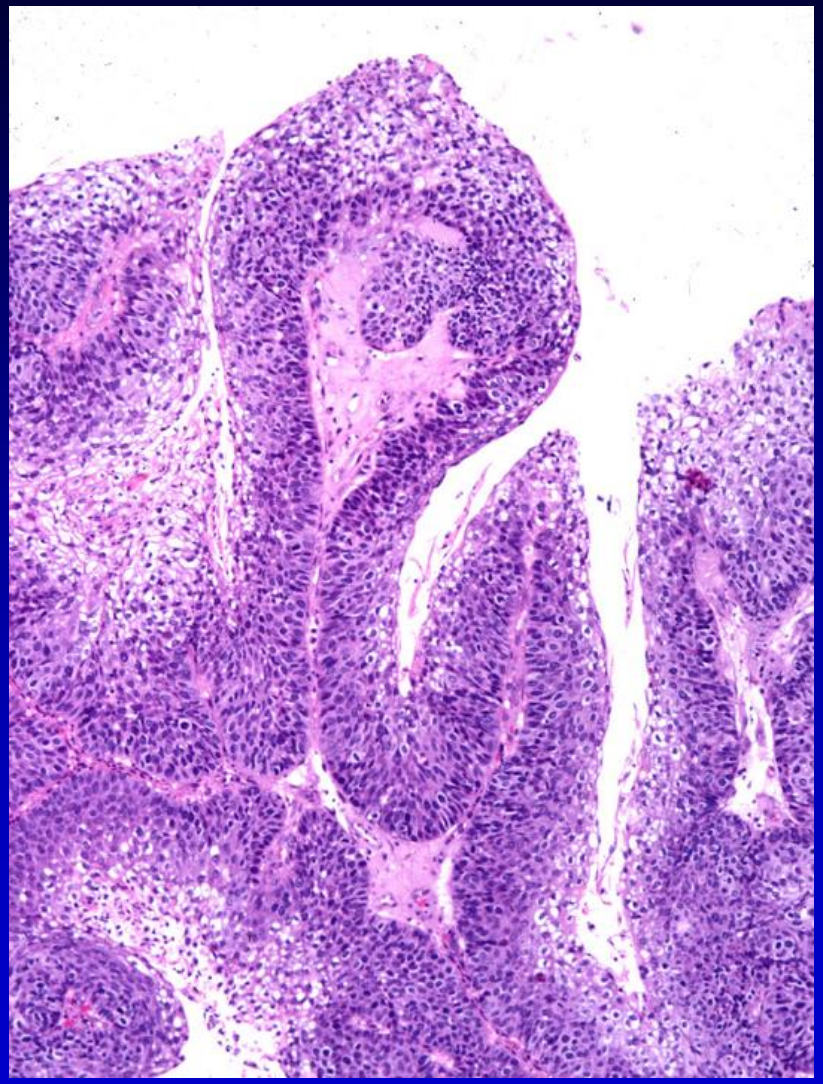
Hybrid Oropharyngeal SCC, HPV-positive

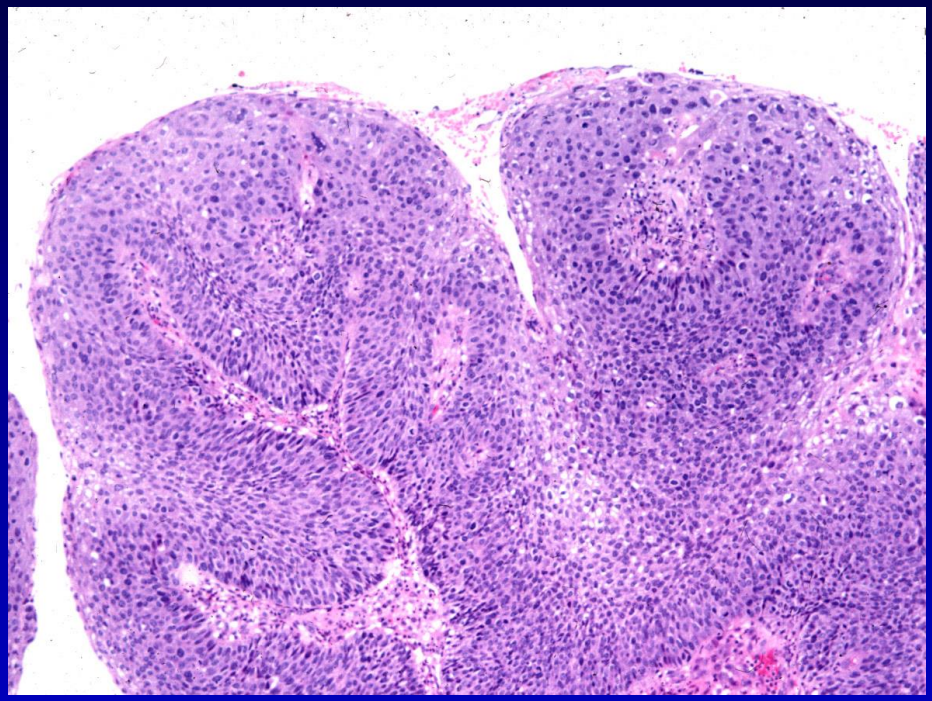


Papillary Squamous Cell Carcinoma (PSCC)

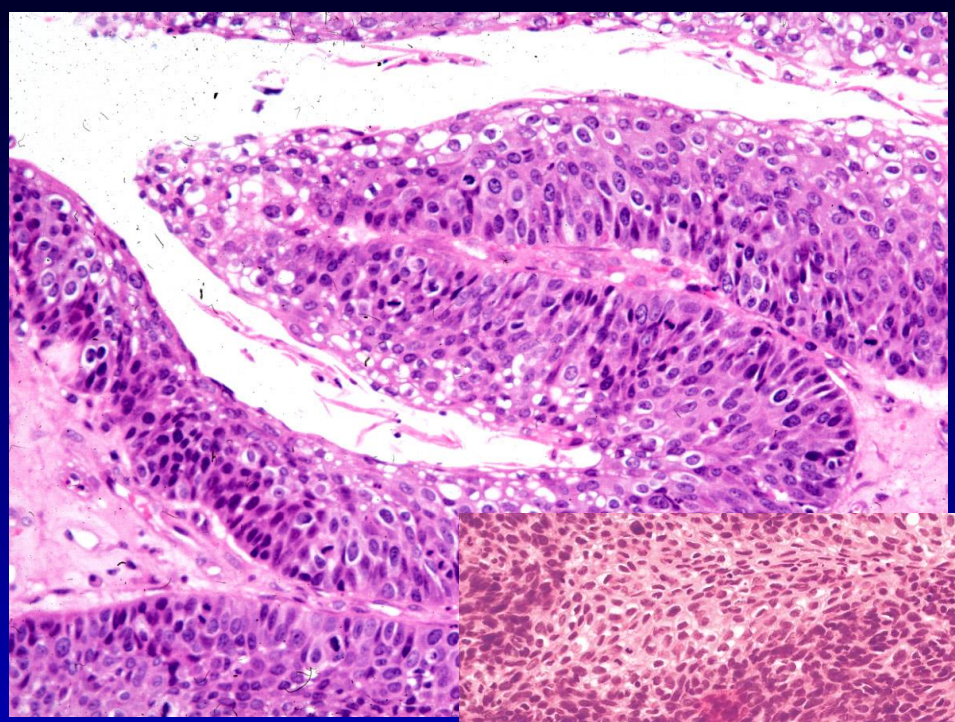


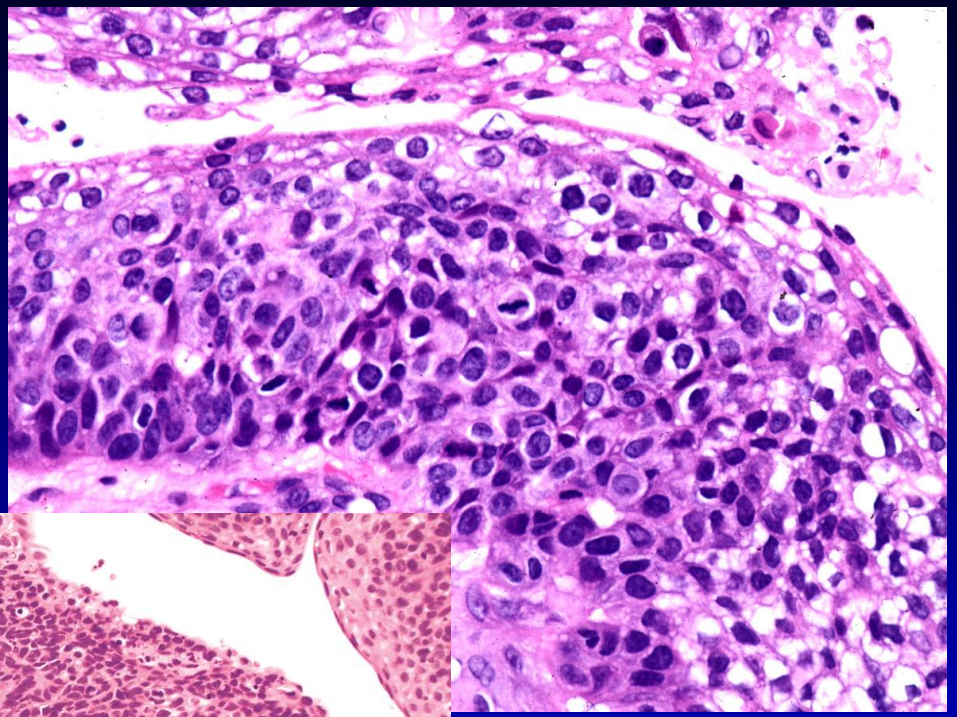
PSCC

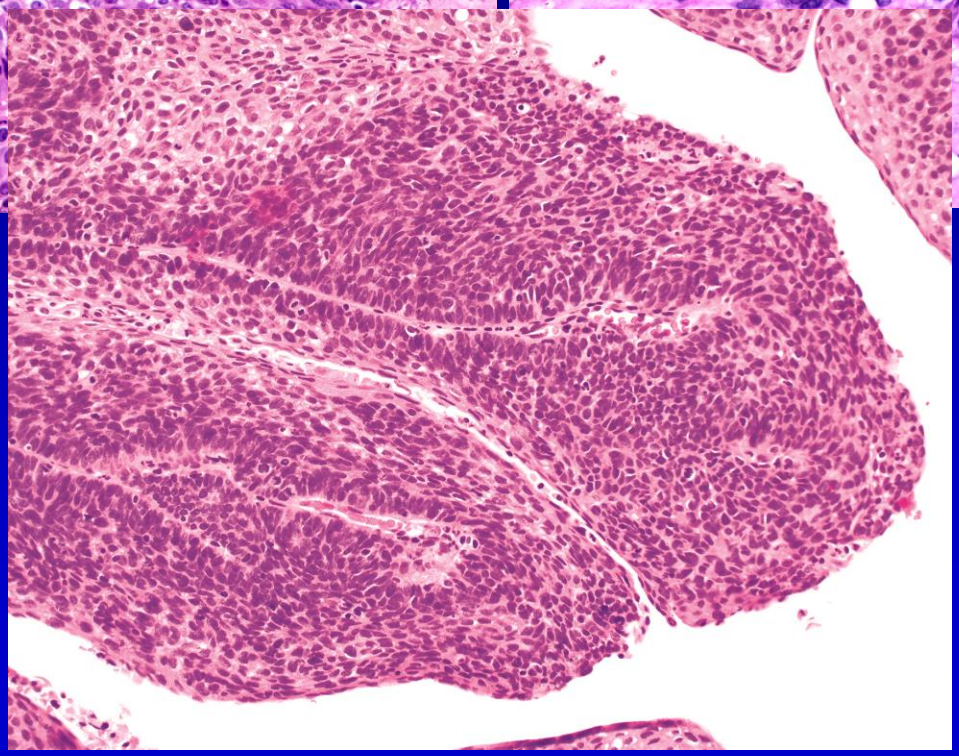




PSCC







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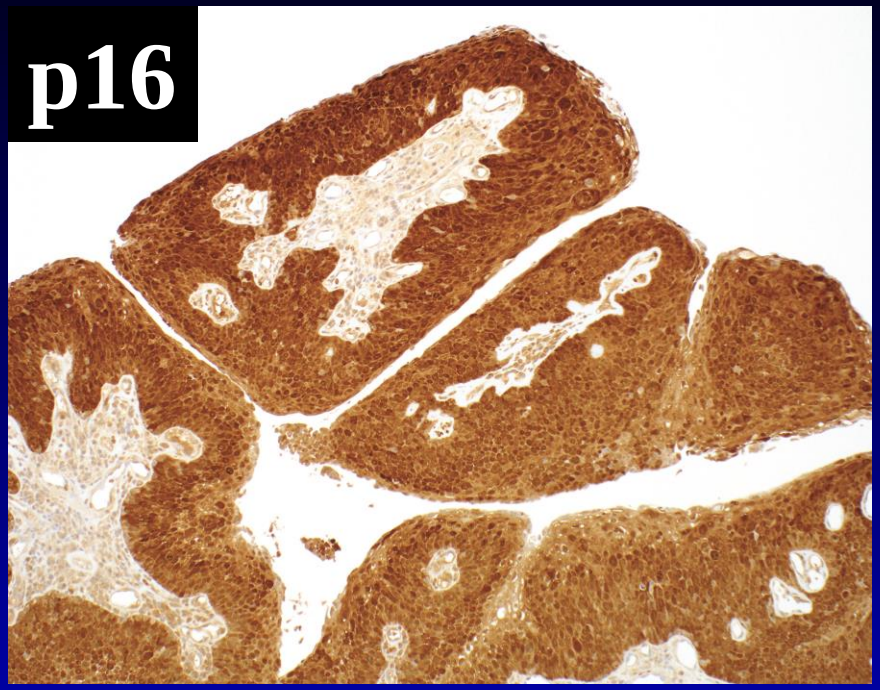
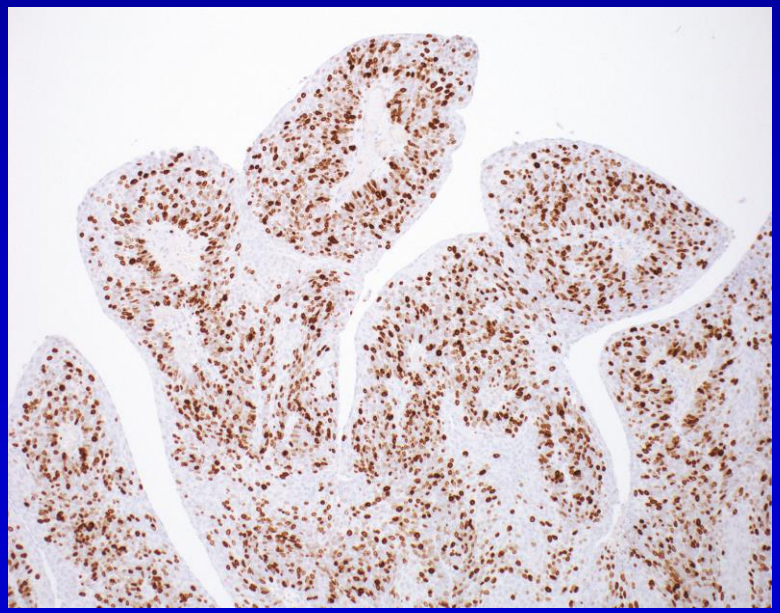
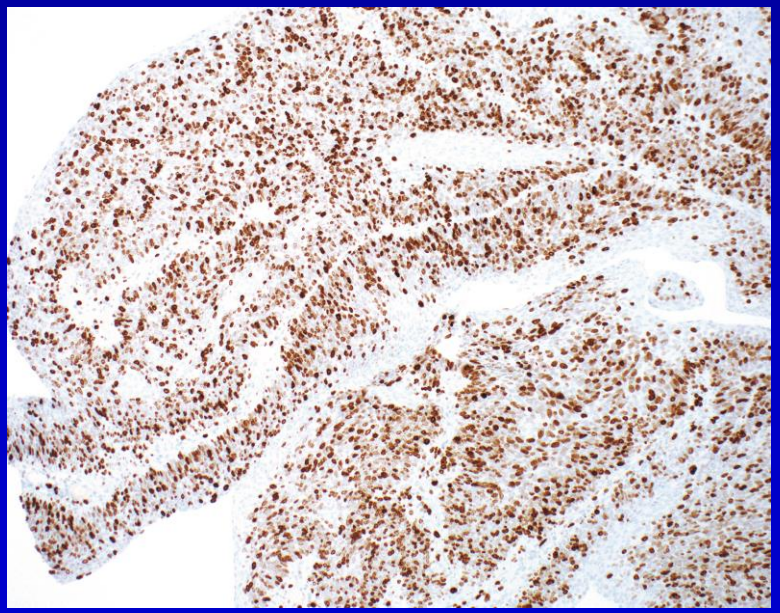
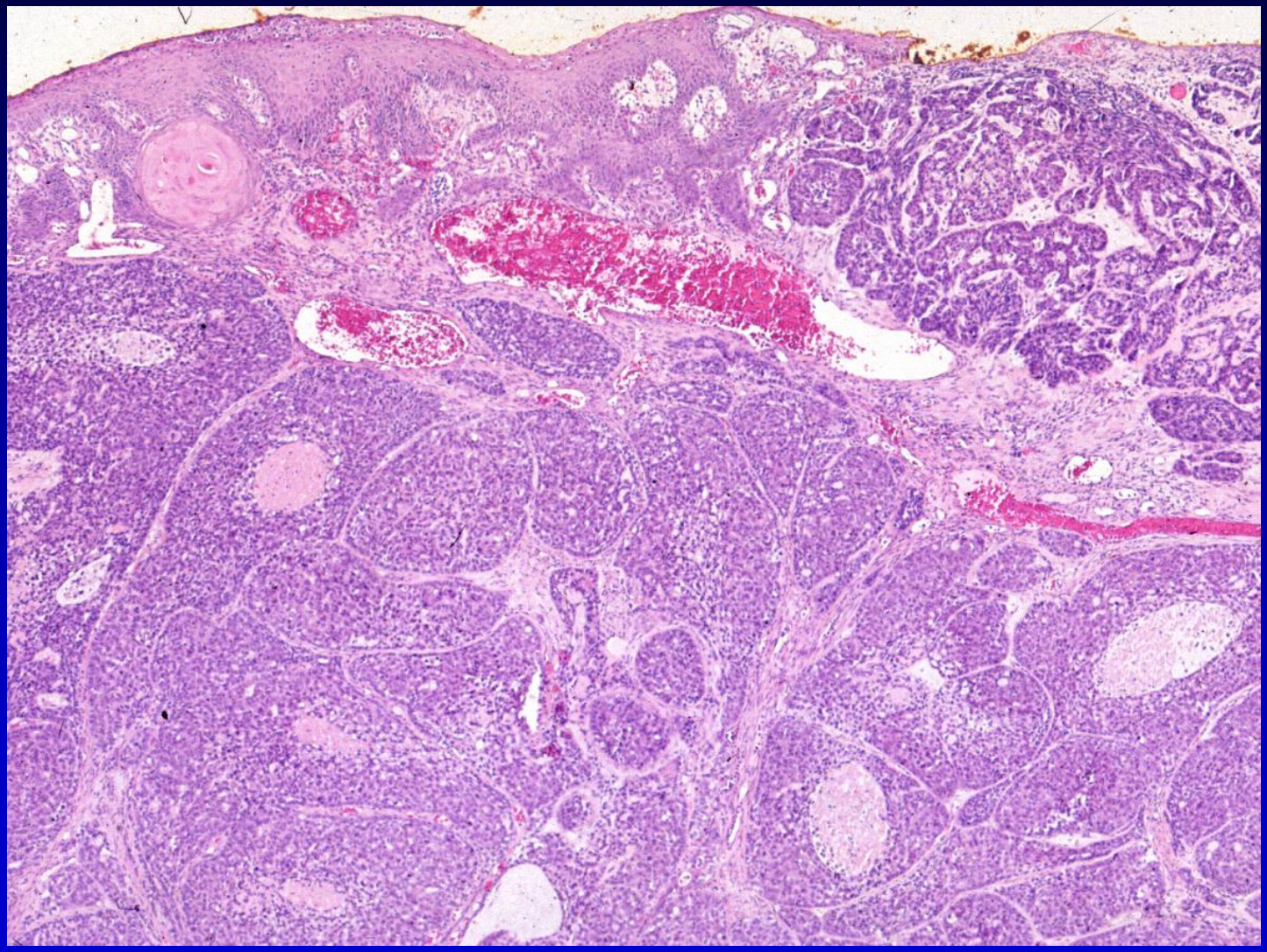




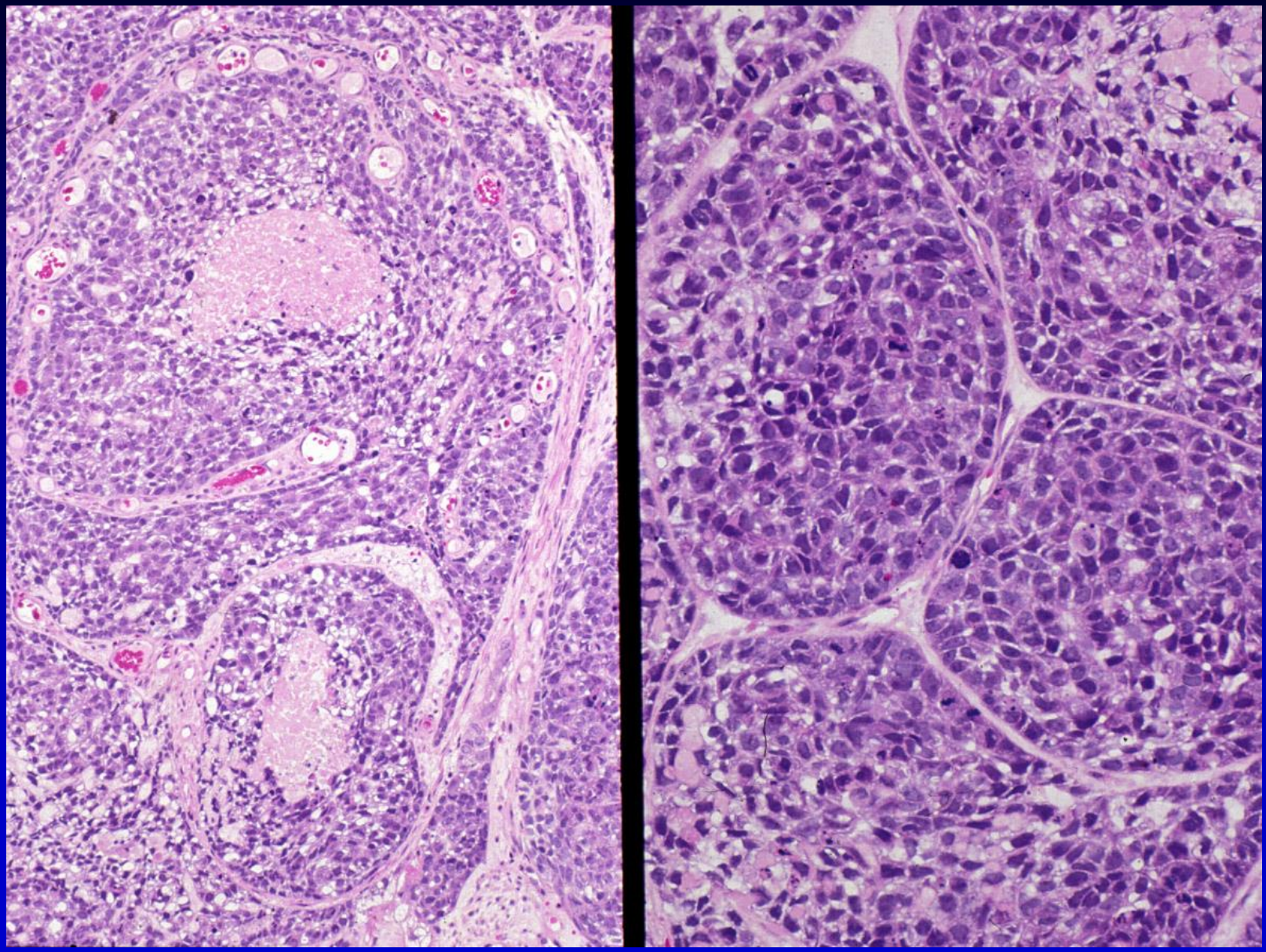
Ki67



Basaloid Squamous Cell Carcinoma (BSCC)



BSCC



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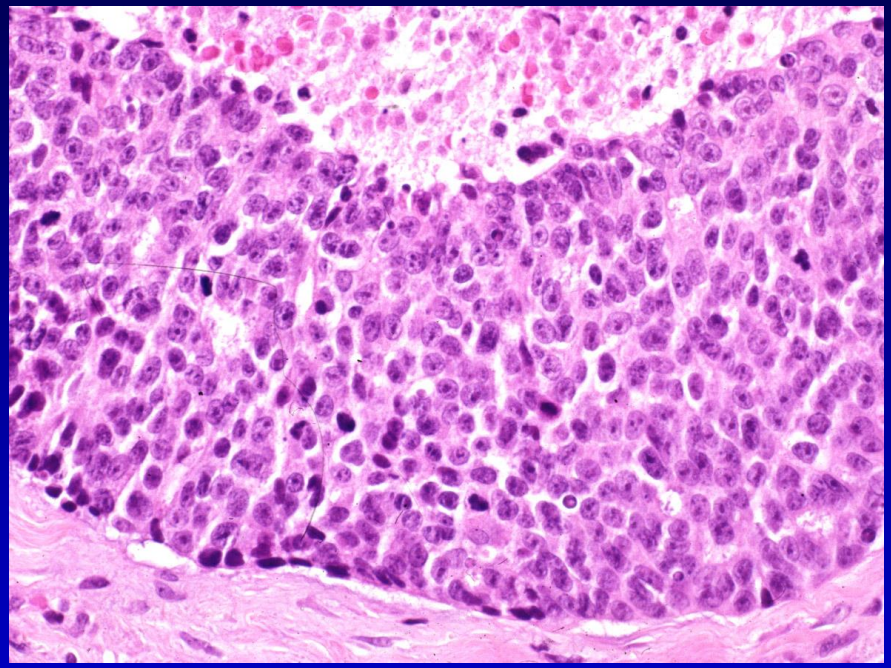
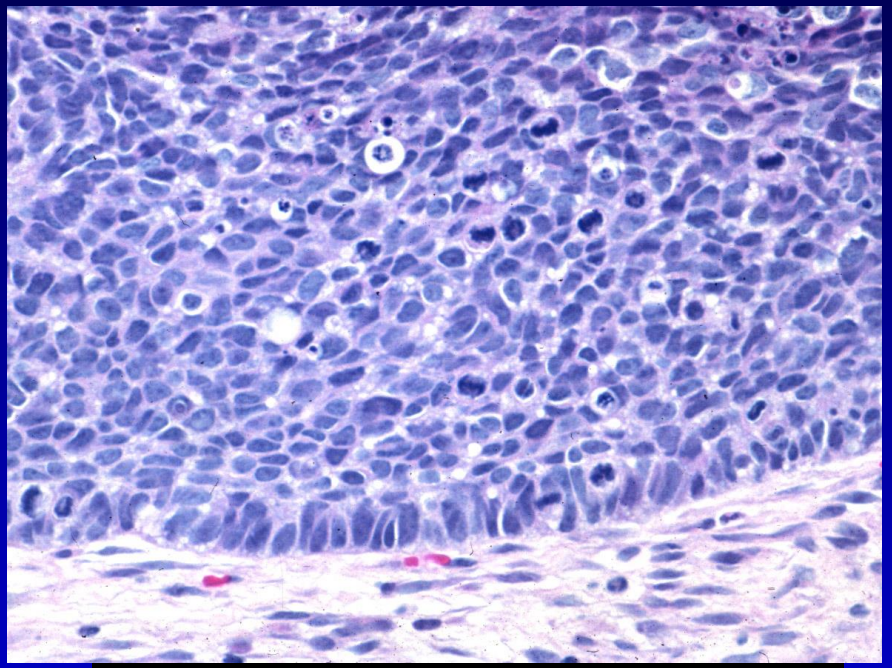
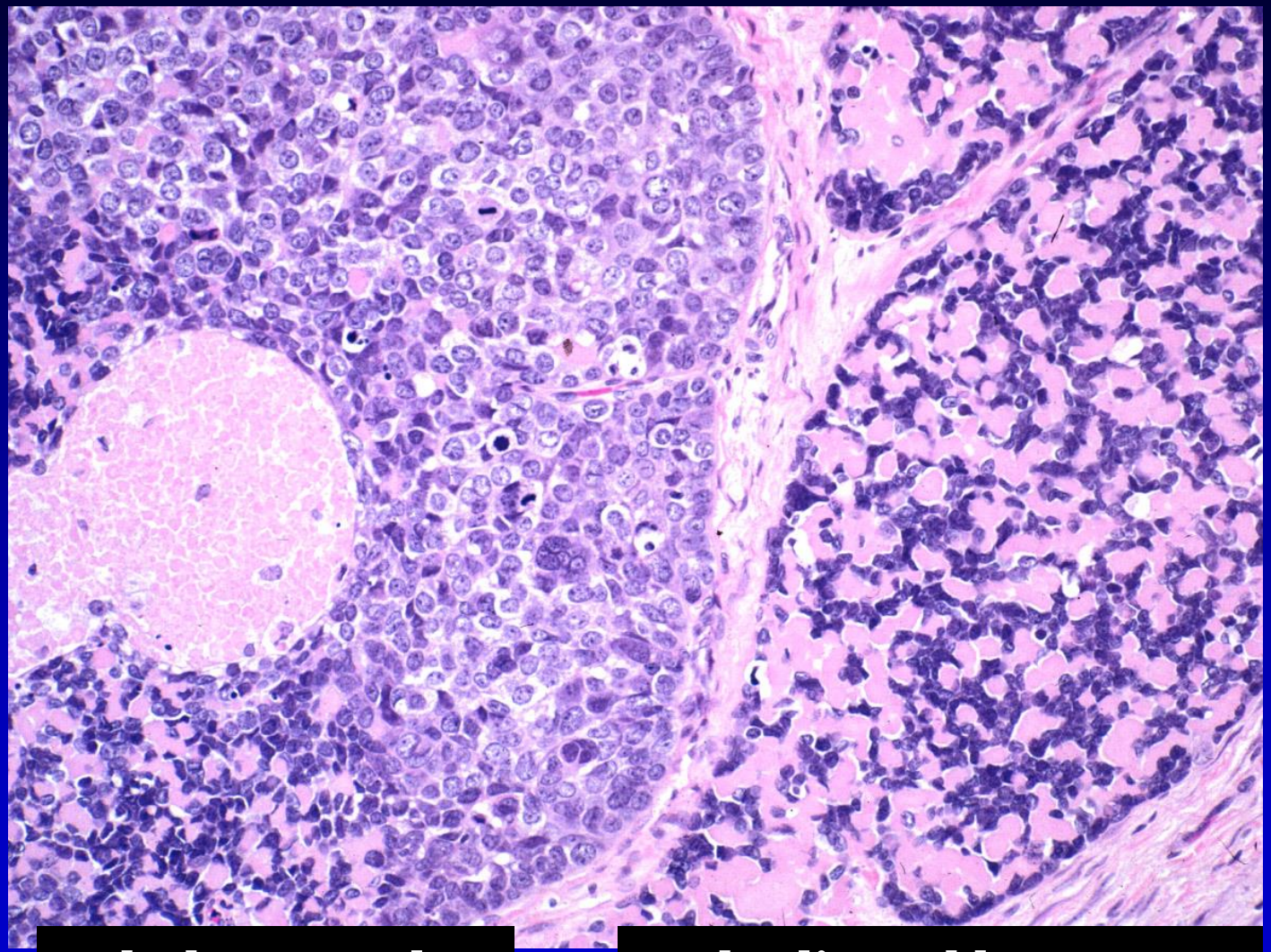




Nuclear palisading

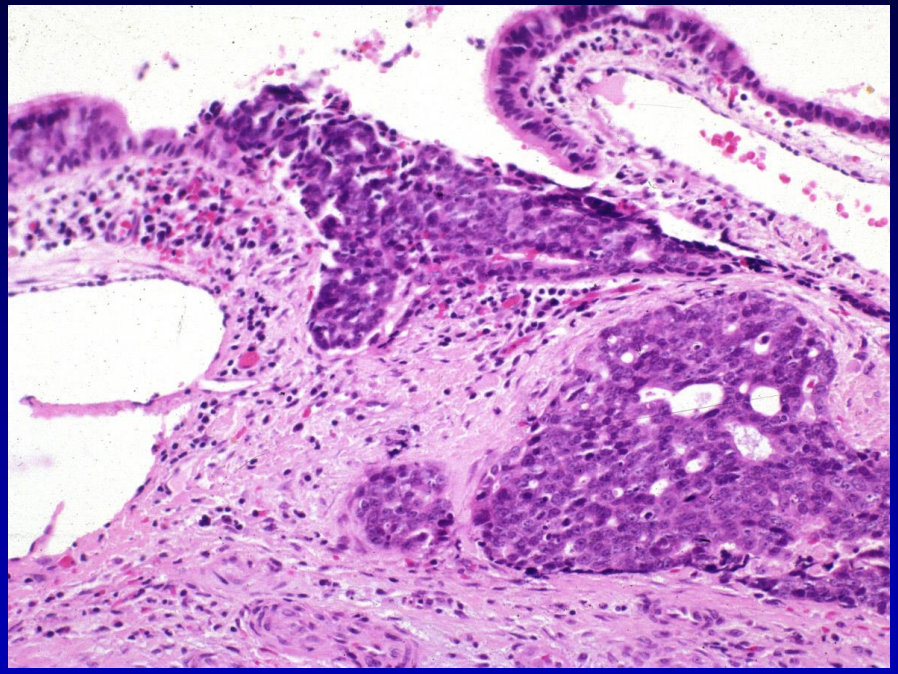
BSCC



Lobular growth, comedonecrosis

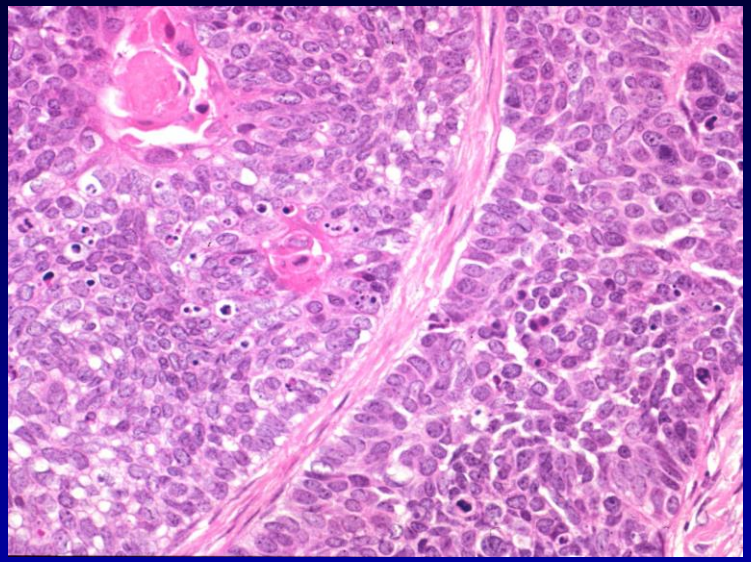
Reduplicated basement membrane-like material

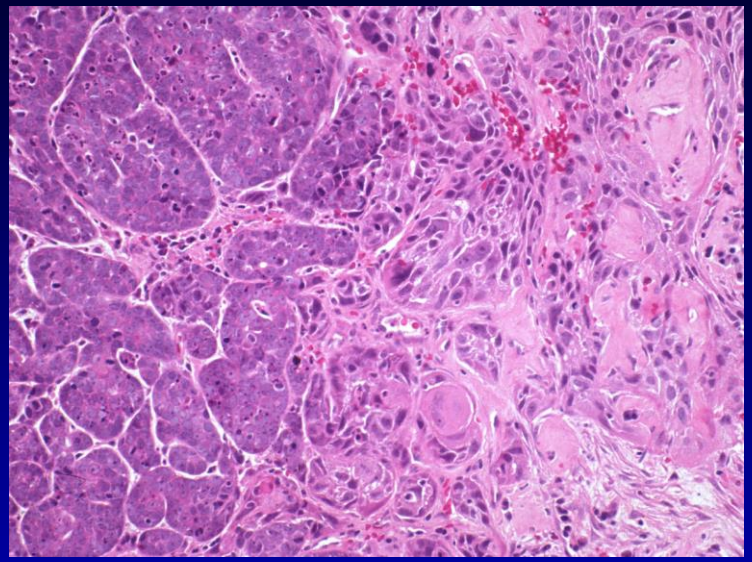
BSCC

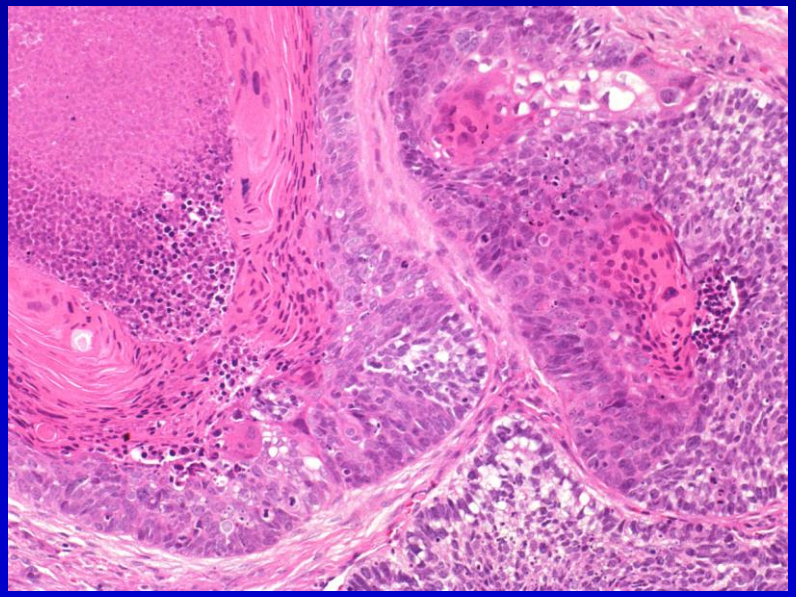


CIS

BSCC – Squamous Diff.







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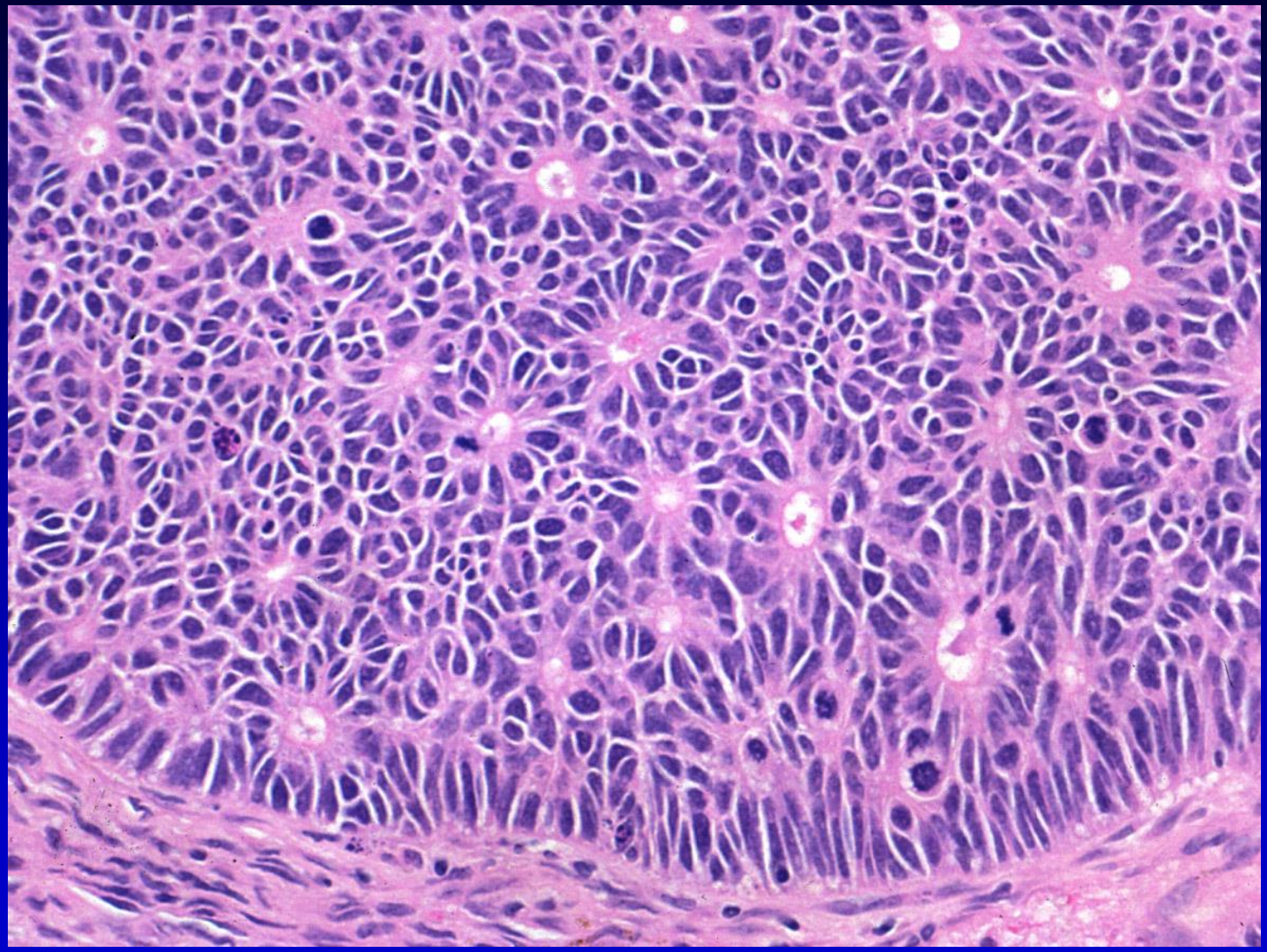
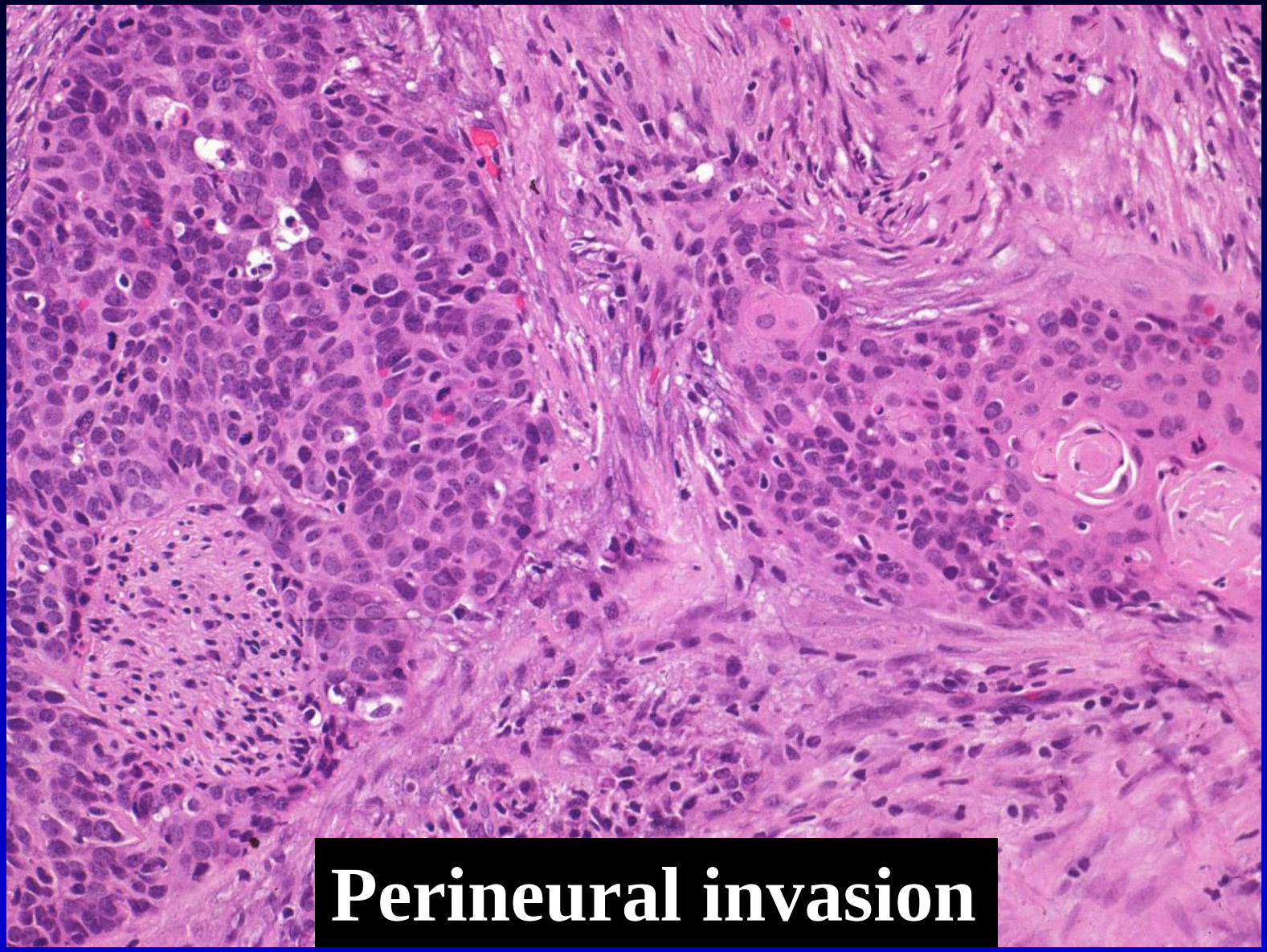


Rosettes & Nuclear Palisading

BSCC



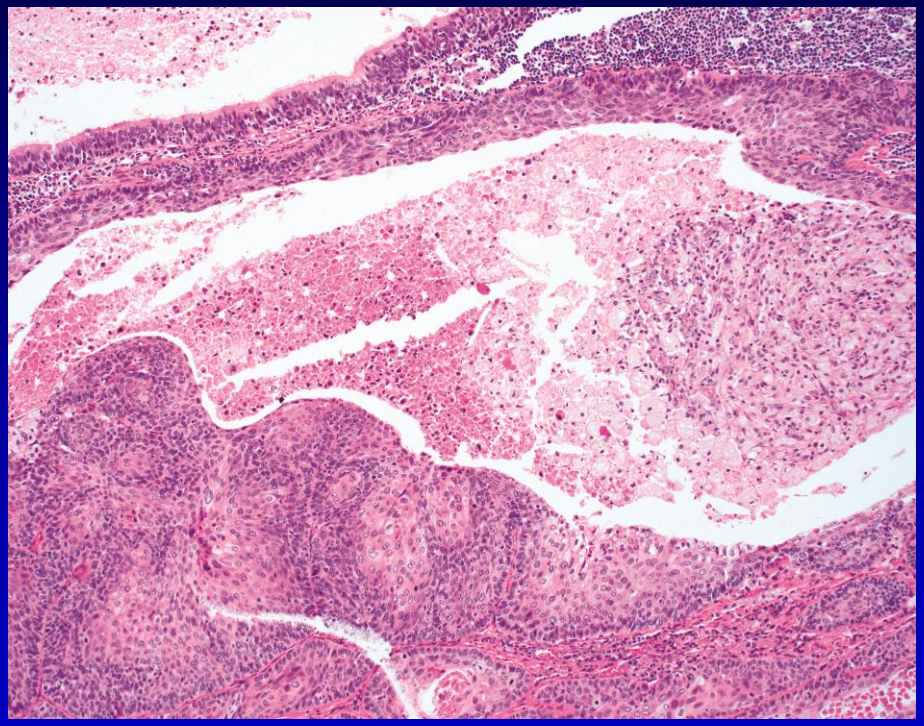
BSCC

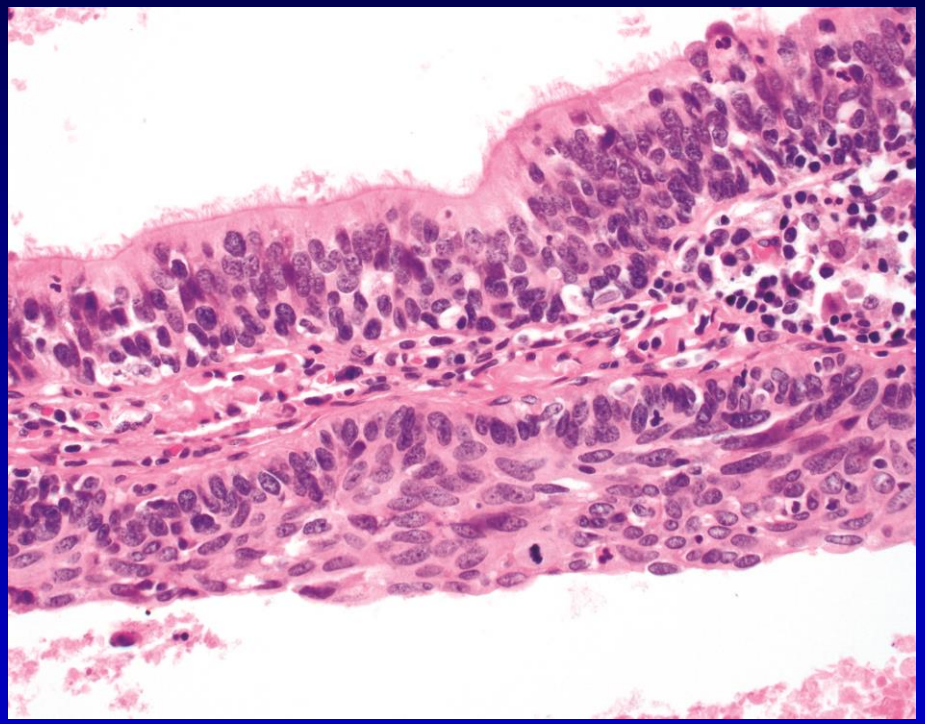
- **HPV-positive:**
  - **Better overall prognosis than histologically similar non-HPV associated head and neck BSCC (Am J Surg Pathol 2008;32:1044-50)**
- **Any tumor appearing to arise in the larynx/hypopharynx but that involves the oropharynx should be tested for HPV (p16)**

BSCC
Treatment and Prognosis

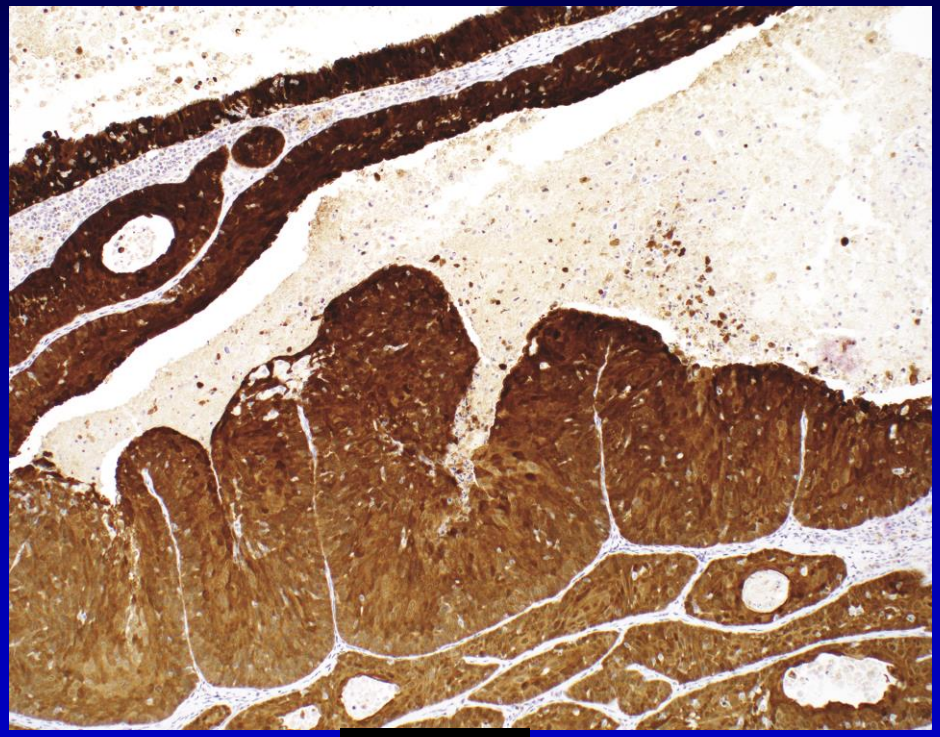
- Aggressive management:
  - Complete surgical resection
  - Radiotherapy and chemotherapy
- HPV-negative:
  - dismal prognosis
- Active smokers and those with nodal metastases at presentation have worse prognosis
- Lymphatic and hematogenous spread:
  - Regional lymph nodes (50-70%)
  - Lung, bone, skin and brain

Adenosquamous (Ciliated Cell) Carcinoma





Adenosquamous (Ciliated Cell) Carcinoma



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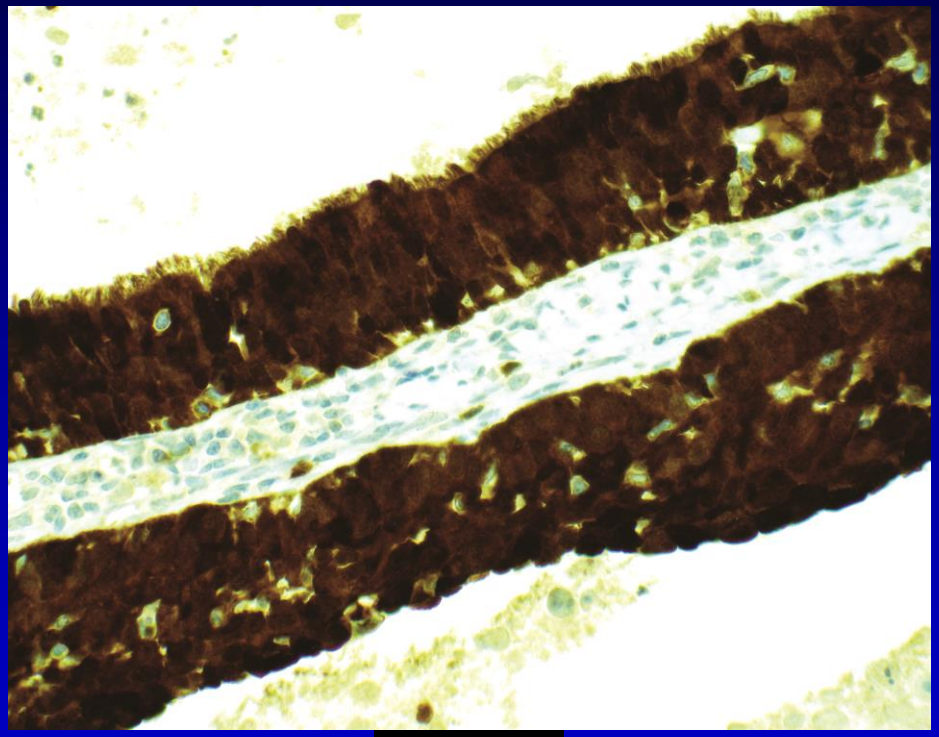

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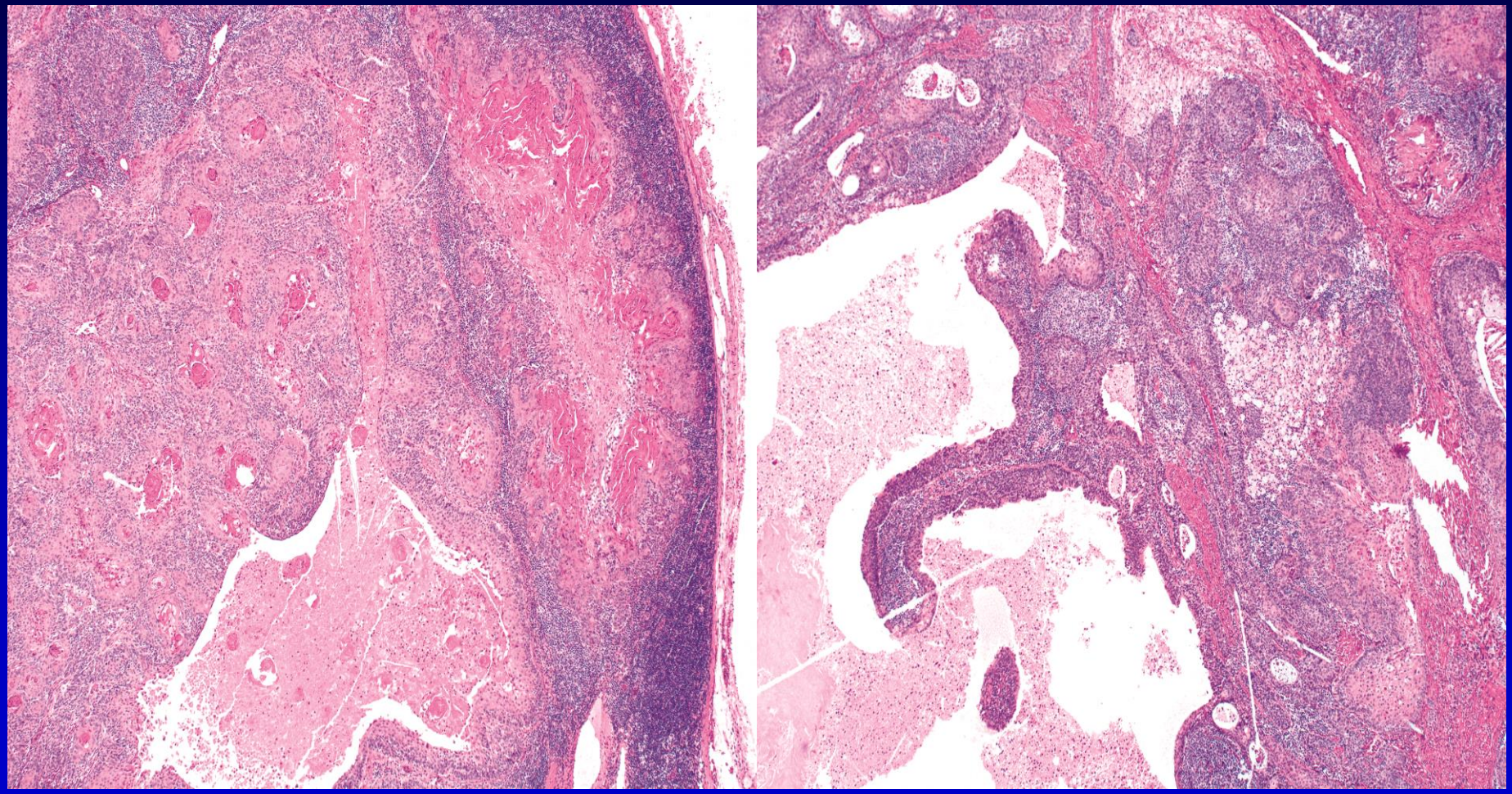
Metastatic Adenosquamous (Ciliated Cell) Carcinoma



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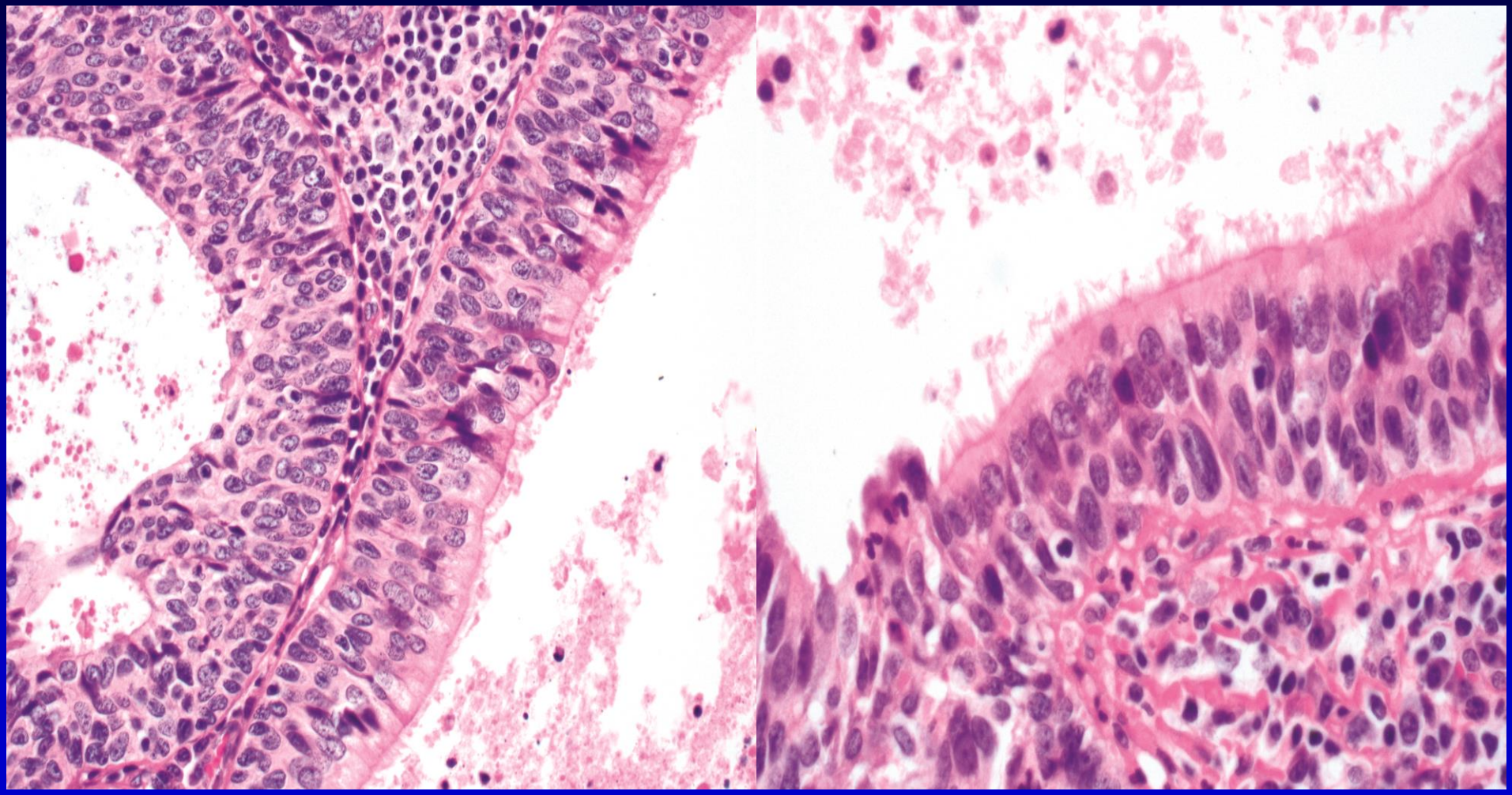
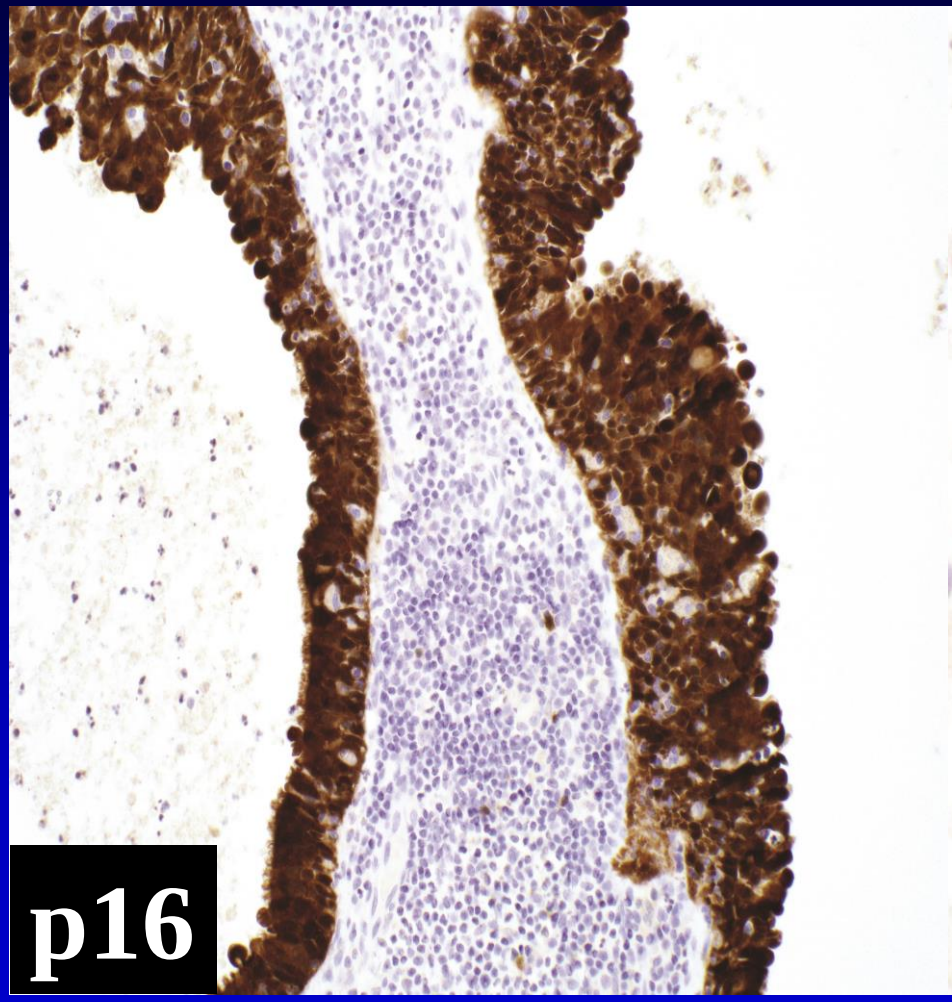
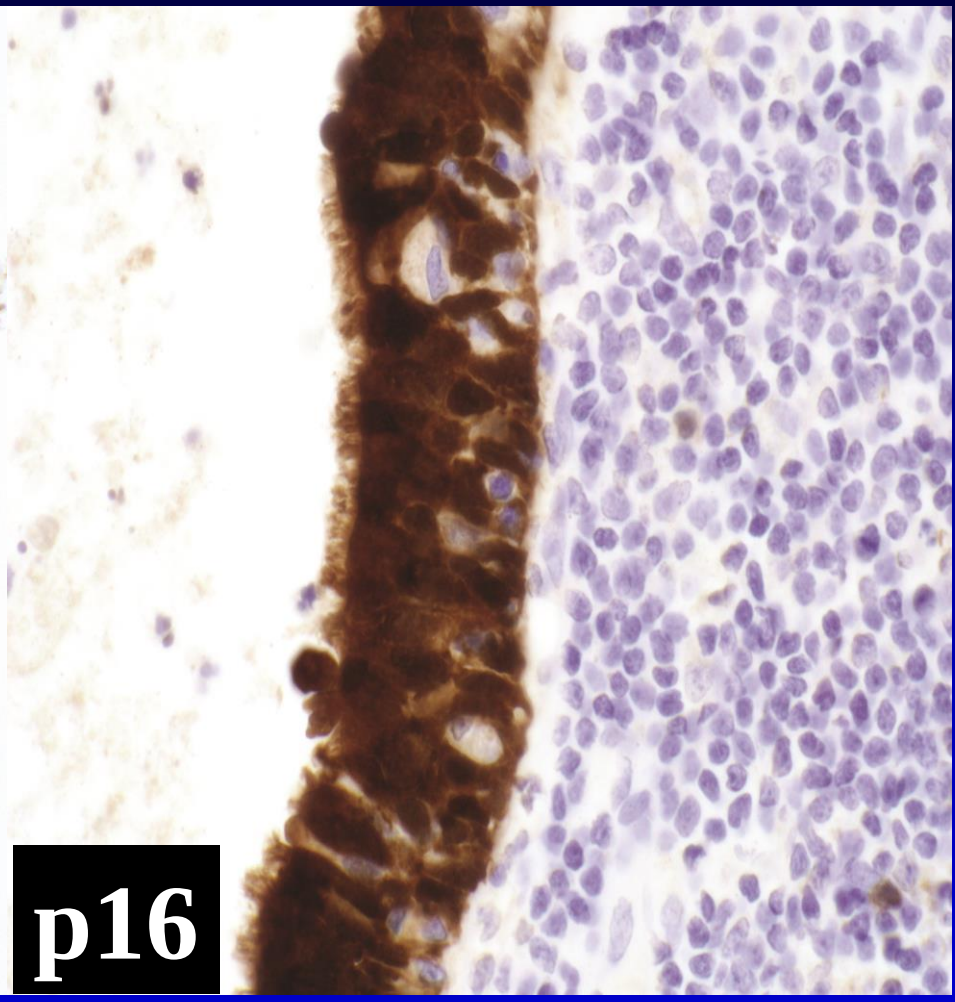


Metastatic Adenosquamous (Ciliated Cell) Carcinoma

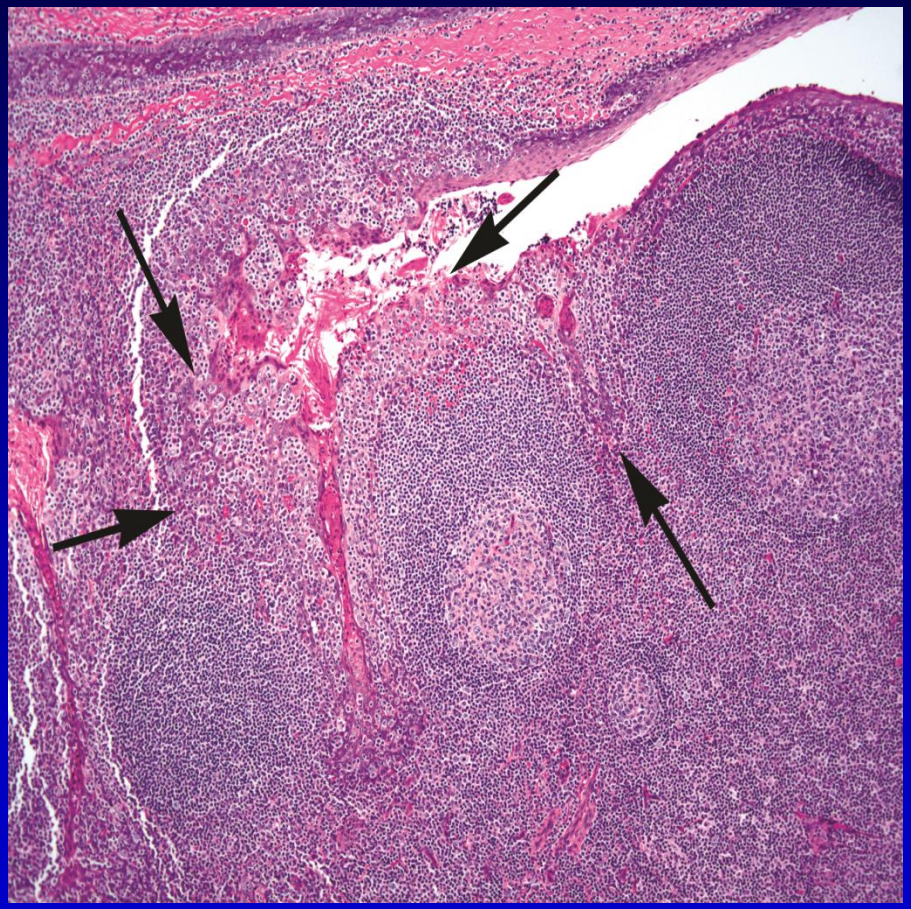


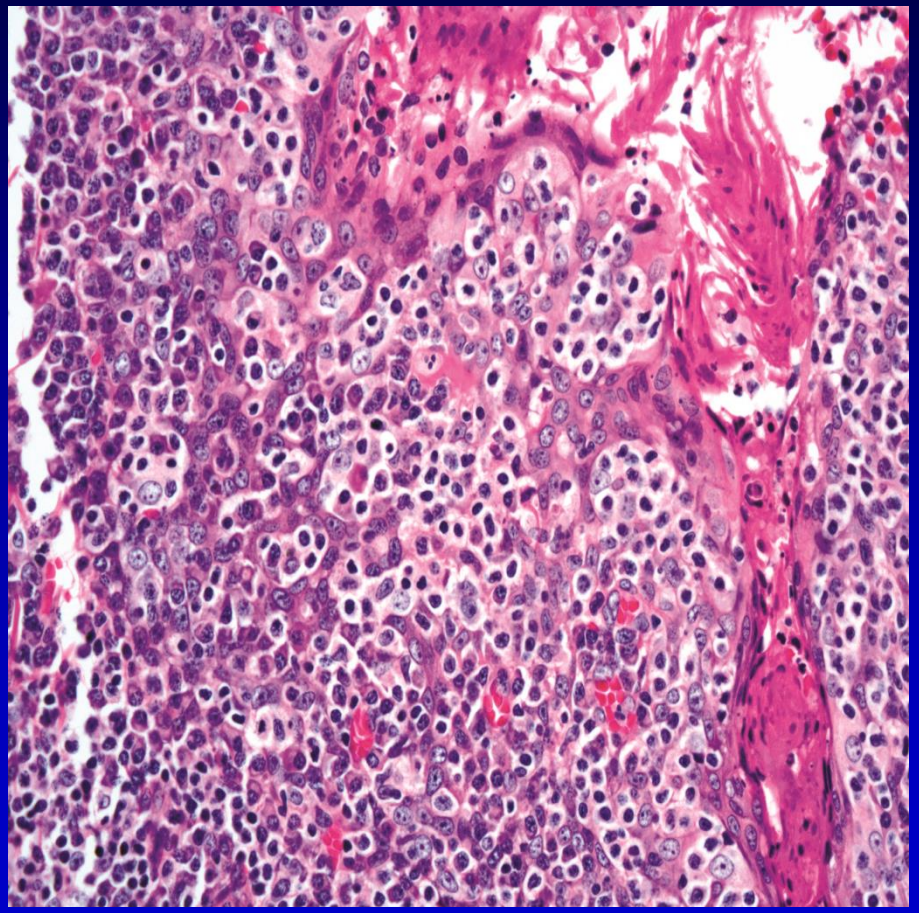


Ciliated HPV-Associated Carcinoma (aka Ciliated Adenosquamous Carcinoma)

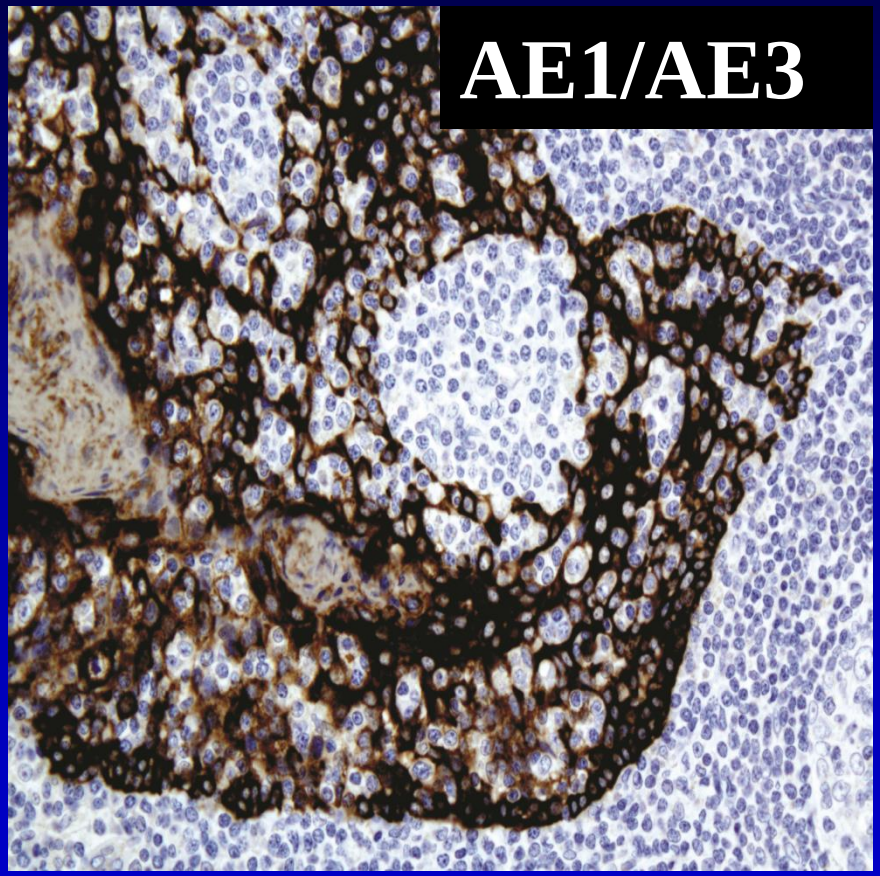
- **Bishop JA, Westra WH. Am J Surg Pathol 2015;39:1591-1595**
- **Radkay-Gonzalez L, et al. Head Neck Pathol 2016;10:167-175**

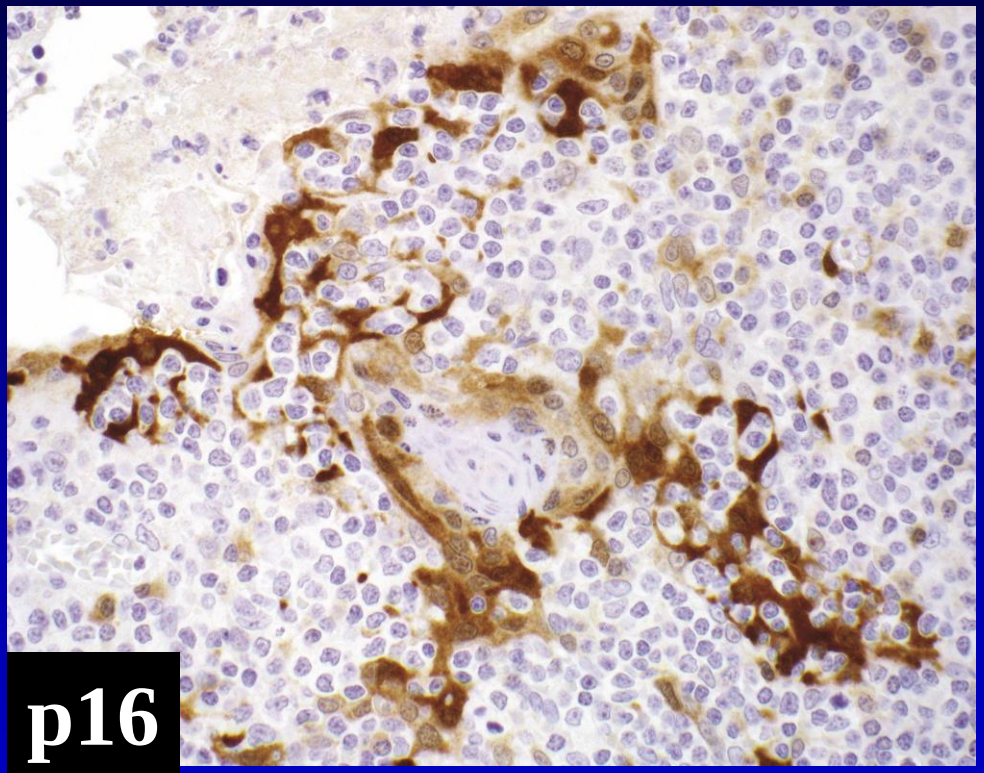
Oropharyngeal Reticulated Epithelium



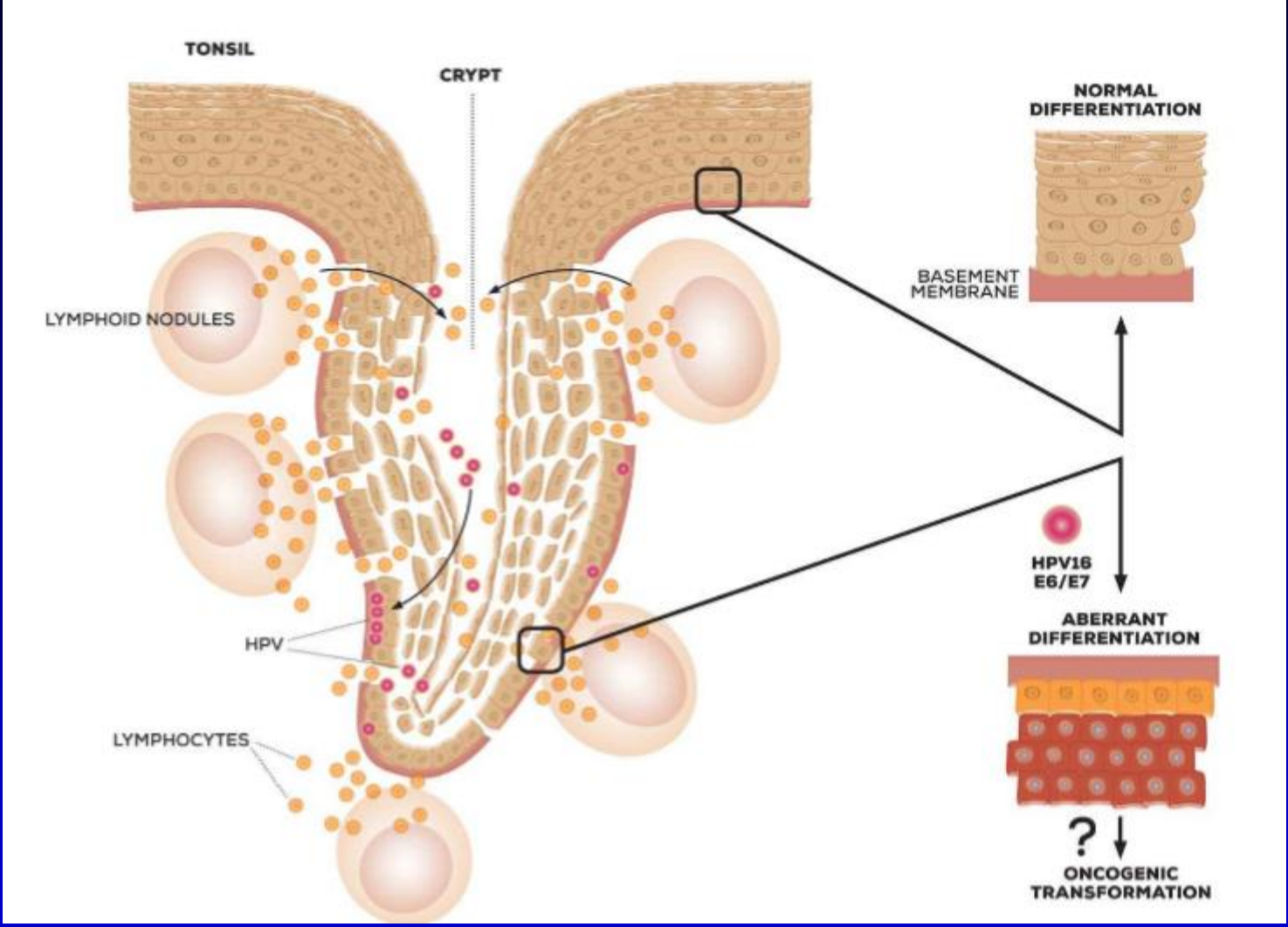


Oropharyngeal Reticulated Epithelium Immunohistochemistry



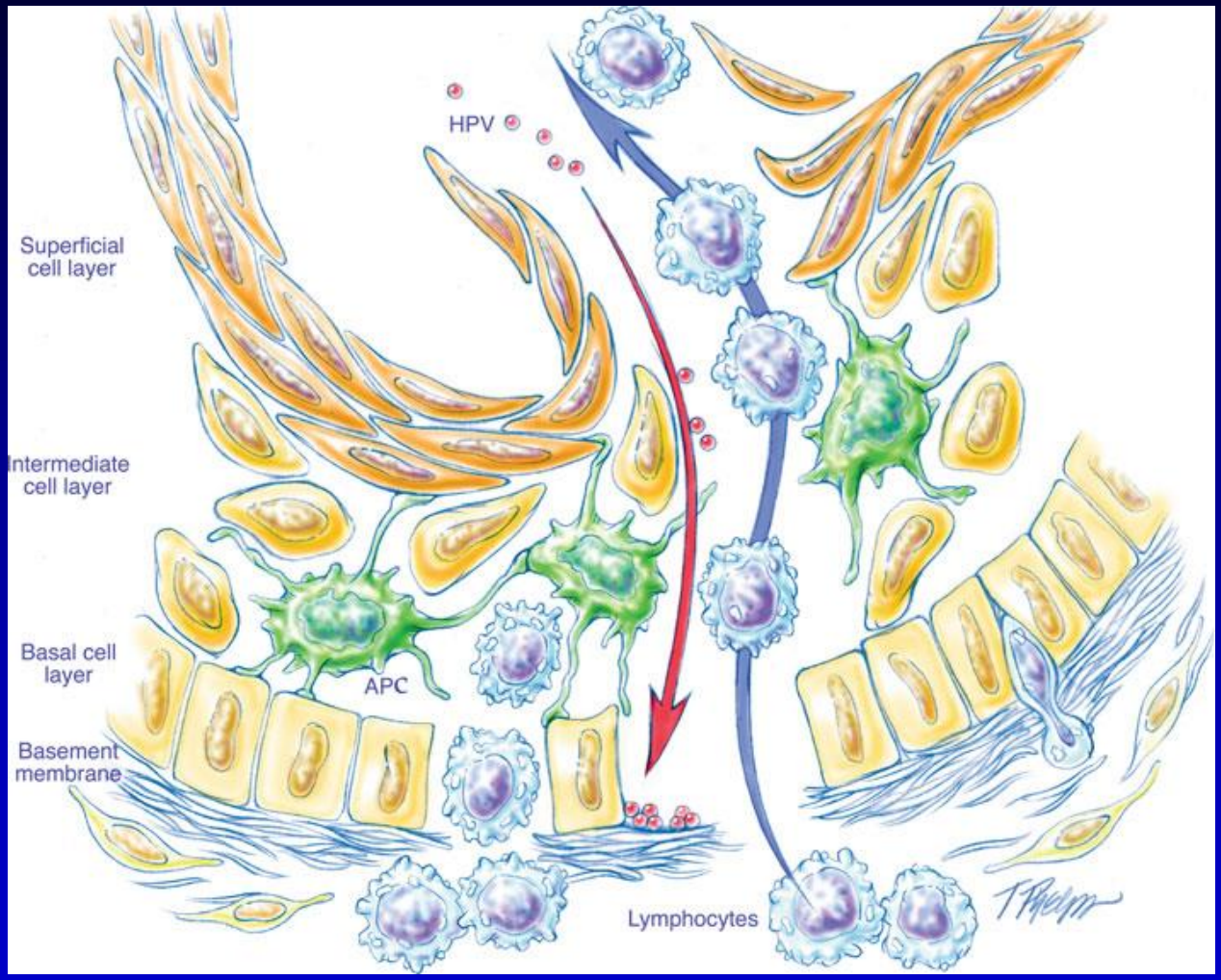


HPV & Reticulated Epithelium



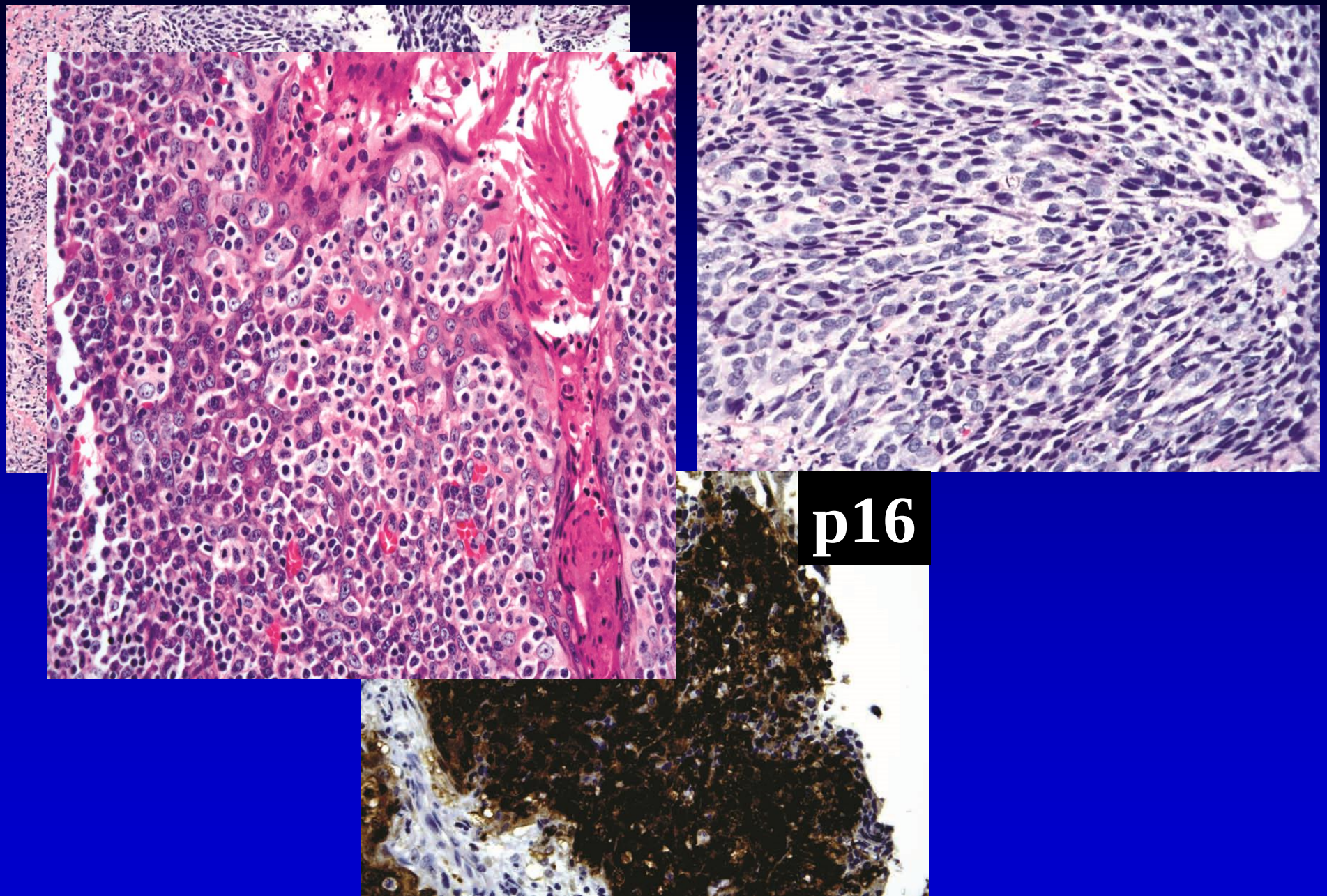
Berman TA, Schiller JT. Cancer 2017;123:2219-29

Reticulated Epithelium



Westra WH: Head & Neck Pathol 2012;6:S48-S54

Carcinoma involving Tonsillar Crypt ≠ CIS



CAP Testing Guidelines for High Risk (HR)-HPV in H&N SCC Lewis JS, et al. Arch Pathol Lab Med 2018;142:559-597

- Staining with IHC p16:
  - should be used as an initial screening method
  - nuclear & cytoplasmic positivity
  - > 70% cut off
- 14 Guideline statements
  - Strong recommendation
  - Recommendation
  - Expert consensus opinion
  - No recommendation

CAP Testing Guidelines for High Risk (HR)-HPV in H&N SCC

- **#1: Strong recommendation – should perform HR-HPV on all patients with newly diagnosed OPSCC, including all histologic subtypes; on primary tumor or on regional LN metastasis when clinical findings c/w OP origin**
- **#2: Recommendation – For oropharyngeal tissue specimens (i.e., noncytology), pathologists should perform HR-HPV testing by surrogate marker p16 IHC. Additional HPV-specific testing may be done at the discretion of the pathologist and/or treating clinician, or in the context of a clinical trial**

CAP Testing Guidelines for High Risk (HR)-HPV in H&N SCC

- **#3: Expert Consensus Opinion – Pathologists should *not* routinely perform HR-HPV testing on patients with non-SCCs of the oropharynx (neuroendocrine carcinomas; salivary gland carcinomas)**
- **#4: Recommendation – Pathologists should *not* routinely perform HR-HPV testing on patients with nonoropharyngeal primary tumors of the H&N**
- **#5: Recommendation – Pathologists should routinely perform HR-HPV testing on patients with metastatic SCC of unknown primary in a cervical upper or mid jugular chain lymph node. An explanatory note on the significance of a positive HPV result is recommended**

CAP Testing Guidelines for High Risk (HR)-HPV in H&N SCC

- **#6: Expert Consensus Opinion – For tissue specimens (i.e., noncytology) from patients presenting with metastatic SCC of unknown primary in a cervical upper or mid jugular chain lymph node, pathologists should perform p16 IHC**

NOTE: Additional HR-HPV testing on p16-positive cases should be performed for tumors located outside of level II or III (noncytology testing) in the neck and/or for tumors with keratinizing morphology

CAP Testing Guidelines for High Risk (HR)-HPV in H&N SCC

- **#7: Expert Consensus Opinion – Pathologists should perform HR-HPV testing on head and neck fine needle aspiration (FNA) SCC samples from all patients with known OPSCC not previously tested for HR-HPV, with suspected OPSCC, or with metastatic SCC of unknown primary**

NOTE: No recommendation is made for or against any specific testing methodology for HR-HPV testing in FNA samples. If the result of HR-HPV testing on the FNA sample is negative, testing should be performed on tissue if it becomes available. If pathologists use cytology samples for p16 IHC testing, they should validate the criteria (i.e., cutoff) for a positive result

CAP Testing Guidelines for High Risk (HR)-HPV in H&N SCC

- **#8: Expert Consensus Opinion – Pathologists should report p16 IHC positivity as a surrogate for HR-HPV in tissue specimens (i.e., non-cytology) when there is at least 70% nuclear and cytoplasmic expression with at least moderate to strong intensity.**

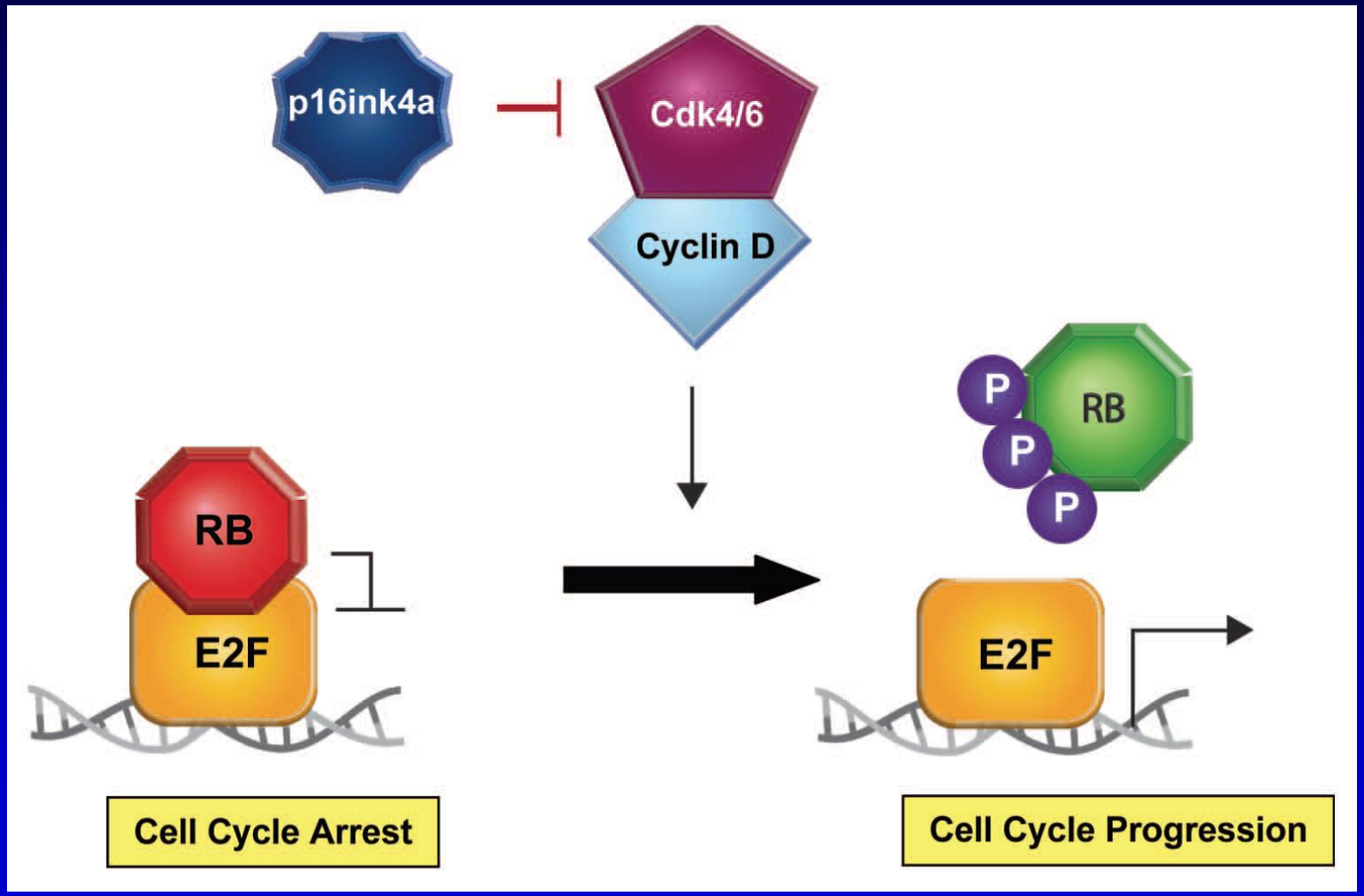
CAP Testing Guidelines for High Risk (HR)-HPV in H&N SCC

- **#9: Expert Consensus Opinion – Pathologists should *not* routinely perform low-risk HPV testing on patients with head and neck carcinomas**
- **#10: Expert Consensus Opinion - Pathologists should *not* repeat HPV testing on patients with locally recurrent, regionally recurrent, or persistent tumor if primary tumor HR-HPV status has already been established. If initial HR-HPV status was never assessed or results are unknown, testing is recommended. HPV testing may be performed on a case-by-case basis for diagnostic purposes if there is uncertainty regarding whether the tumor in question is a recurrence or a new primary SCC**

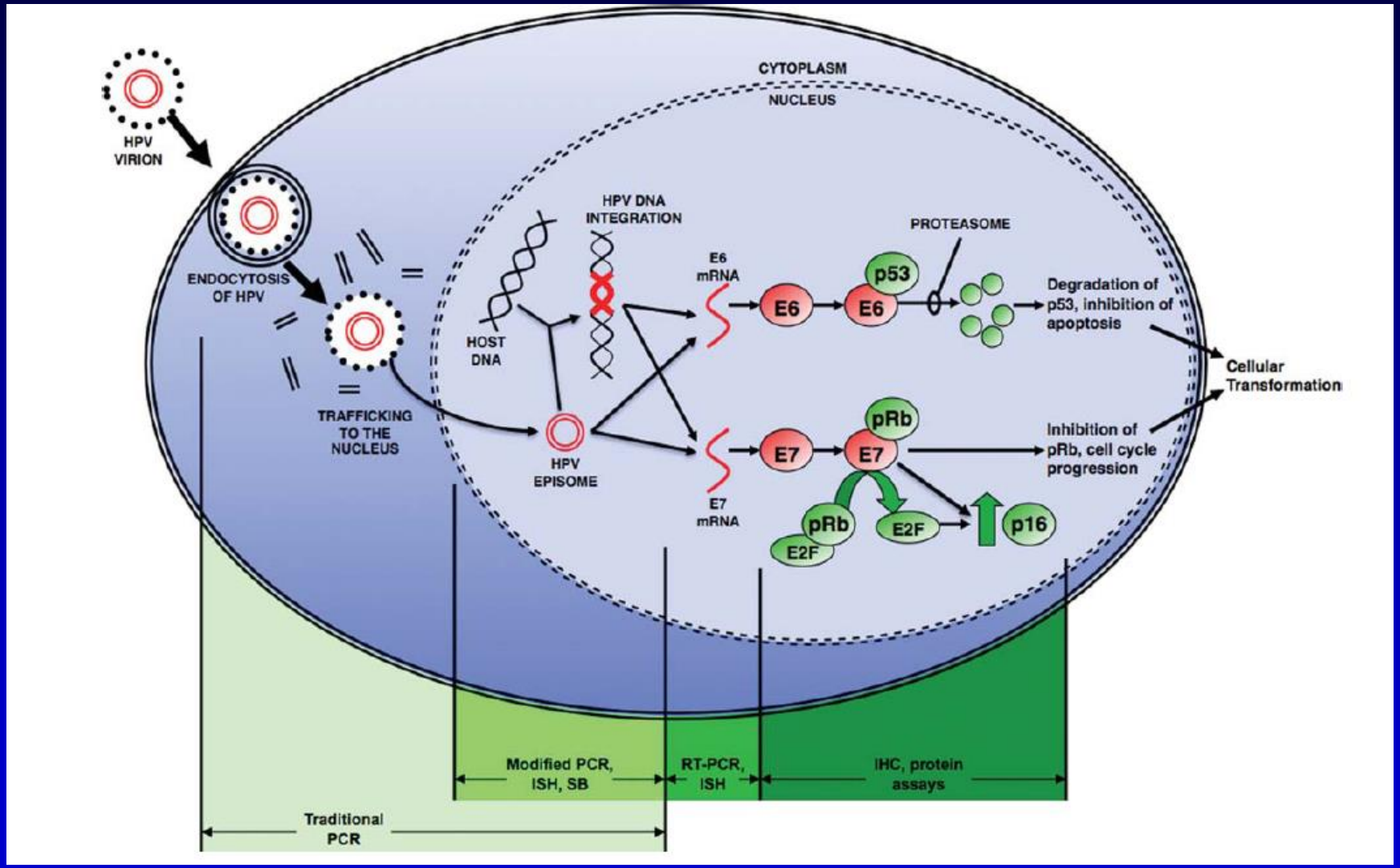
CAP Testing Guidelines for High Risk (HR)-HPV in H&N SCC

- **#11: Expert Consensus Opinion – Pathologists should *not* routinely perform HR-HPV testing on patients with distant metastases if primary tumor HR-HPV status has been established**
- **#12: Expert Consensus Opinion – Pathologists should report primary OPSCCs that test positive for HR-HPV or its surrogate marker p16 as HPV-positive/p16-positive**
- **#13: Expert Consensus Opinion – Pathologists should *not* provide a tumor grade or differentiation status for HPV-positive/p16-positive OPSCCs**

p16 functions to activate RB-dependent cell cycle arrest



Oropharyngeal HPV-related SCC



Distinct oncogenic pathways leading to p16 induction

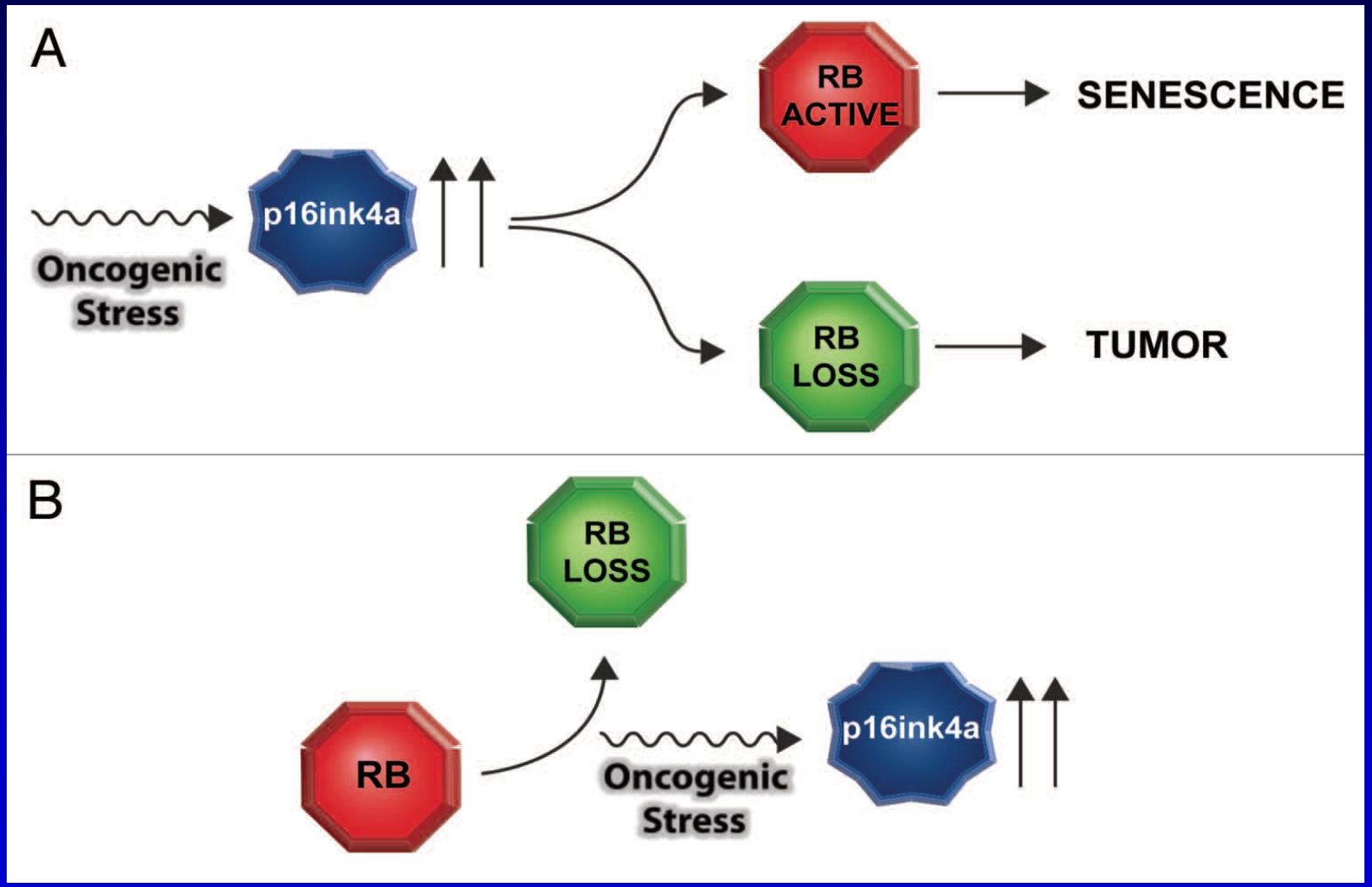
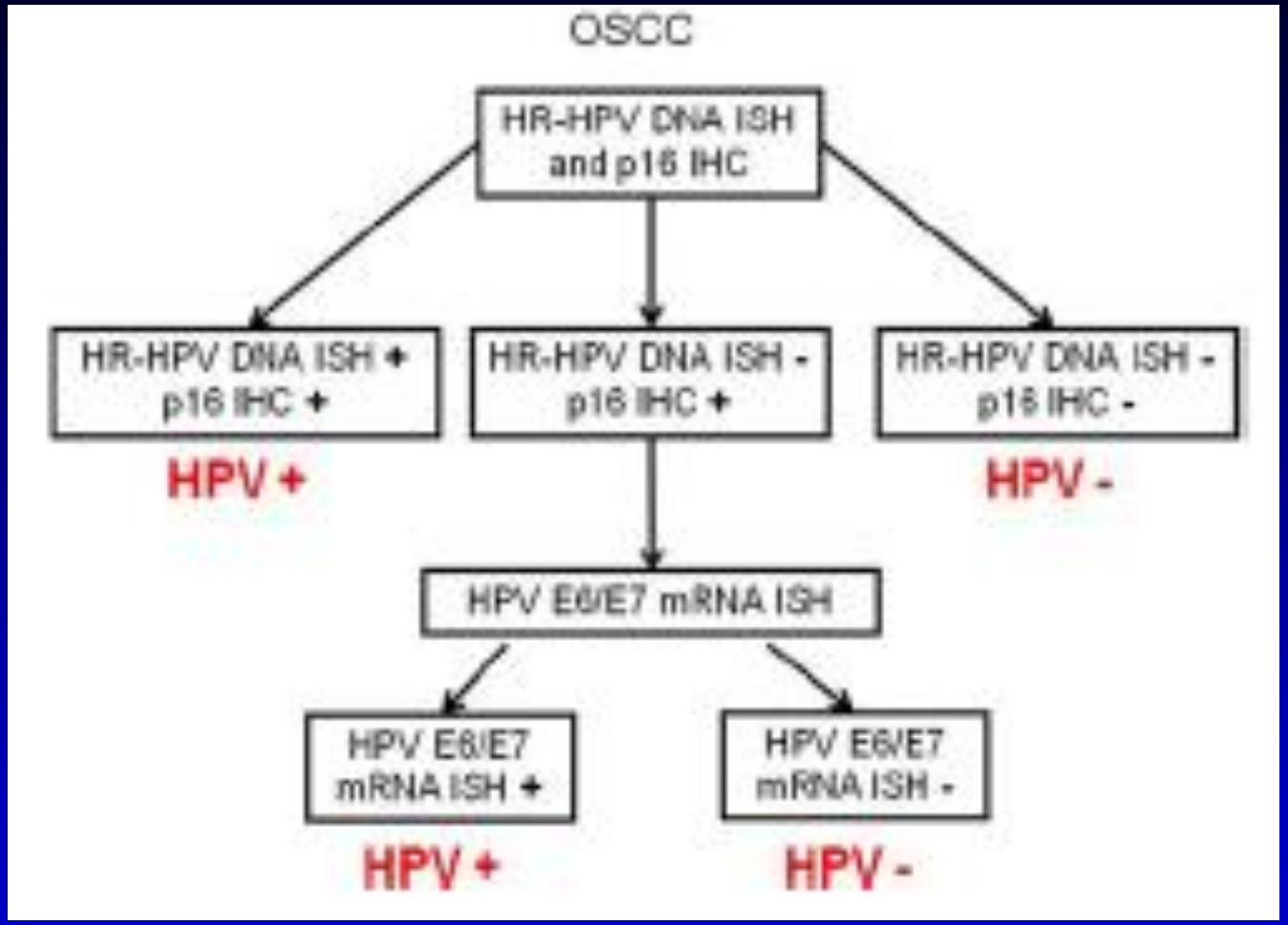


Table 1 – A summary of HPV testing methods.

Method	Advantages	Disadvantages
Routine histology	Very inexpensive In some situations there is insufficient material for anything further Informs appropriate ordering and interpretation of other HPV tests	Not sufficiently specific to be used alone
PCR for HPV DNA	Highly sensitive	Unable to distinguish biologically relevant from irrelevant infections Risk of cross-contamination
PCR for E6/E7 mRNA	Highly sensitive Highly specific—the "gold standard" for regarding a tumor as HPV-related	Requires considerable technical expertise Optimally performed on fresh frozen tissue
DNA in situ hybridization	Highly specific Easy to integrate into pathology laboratory Allows a tissue context to an HPV result	Not highly sensitive at low copy numbers Sometimes difficult to interpret
RNA in situ hybridization	Highly sensitive Highly specific Approaches the gold standard for defining HPV-related cancer	Limited experience Not yet optimized to run on most automated platforms
p16 Immunohistochemistry	Highly sensitive Inexpensive Powerful prognostic predictor Widely available in most pathology laboratories	Not highly specific for HPV Must be correctly interpreted (at least 50% staining, nuclear and cytoplasmic) Cannot be used outside of the oropharynx
Liquid-phase assays for cytopathology specimens	Highly sensitive Highly specific Precludes need to construct cell block Already in wide use for cervical cancer screening	Limited experience Not yet validated for widespread clinical use on head and neck cancers
p16+ another method	Allows for combining the high sensitivity of p16 with a more HPV-specific method Gives insight into the biologic significance of detected HPV	Increased cost Decreased turnaround time in stepwise algorithmic approaches

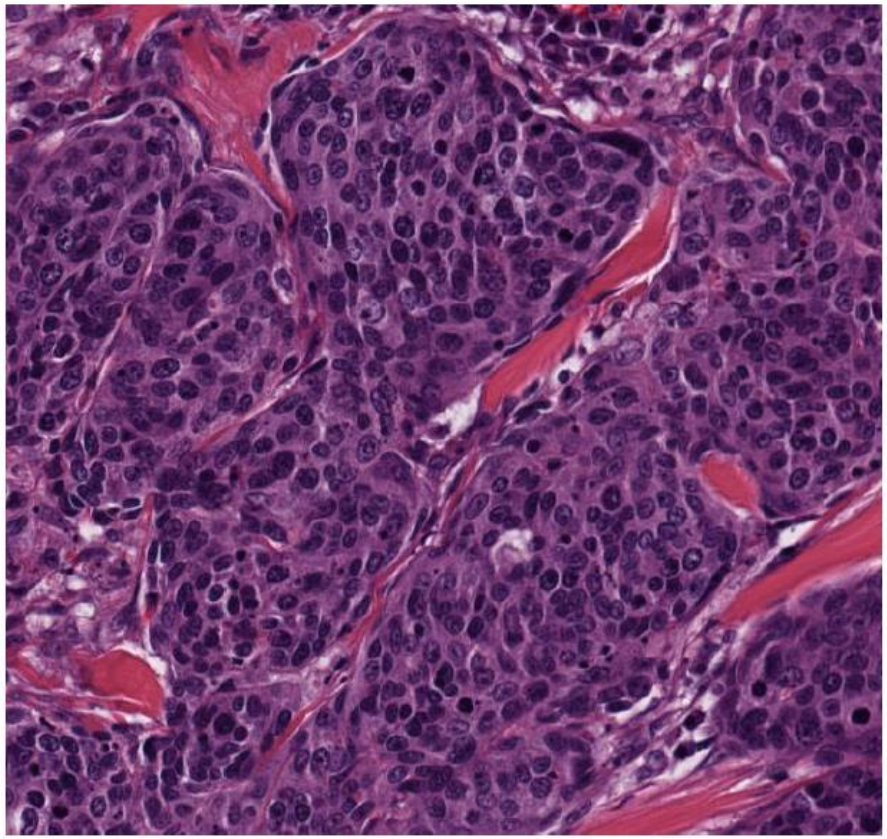
Bishop JA, et al. Sem Diagn Pathol 2015;32:344-51

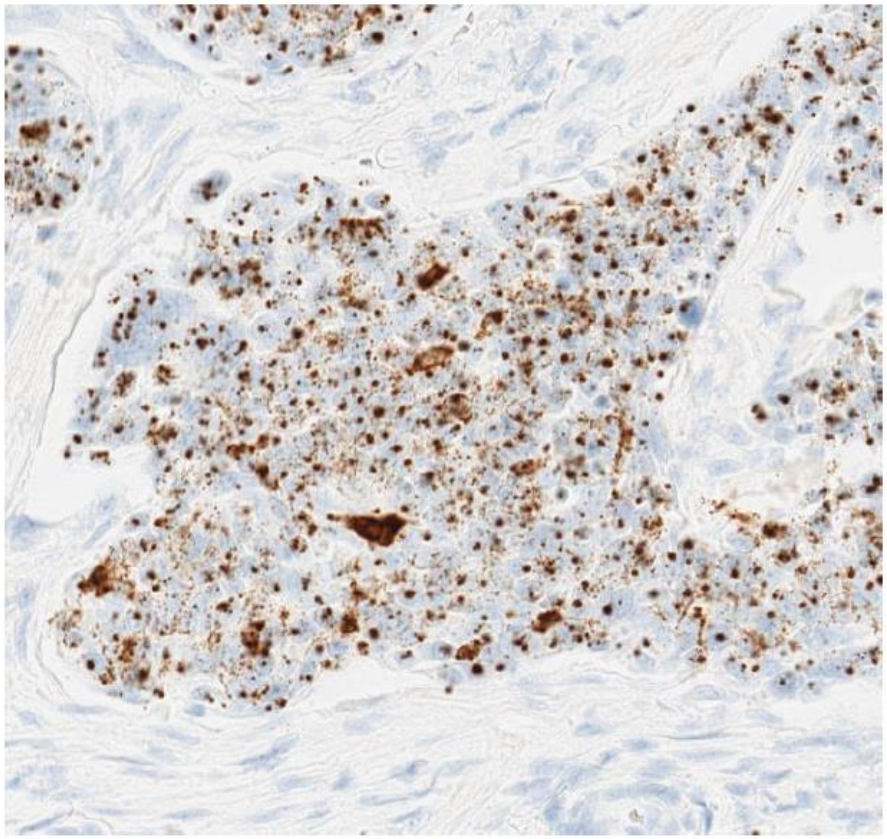


Volpi CC, et al. Hum Pathol 2018;74:32-42

H&E

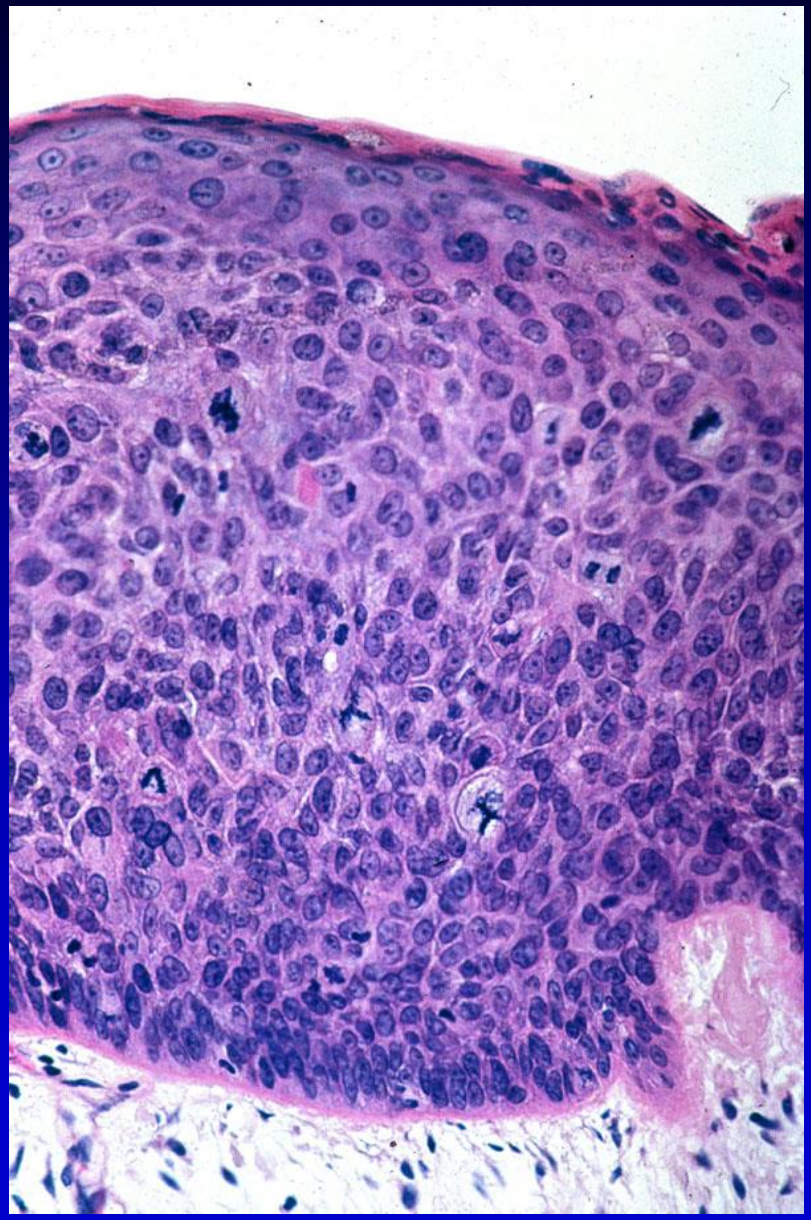
HPV RNA ISH 16/18 (High Risk) Detected

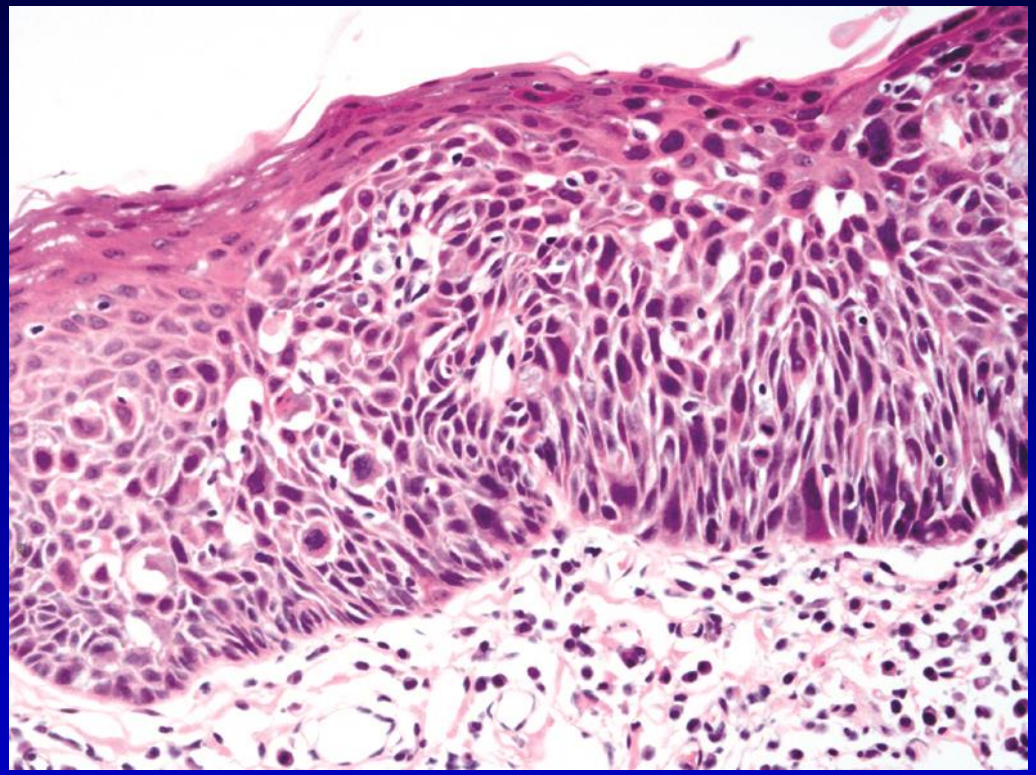




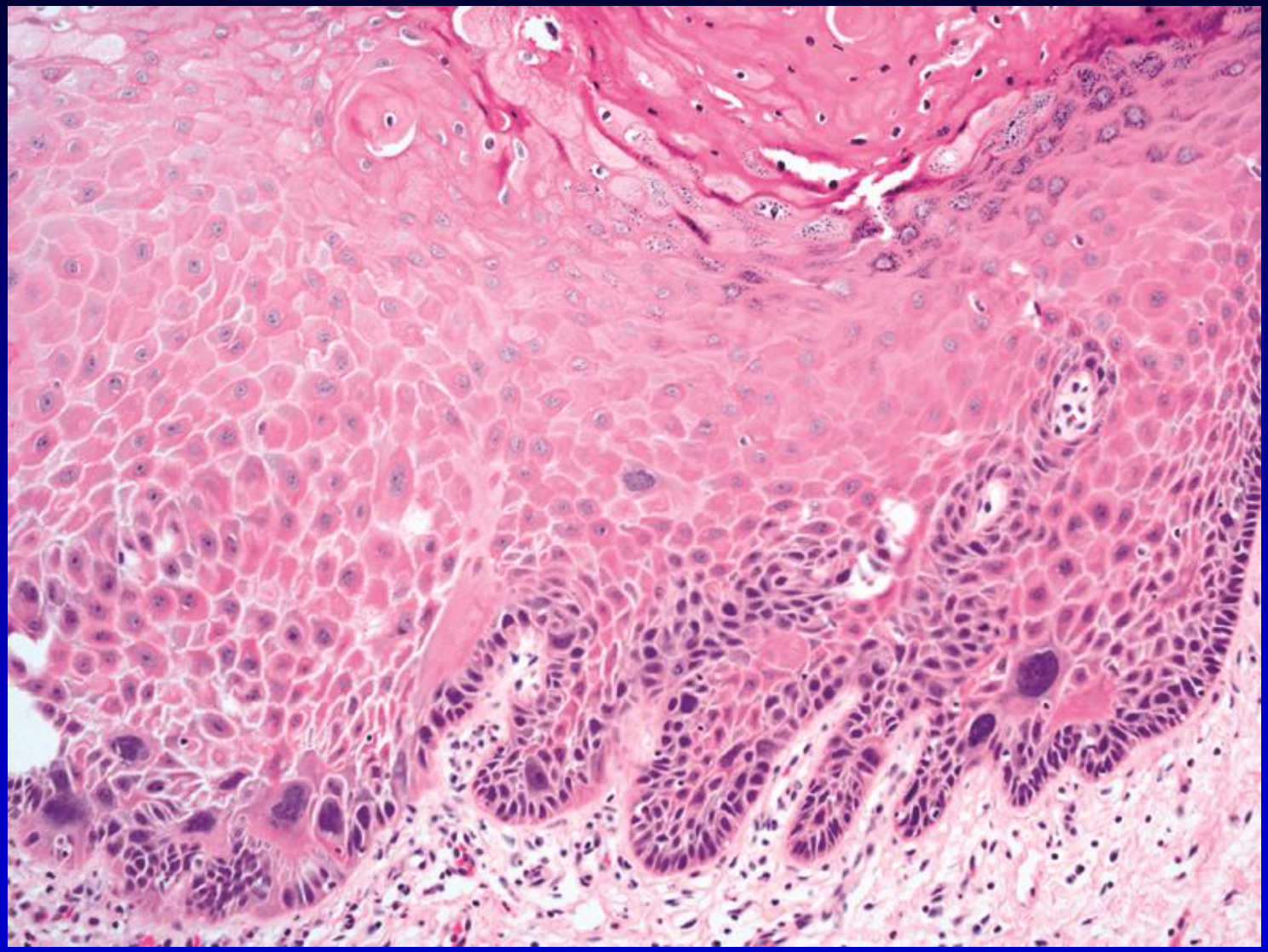
RNA probe cocktails specific for E6/E7 mRNA of HPV types 16 and 18

High-Grade Keratinizing Dysplasia

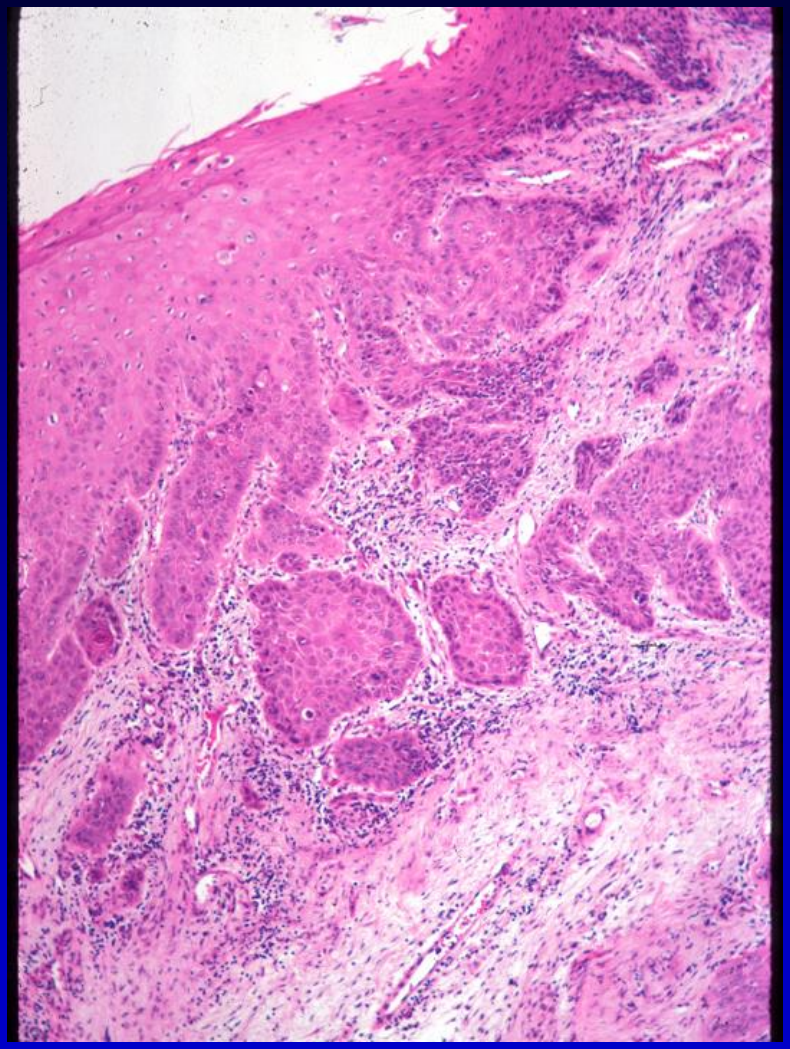


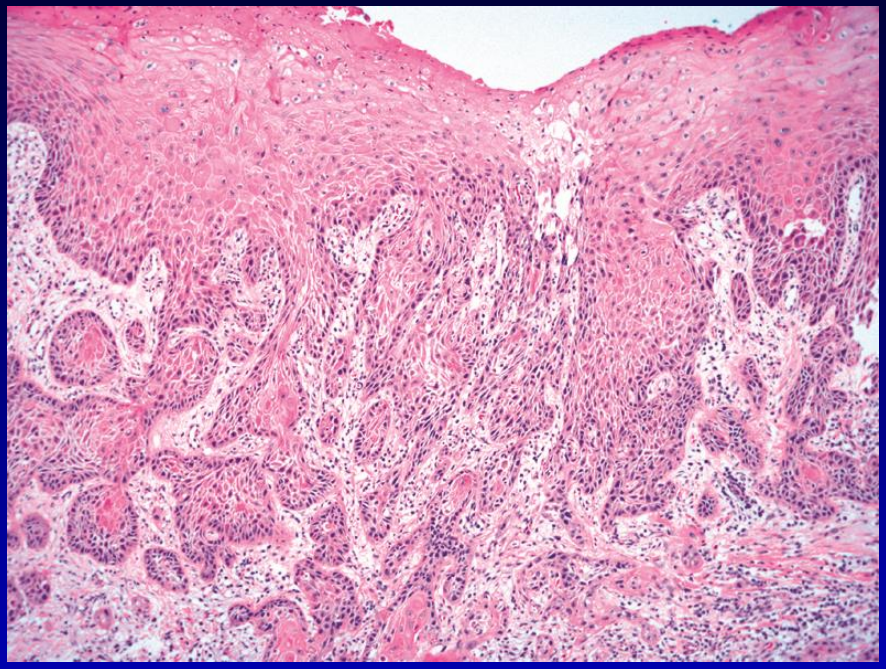


High-Grade Keratinizing Dysplasia

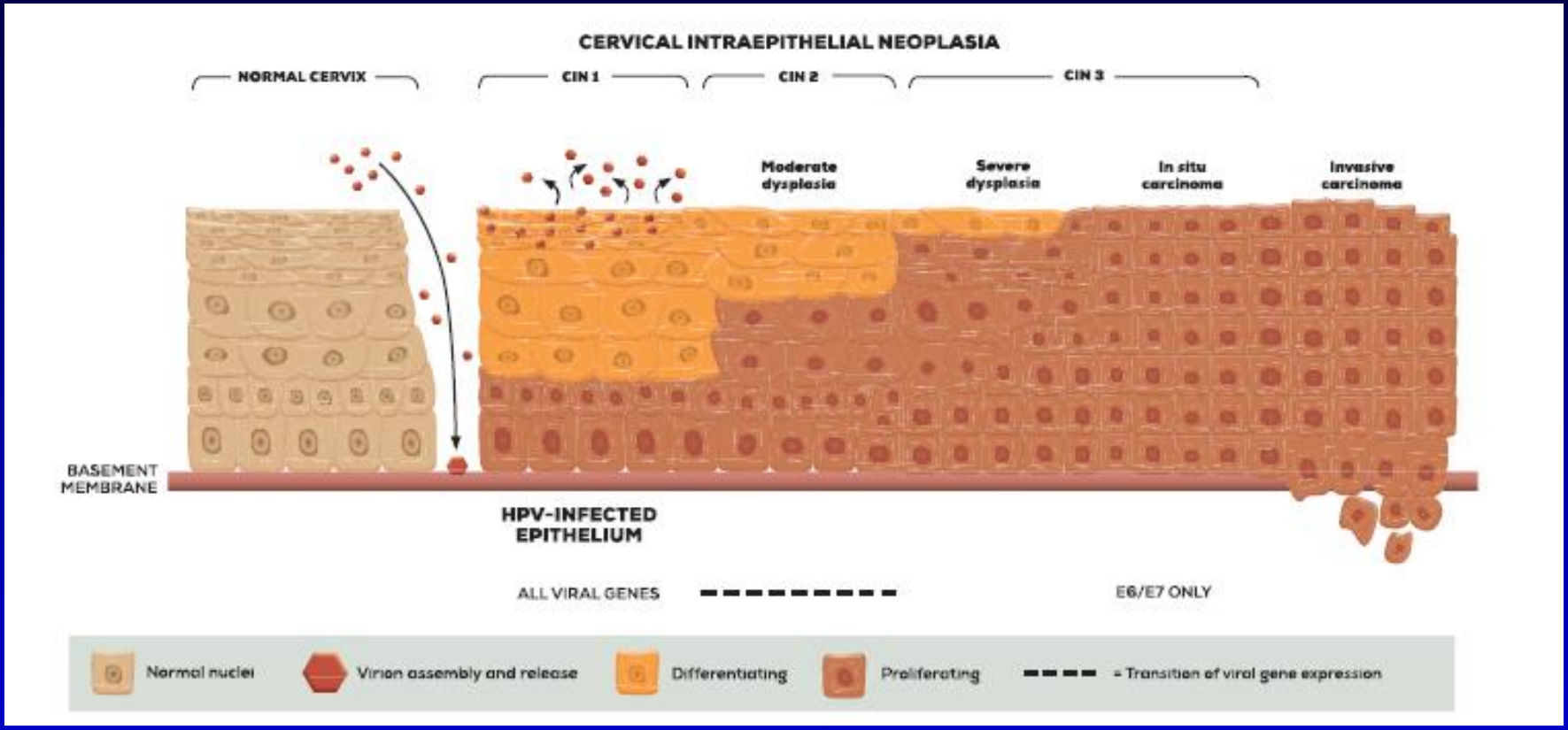


“Drop Off” Carcinoma





Cervical Intraepithelial Dysplasia



High-Grade Keratinizing Dysplasia

Keratinizing Dysplasia

IHC Staining

- p16, p53 and Ki67 (MIB1):
  - p16 of limited diagnostic utility in keratinizing dysplasias of the UADT
  - p53: increase expression
  - Ki67: increase intraepithelial proliferation rate through all epithelial layers
- Overall of limited utility

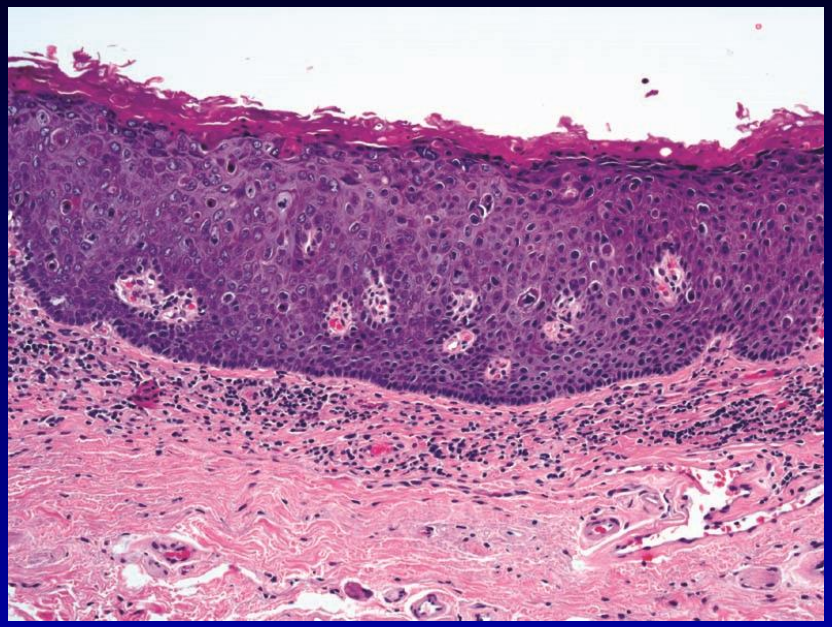
Oral Dysplasia and HR-HPV

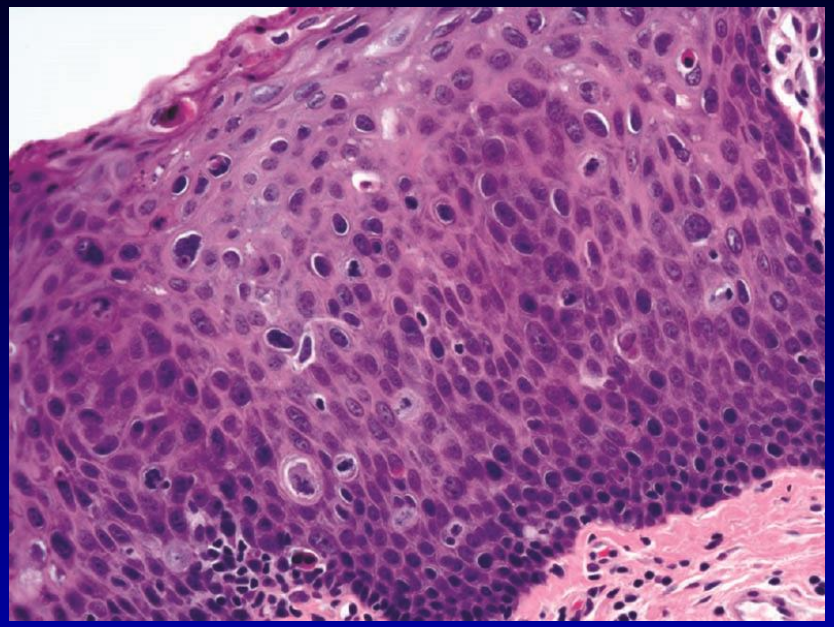
- **HR-HPV infection found in oral keratinizing dysplasias*:**
  - **Majority clinically oral leukoplakias**
  - **Most adult men; Ventral tongue & FOM**
  - **Diffuse loss of squamous differentiation with karyorrhexis & apoptosis, brightly eosinophilic apoptotic cells throughout epithelium, and conventional dysplastic changes**
  - **↑↑ proliferation index throughout epithelial layers**
  - **p16+IHC & high-risk HPV subtypes**

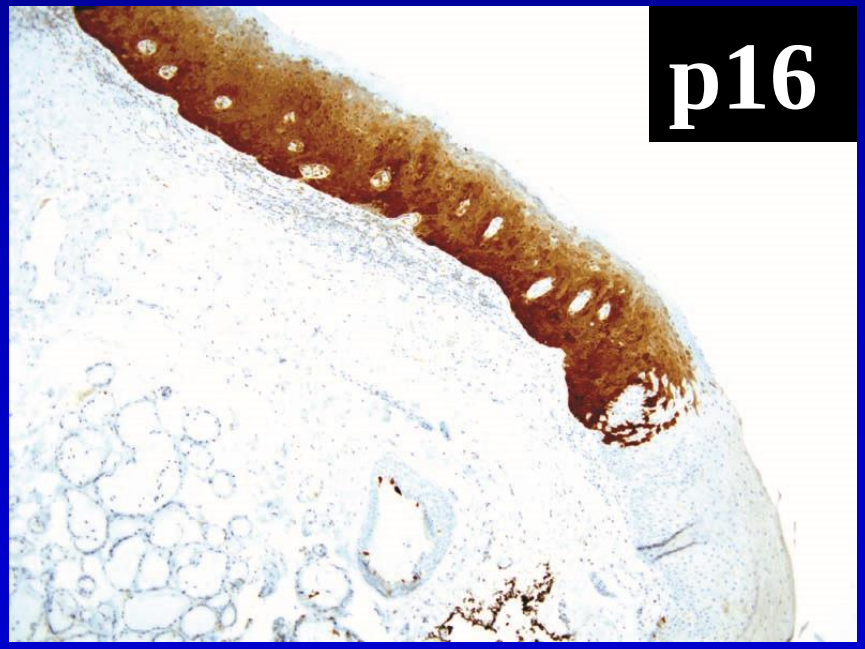
***Woo SB, et al. Modern Pathol 2013;26:1288-97**

*** McCord C, et al. Oral Surg Oral Med Oral Pathol Oral Radiol 2013;115:541-9**

HR-HPV FOM Dysplasia







HPV-Associated H&N Cancers

- Primarily oropharyngeal (tonsil and base of tongue) origin
- Identified in non-oropharyngeal locations (e.g., sinonasal tract, others)
- Identified in carcinomas with morphologies other than nonkeratinizing carcinoma

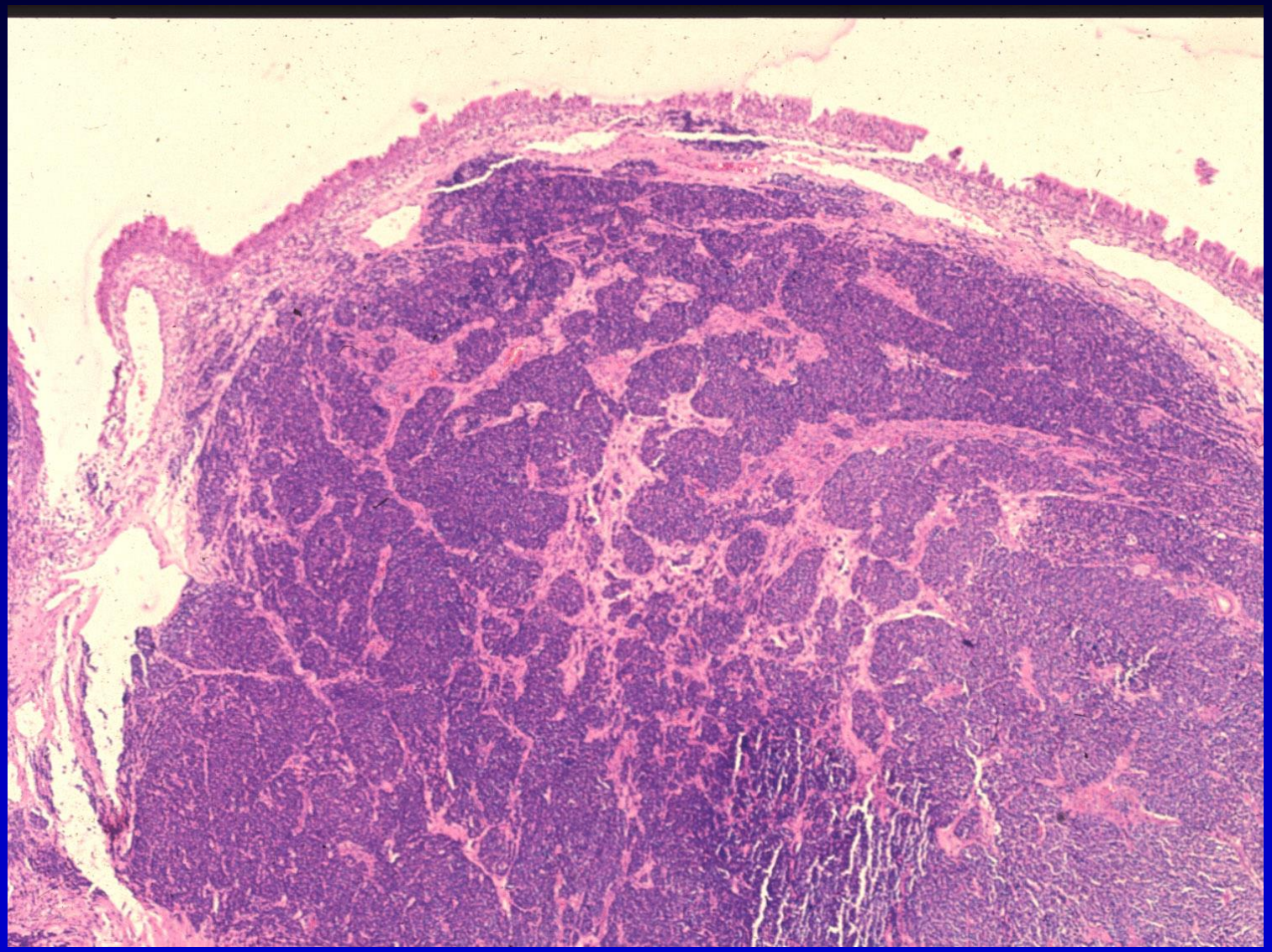
Neuroendocrine Carcinoma (NEC) Definition

- Heterogeneous group of malignant neoplasms with divergent differentiation along epithelial and neuroendocrine cell lines

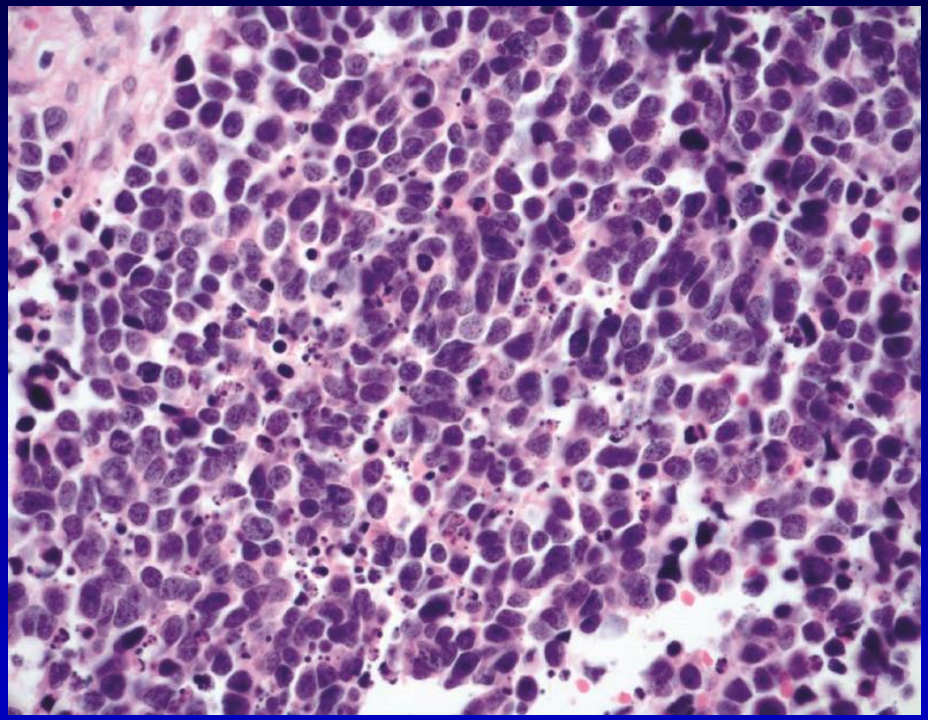
NEC of the Head and Neck
2017 WHO Classification

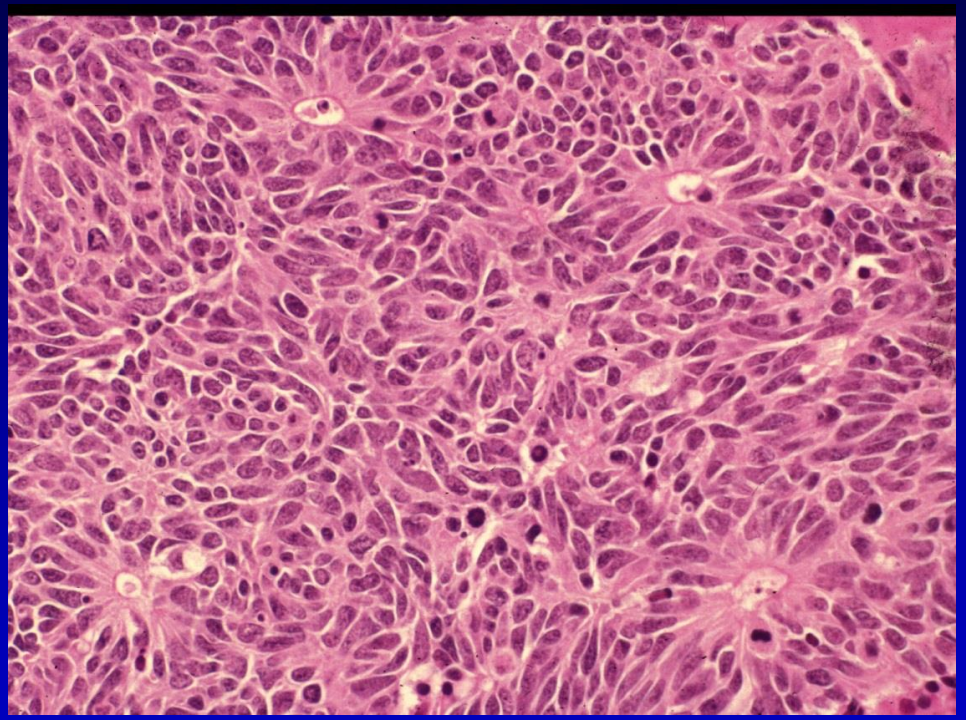
- **Well-differentiated NEC (WDNEC) = Carcinoid Tumor**
- **Moderately-differentiated NEC (MDNEC) = Atypical Carcinoid**
- **Poorly-differentiated NEC = Small Cell Carcinoma (SmCC)**
- **Poorly-differentiated NEC = Large Cell Carcinoma (LCNEC)**

PDNEC - SmCC

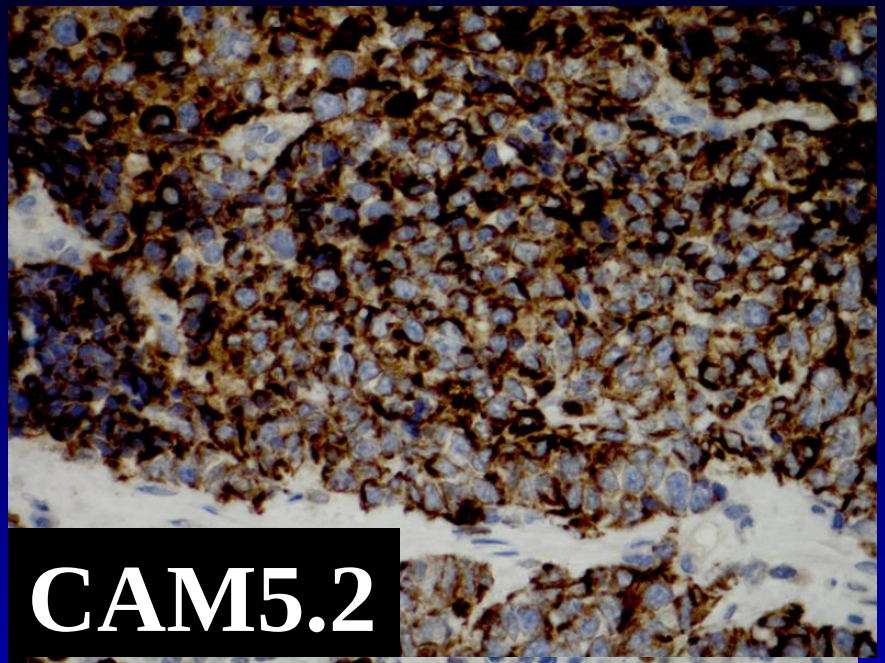


PDNEC - SmCC





PDNEC - SmCC



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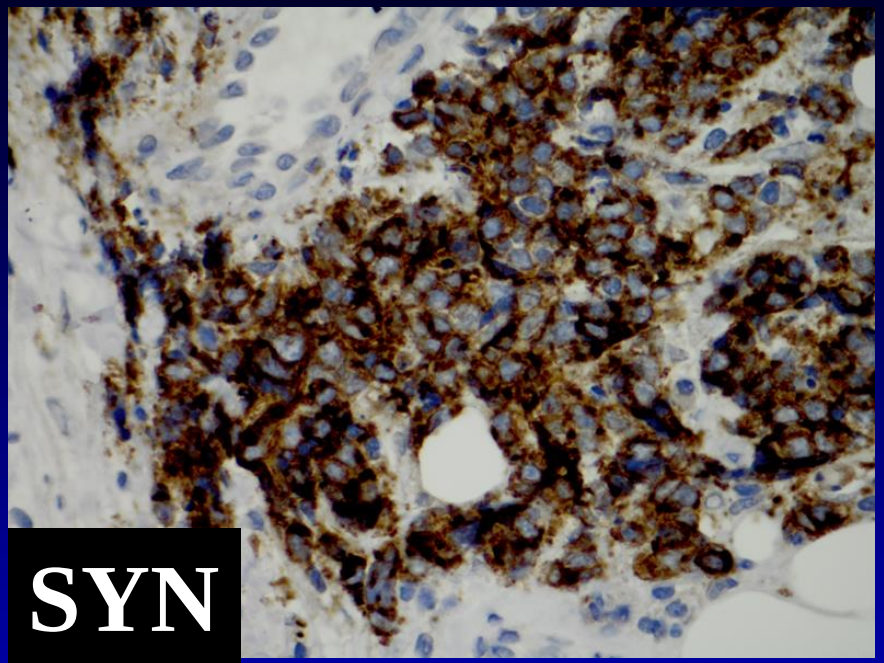
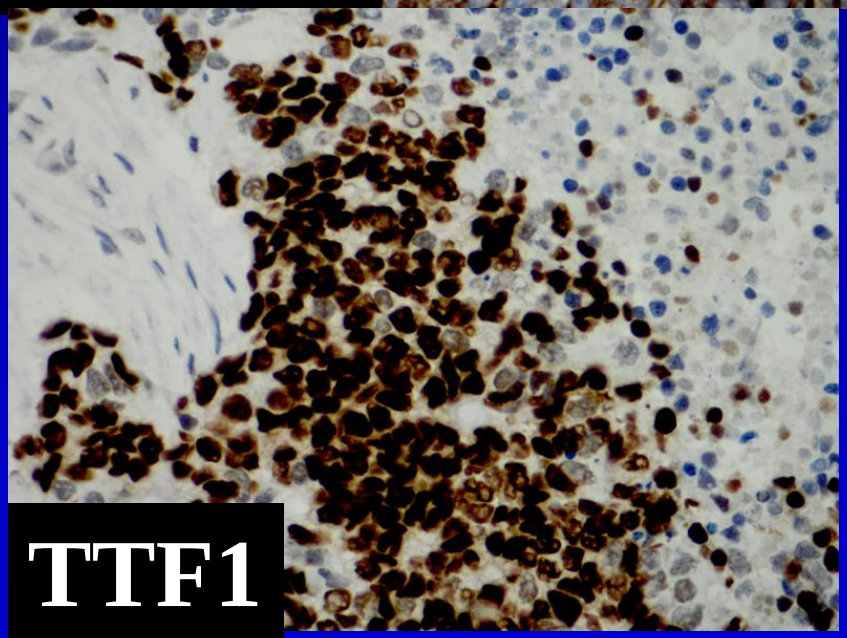


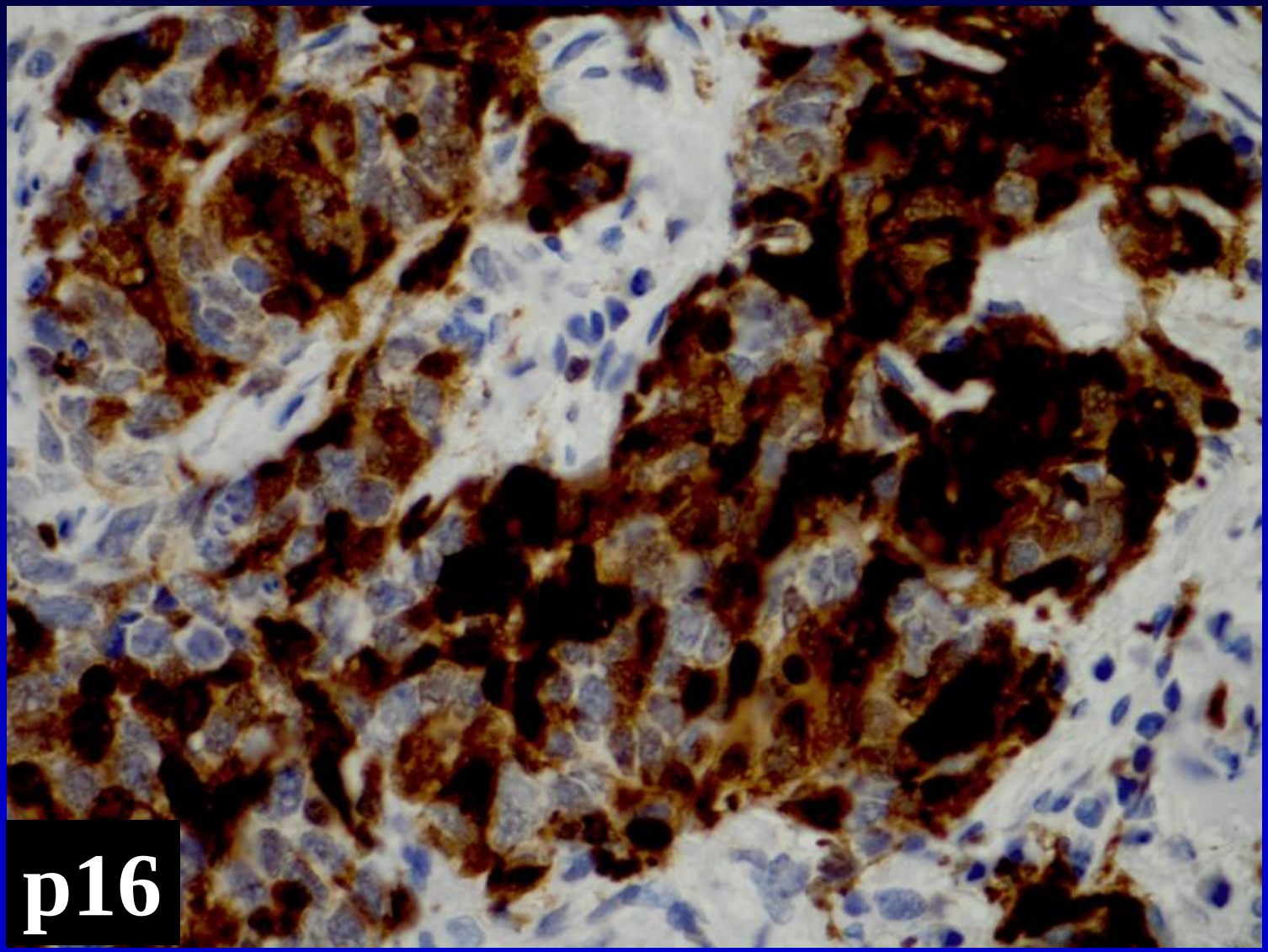
SYN



TTF1

p63/p40: negative
CK5/6: negative

Oropharyngeal SmCC (HPV-Associated SmCC)



HPV-Related Small Cell Carcinoma of the Oropharynx

- Bishop & Westra. AJSP 2011;35:1679-1684
- Kraft S, Faquin WC, Krane JF. AJSP 2012;36:321-330
  - 17 cases
  - M > F; 6^{th}-7^{th} decades
  - Tonsil, base of tongue, neck
  - Smoking history
  - Presentation with neck metastases including occult primary

HPV-Associated Oropharyngeal SmCC

- Subset of HPV-related oropharyngeal carcinomas with small cell morphology
- Recognition and distinction from HPV-related squamous cell carcinoma important
- Overlapping morphology
- CK5/6 and p63 may represent a key differentiating markers
- Despite presence of HPV, small cell phenotype indicate a greater propensity for aggressive clinical behavior

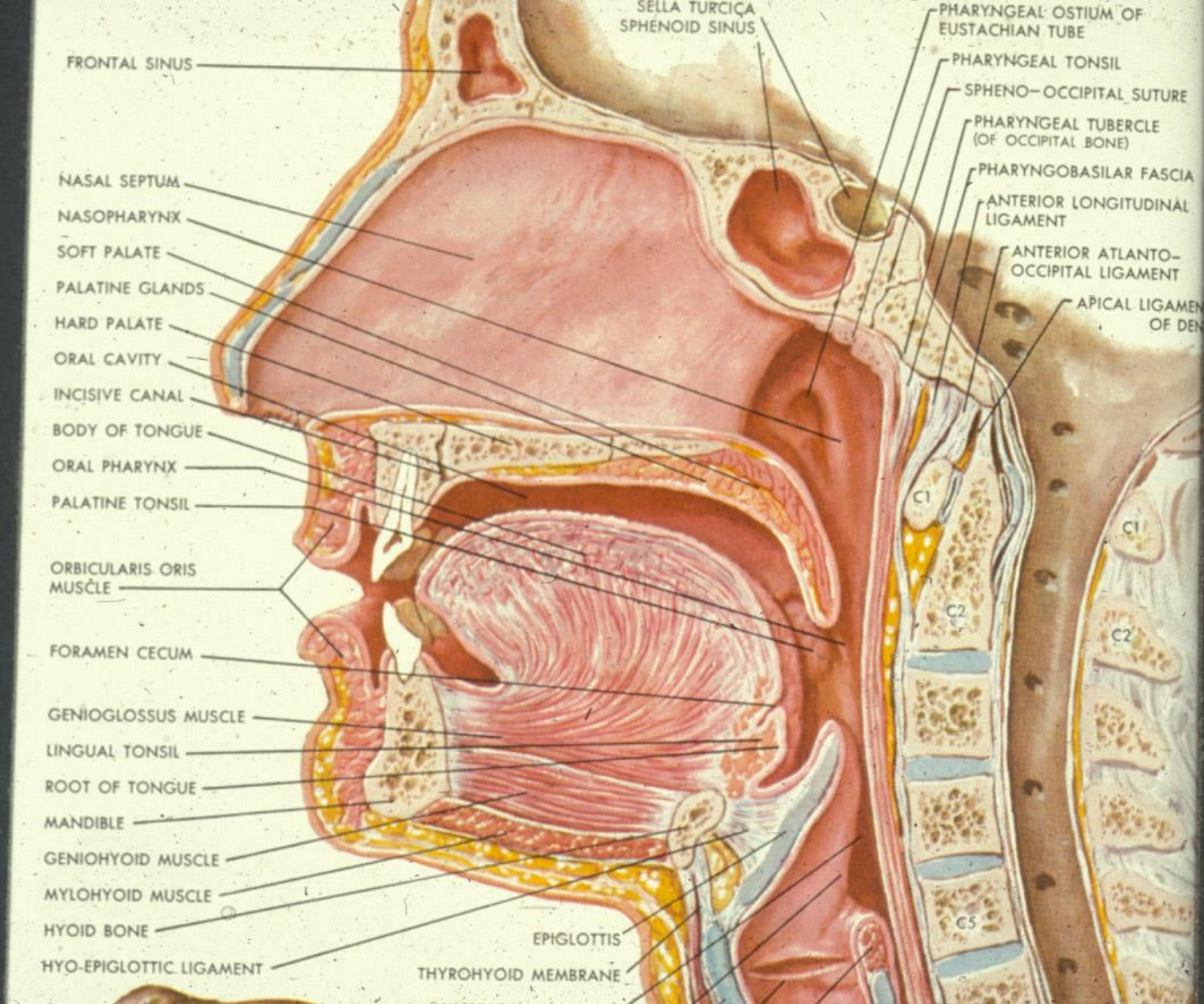
PDNEC - LCNEC
Clinical Features

- More common in men than women
- Occur over a wide age range average age of 59 years
- Predilect to the supraglottic larynx >> SNT >>> other
- Most patients are smokers
- May be associated with HPV (Oropharynx, SNT, larynx):
  - Mixed information in the literature relative to prognosis
  - Thompson ED et al. Am J Surg Pathol 2016;40:471-8:
    - HPV association may not impart more favorable prognosis

Criteria for (Laryngeal) LCNEC

Lewis J, et al. Head Neck Pathol 2010;4:198-207

Requisite criteria	Other typical features
Tumor cells with moderate to abundant cytoplasm	Nuclei with prominent nucleoli
Features of neuroendocrine differentiation (organoid nesting, trabecular growth, rosettes, and peripheral palisading)	Cellular pleomorphism
Mitotic activity > 10/10 hpf (2 mm^2)	Large areas of necrosis
Confirmation of neuroendocrine differentiation using immunohistochemical staining	


SELLA TURCICA
SPHENOID SINUS
PHARYNGEAL OSTIUM OF EUSTACHIAN TUBE
PHARYNGEAL TONSIL
SPHENO–OCCIPITAL SUTURE
PHARYNGEAL TUBERCLE (OF OCCIPITAL BONE)
PHARYNGOBASILAR FASCIA
ANTERIOR LONGITUDINAL LIGAMENT
ANTERIOR ATLANTO–OCCIPITAL LIGAMENT
APICAL LIGAMEN
OF DEN
FRONTAL SINUS
NASAL SEPTUM
NASOPHARYNX
SOFT PALATE
PALATINE GLANDS
HARD PALATE
ORAL CAVITY
INCISIVE CANAL
BODY OF TONGUE
ORAL PHARYNX
PALATINE TONSIL
ORBICULARIS ORIS MUSCLE
FORAMEN CECUM
GENIOGLOSSUS MUSCLE
LINGUAL TONSIL
ROOT OF TONGUE
MANDIBLE
GENIOHYOID MUSCLE
MYLOHYOID MUSCLE
HYOID BONE
HYO-EPIGLOTTIC LIGAMENT
EPIGLOTTIS
THYROHYOID MEMBRANE
C1
C2
C5
C1
C2

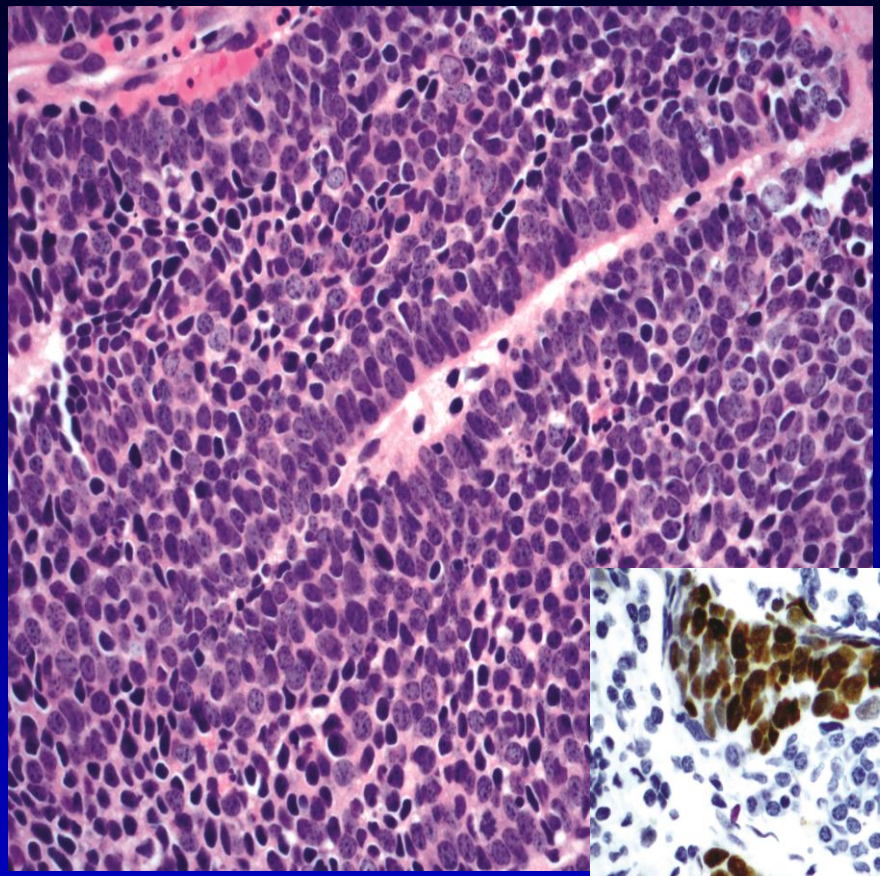
Nasopharyngeal Carcinoma (NPC) WHO Classification (2017)

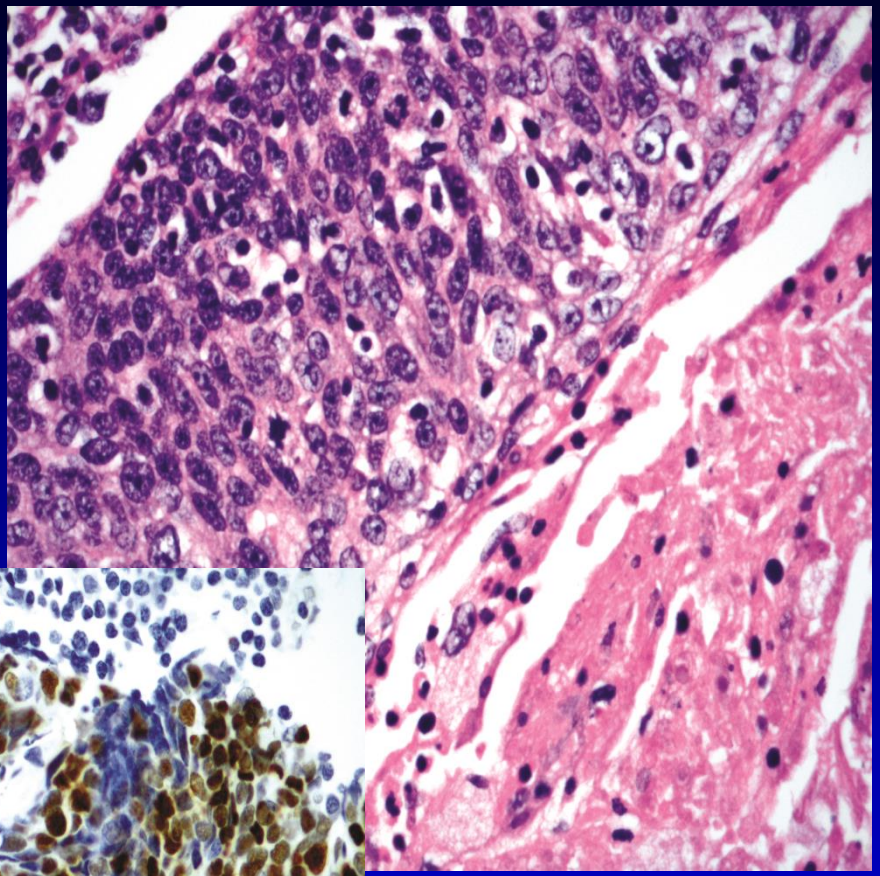
- **Keratinizing SCC:**
  - **well-, moderately, poorly-differentiated (WHO 1)**
- **Nonkeratinizing SCC:**
  - **Differentiated type (Transitional Cell or Cylindrical Cell Carcinoma; WHO 2)**
  - **Undifferentiated type (Lymphoepithelioma; WHO 3)**
- **Basaloid SCC**

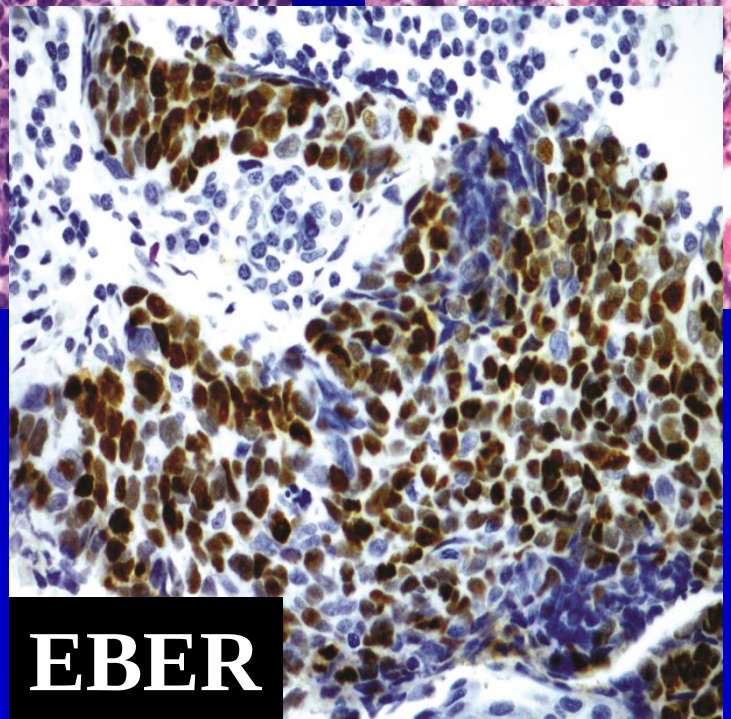
NPC

	Keratinizing	Nonkeratinizing Differentiated	Nonkeratinizing Undifferentiated
Percent	Approximately 25%	Least common < 15%	Most common > 60%
Sex/Age	M > F; 4th- 6th decades	M > F; 4th - 6th decades	M > F; 4th - 6th decades; may occur in children
EBV	Weak association	Strong association	Strong association
XRT Response	Radio-responsiveness is not good	Radioresponsive	Radioresponsive
5-Yr survival	20-40%	75%	75%

NPC, nonkeratinizing differentiated

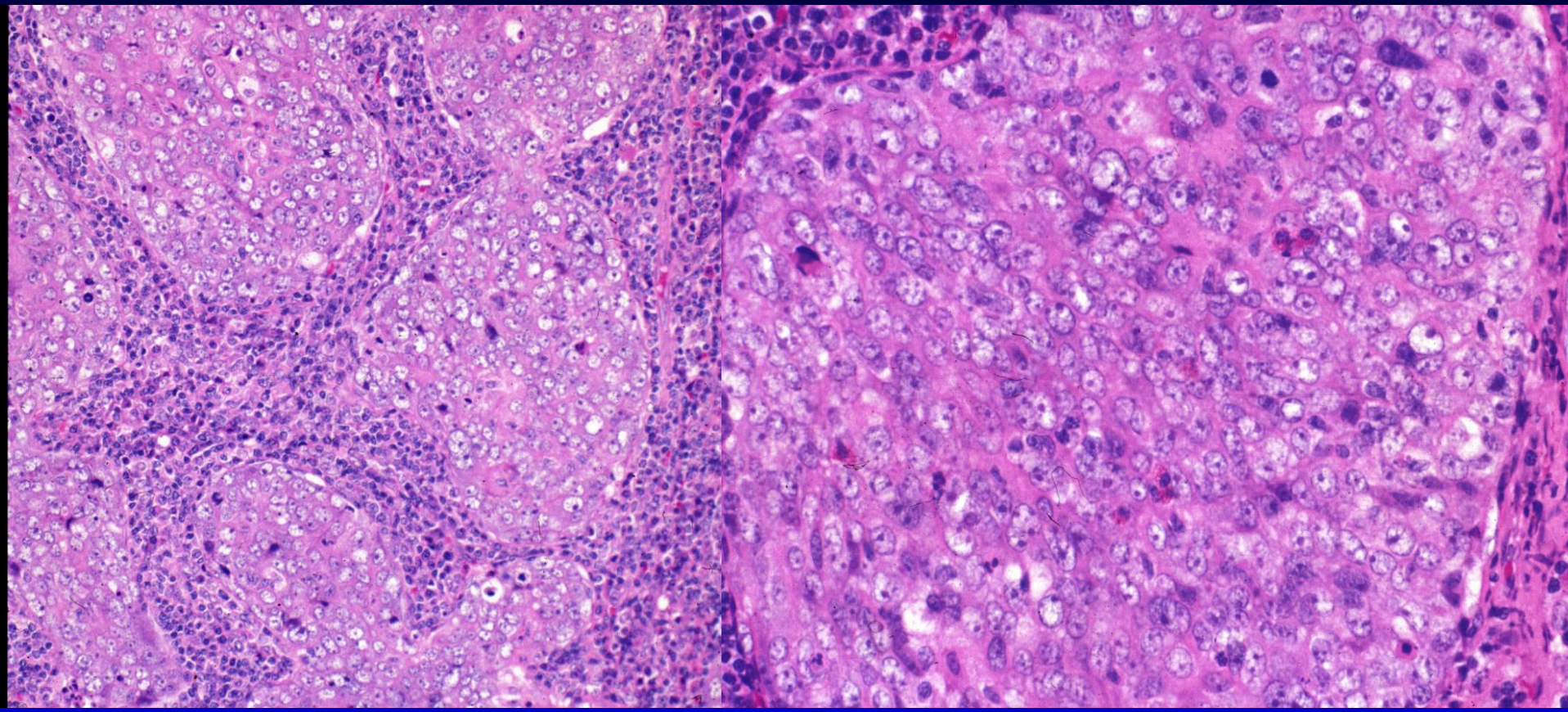




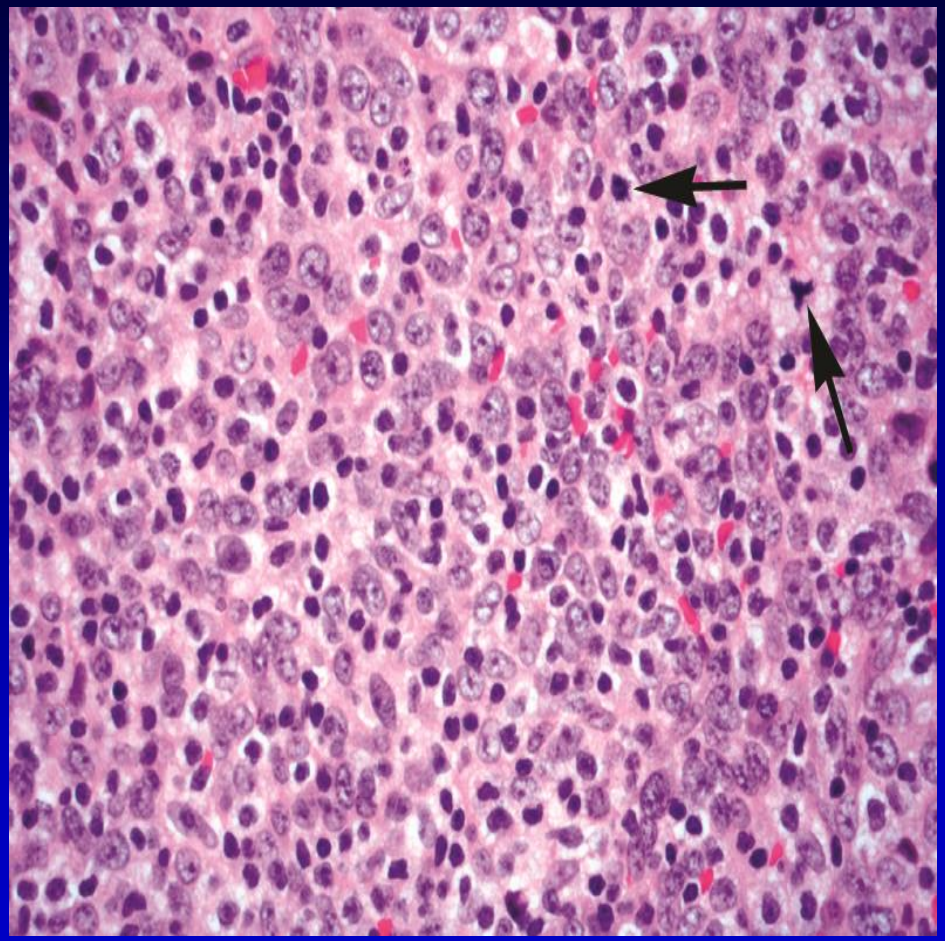


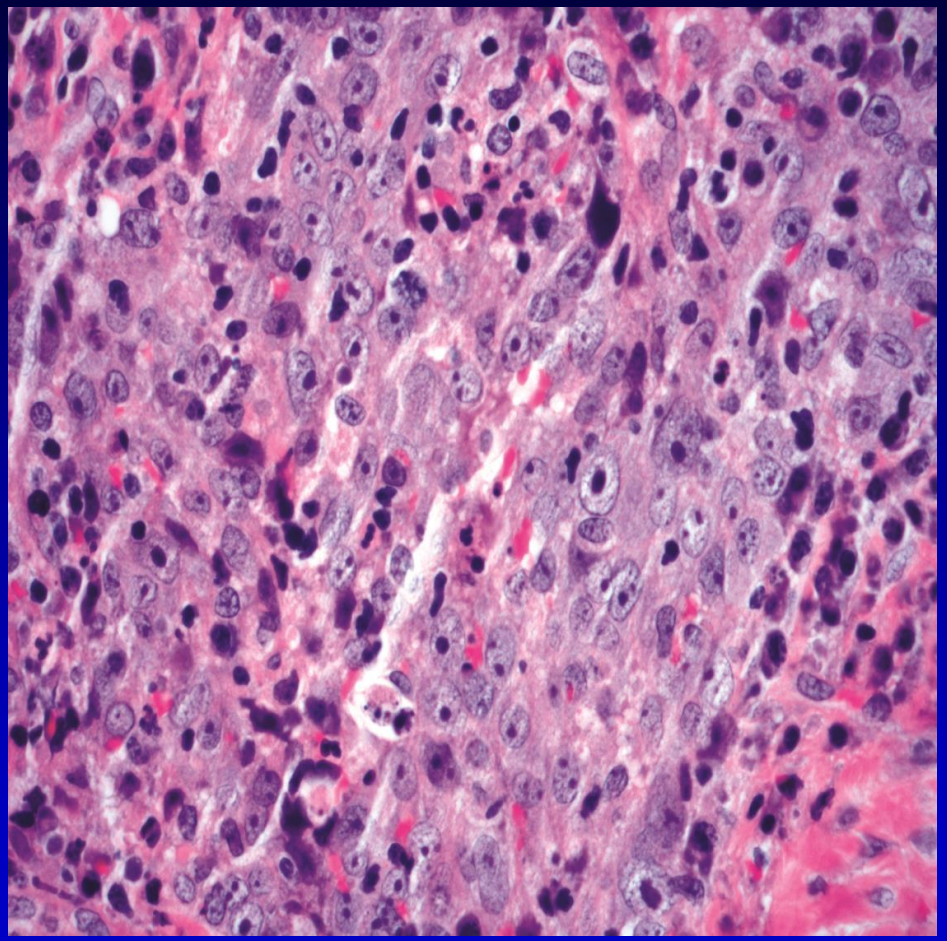
EBER

NPC, nonkeratinizing undifferentiated

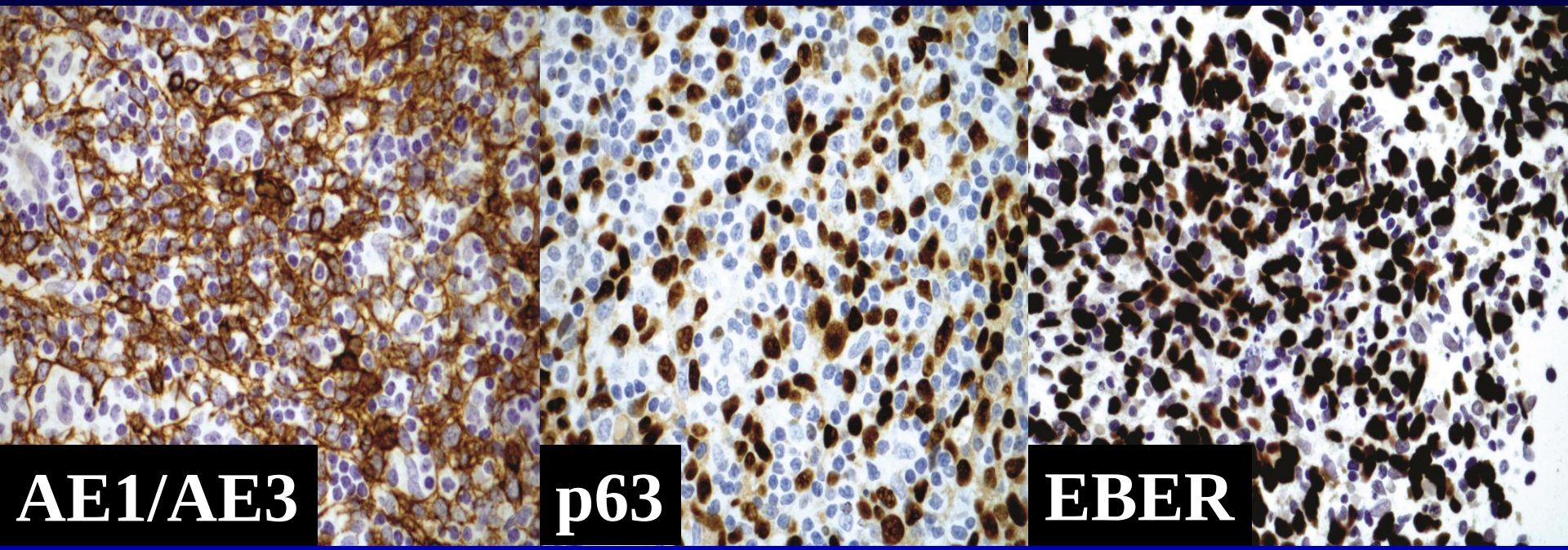


NPC, nonkeratinizing undifferentiated

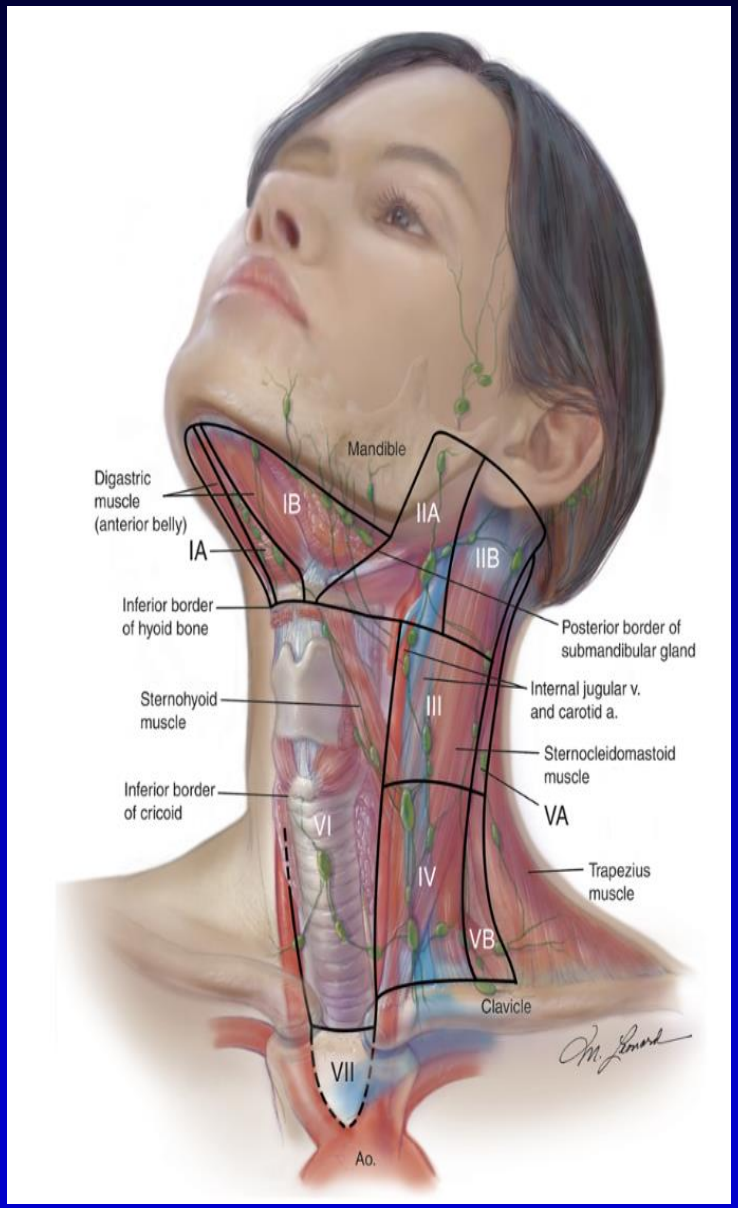




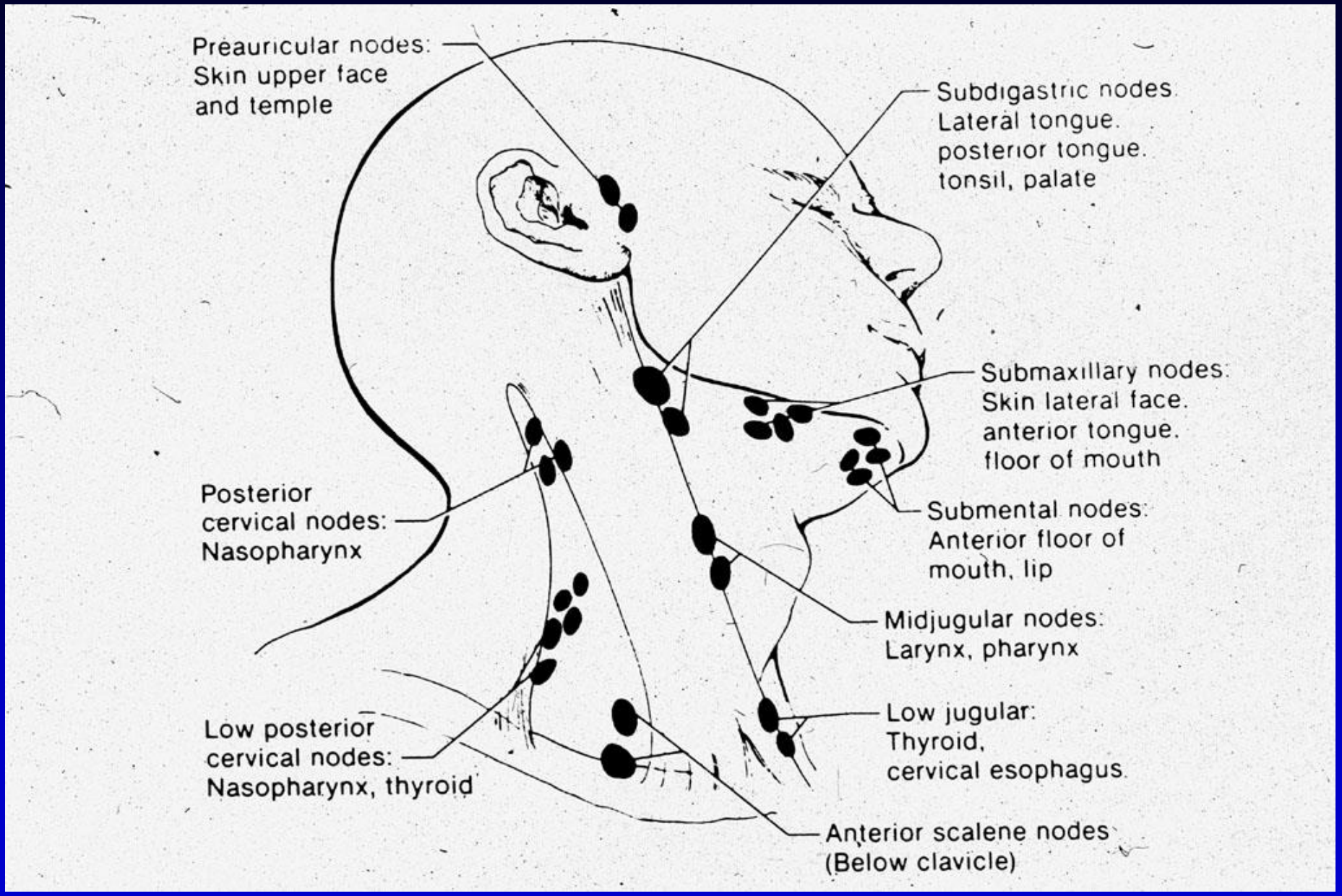
NPC, nonkeratinizing undifferentiated



Cervical Neck Lymph Node Topography



Site Specific Lymph Node Drainage



Metastatic Cervical Carcinoma with an Unknown Primary Tumor (MCCUP)

- **Definition:**

  - Overt neck mass harboring a cytologically or histologically proven metastatic carcinoma in the absence of signs and symptoms of a primary neoplasm or of a clinically detectable mass:

  - **no history of previous malignancy or cancer ablation of any indeterminate lesion**
  - **no history of definite symptoms related to a specific organ system**
  - **no clinical or laboratory evidence of a primary neoplasm**

Luna MA. Chapter 17. In: Barnes L, ed. Surgical Pathology of the H&N. 2009

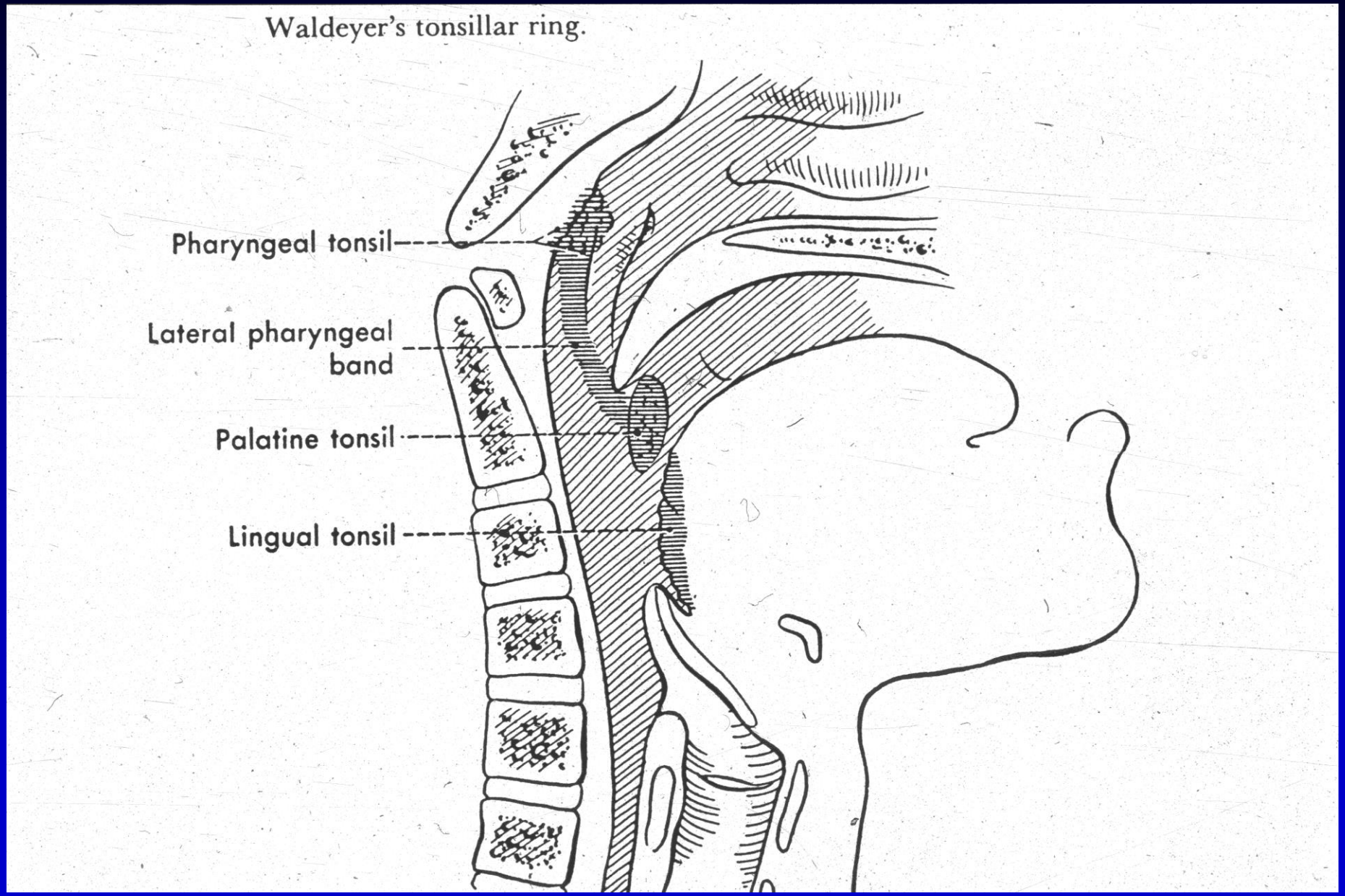
Histology of Metastases from Unknown Primary Tumors

Histology	Location		
	Cervical	Supraclavicular	Total
Squamous carcinoma	153	30	183
Adenocarcinoma	6	54	60
Undifferentiated carcinoma	44	25	69
Thyroid carcinoma	6	5	11
Melanoma	7	0	7
Sarcoma	2	2	4
Salivary gland carcinoma	2	0	2

Location of Primary Head and Neck Carcinomas Originally Considered Occult

Location	Total numbers
Nasopharynx and oropharynx	31
Tonsil/base of tongue	31
Thyroid	21
Hypopharynx	19
Supraglottis	12
Oral cavity	8
Nose and sinuses	4
Esophagus	3
Miscellaneous head and neck	11
Total	140

Waldeyer Tonsillar Tissues



Luna MA. Chapter 17. In: Barnes L, ed. Surgical Pathology of the H&N. 2009

Discovery of Primary Tumor Following Definitive Therapy

Author (Ref.)	Total no. cases	Primary detected (% of total)		Primary found (%)	
				Above clavicle	Below clavicle
Smith et al. (40)	53	15	(28.3)	47	53
Jesse and Neff (12)	127	48	(37.8)	60	40
Jesse et al. (13)	210	37	(17.6)	75	25
Comess et al. (4)	103	42	(40.8)	78	22
France and Lucas (41)	43	12	(27.9)	66	34
Marchetta et al. (42)	33	15	(45.4)	53	47
Acquarelli et al. (43)	31	12	(38.7)	50	50
Total	600	181	(30.0)	61 (average)	39 (average)

Branchiogenic Carcinoma Criteria*

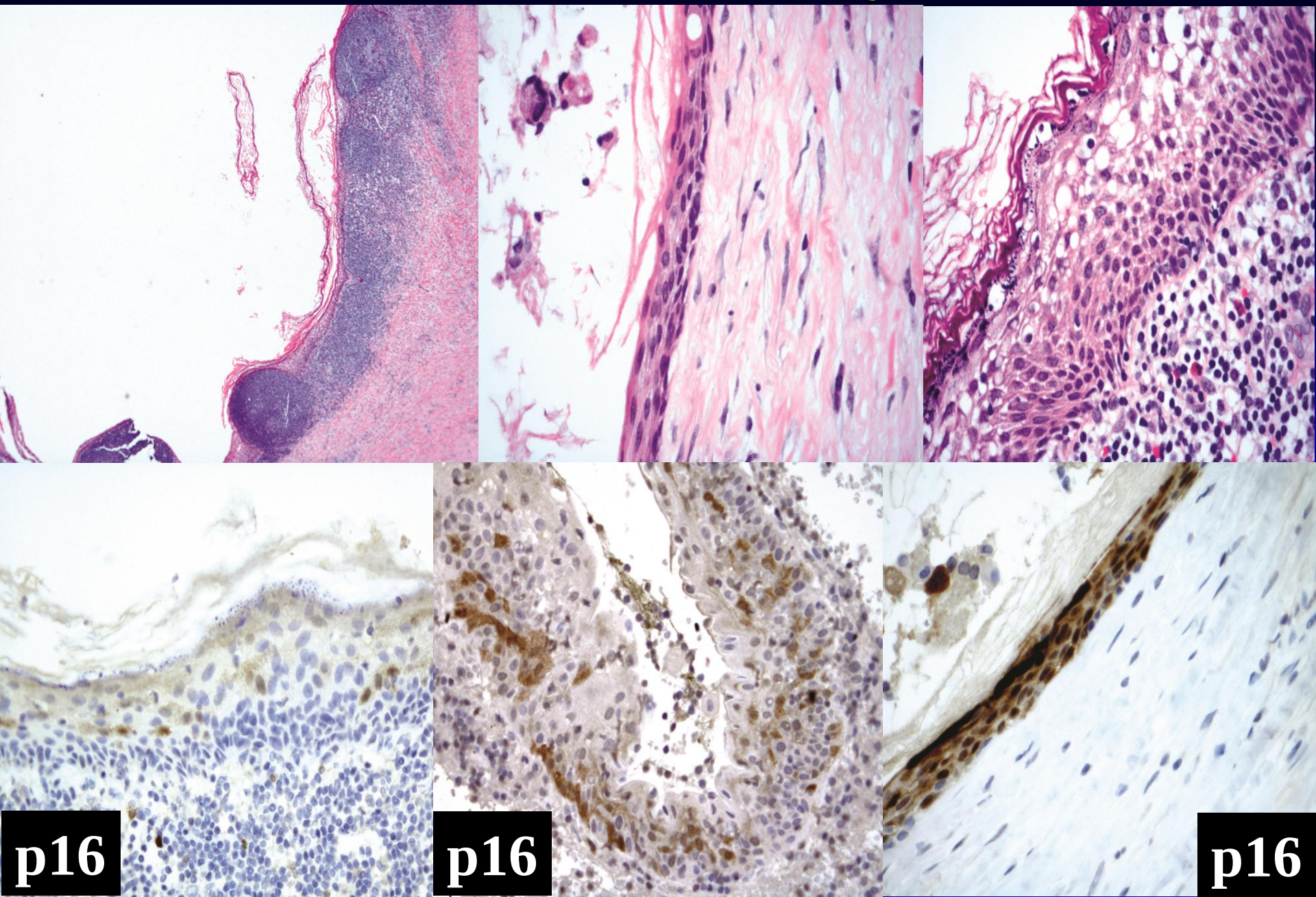
- Cervical tumor occurs along line extending from anterior to the tragus along the anterior border of the SCM to the clavicle
- Histology c/w origin from tissue known to be present in branchial vestige
- No primary source for carcinoma on at least 5-year f/u
- Histologic evidence of carcinoma arising in wall of epithelial-lined cyst

*Martin et al. Ann Surg 1950;132:825-832

Branchial Cleft Cyst

- Benign lateral neck cyst most often of 2nd branchial cleft apparatus
- Bimodal age: 20-40 (75%); <5 yrs (20%):
  - rare (≤5%) in ages >40 years
- Painless cervical swelling typically near angle of mandible along border of SCM

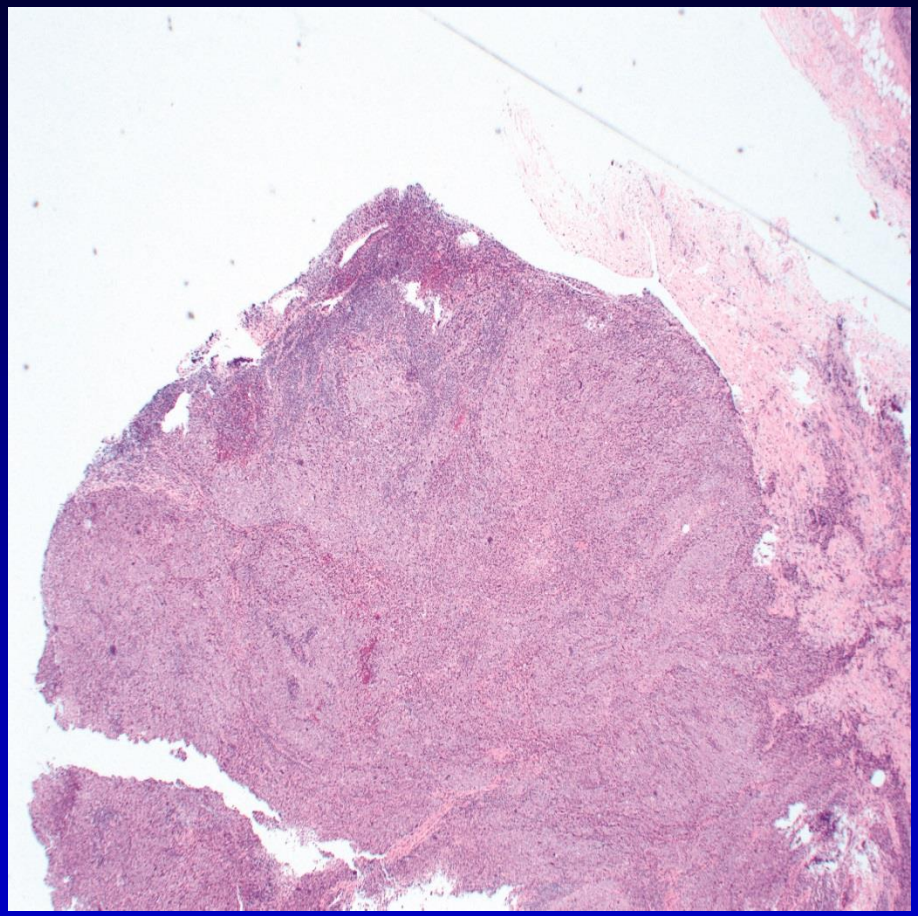
Branchial Cleft Cyst

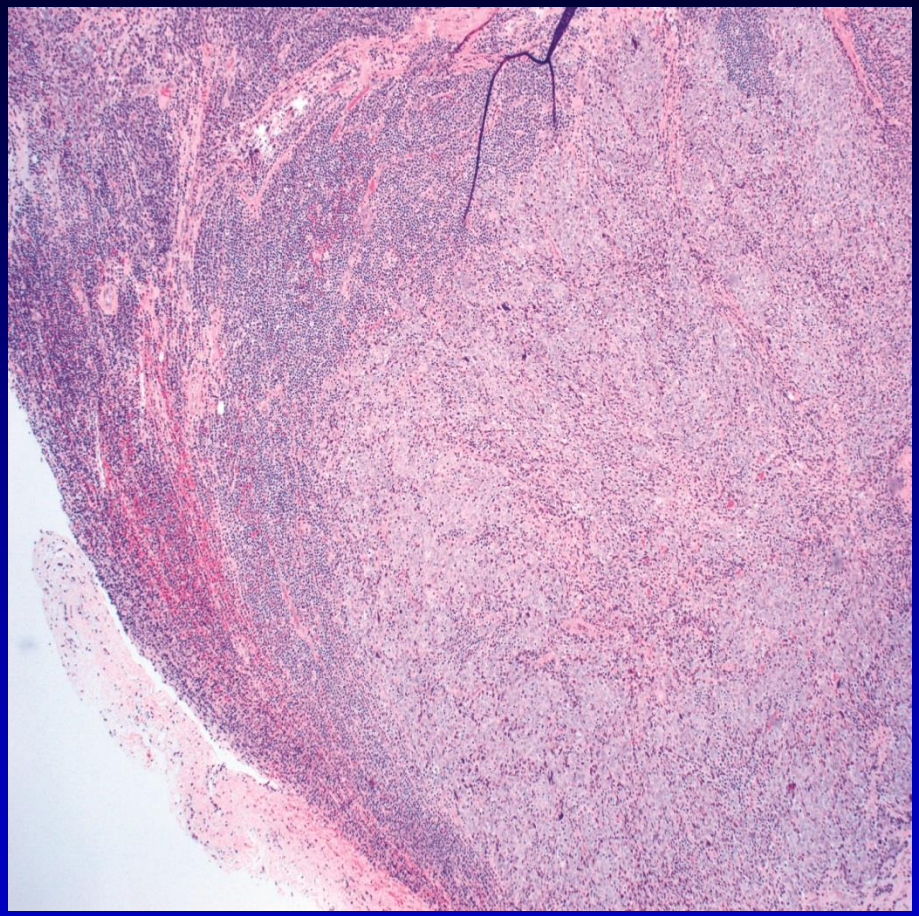


Case History

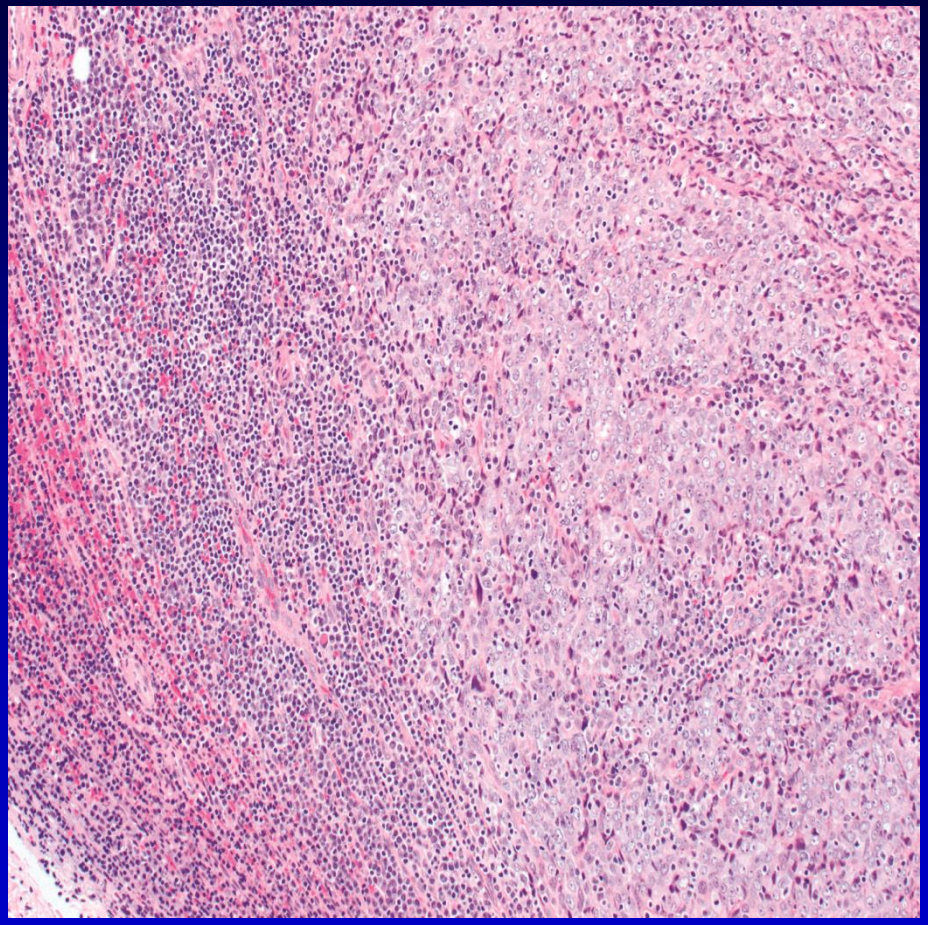
- 39 year old female presented with an enlarging right sided neck mass at Level IIA (subdigastric lymph node)
- There was no past or current history of malignancy
- The lymph node was excised

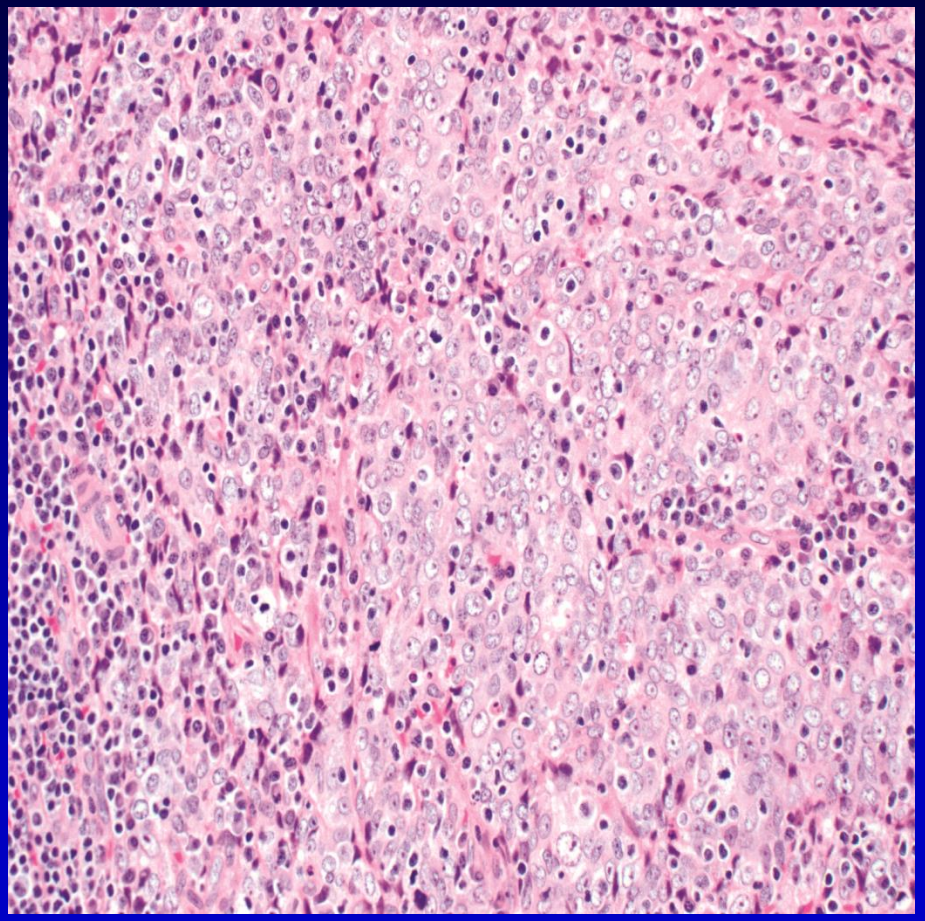
Level IIA Lymph Node



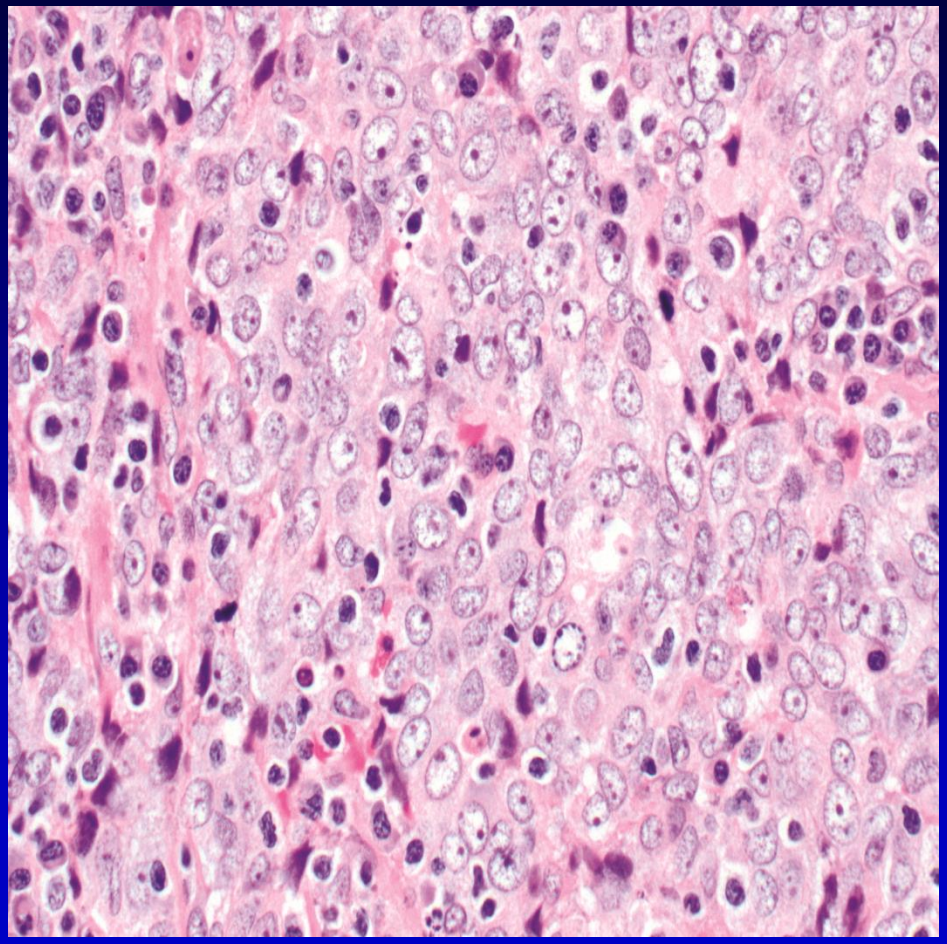


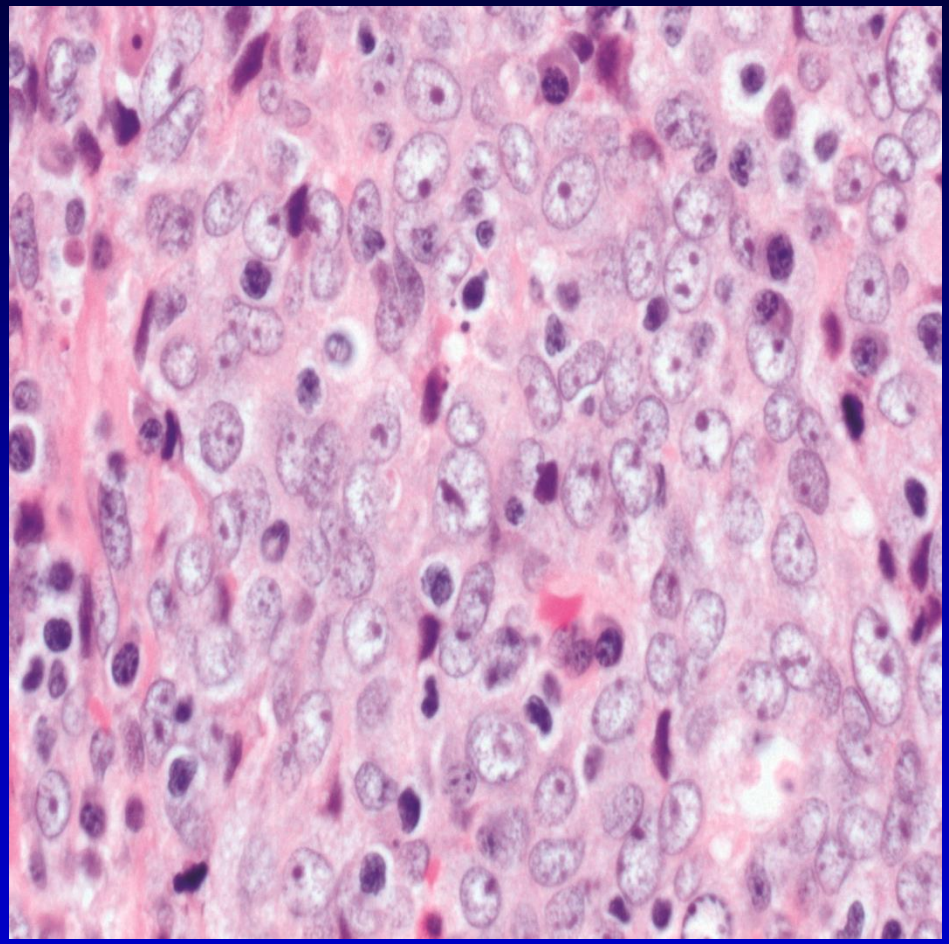
Level IIA Lymph Node



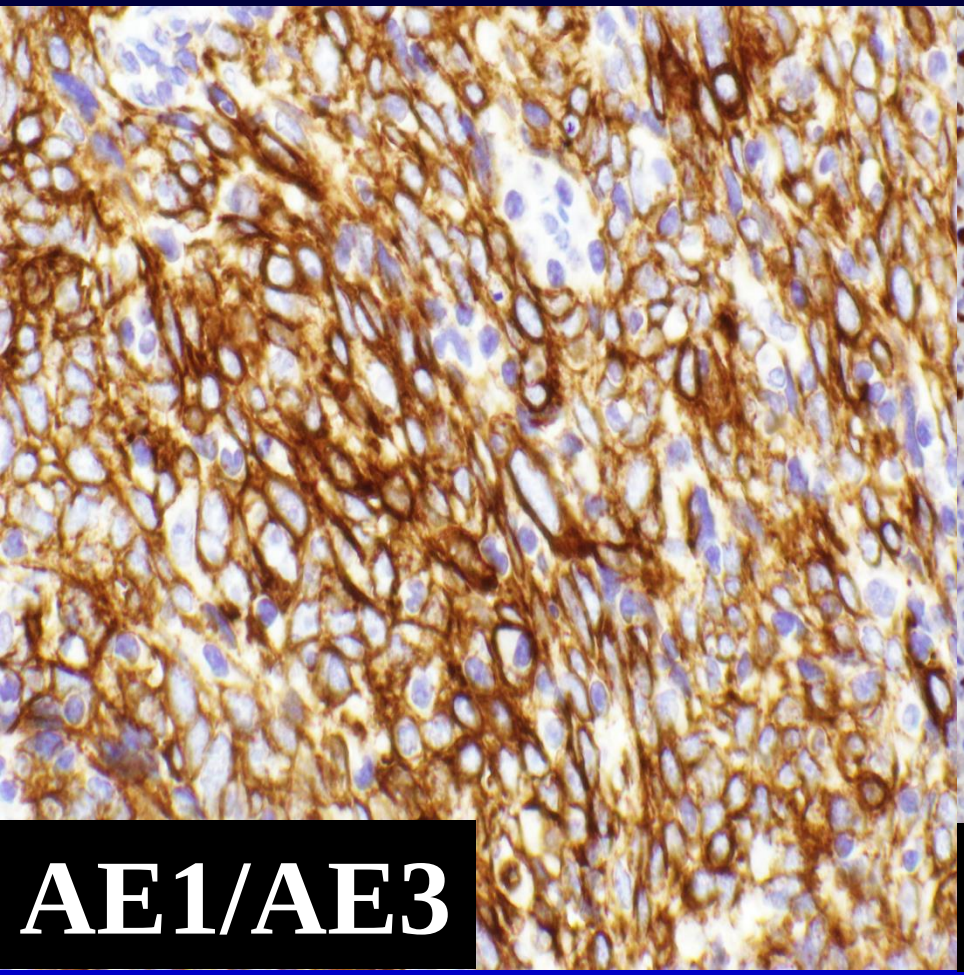


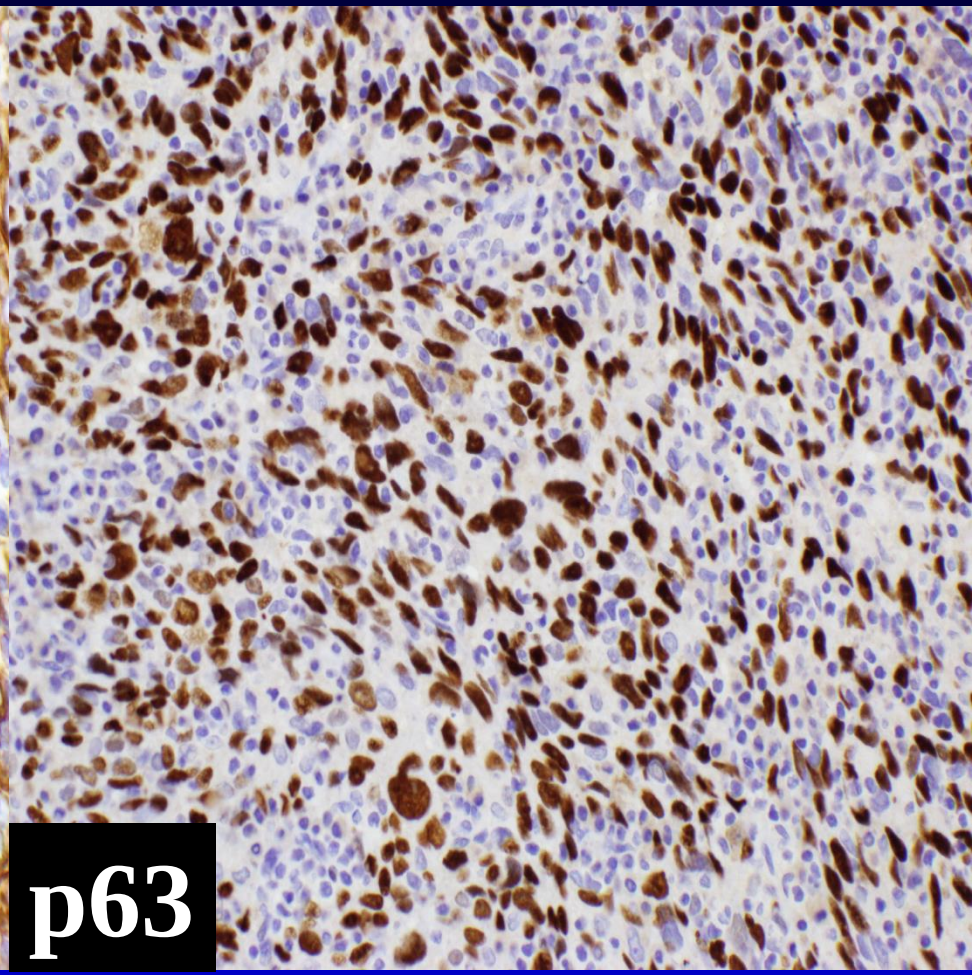
Level IIA Lymph Node





Case

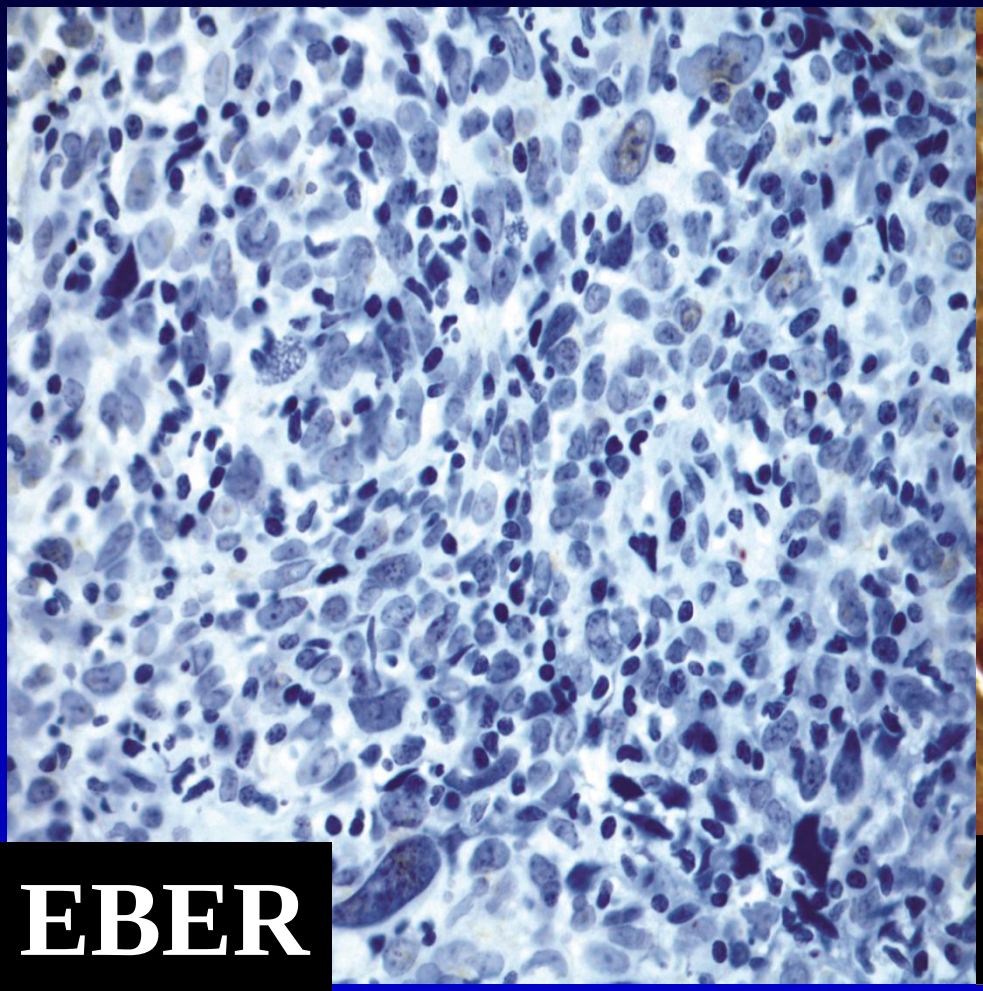




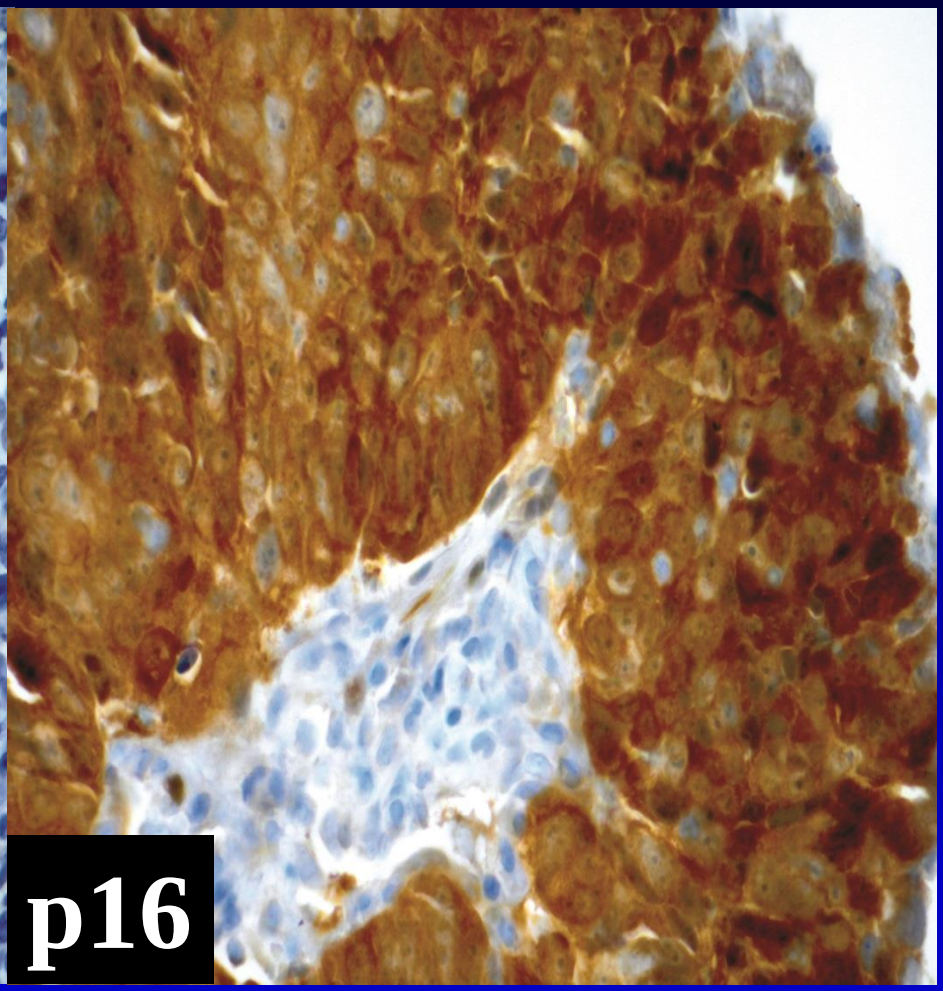
Case
Other IHC

- **Hematolymphoid markers (CD45; CD20) negative**
- **Melanoma markers (S100 protein, HMB45, others) negative**

Case



EBER

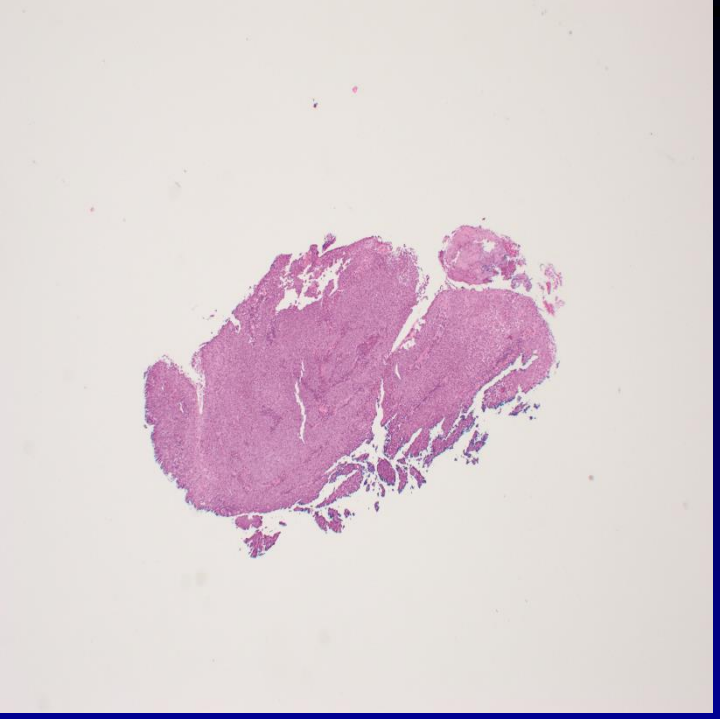


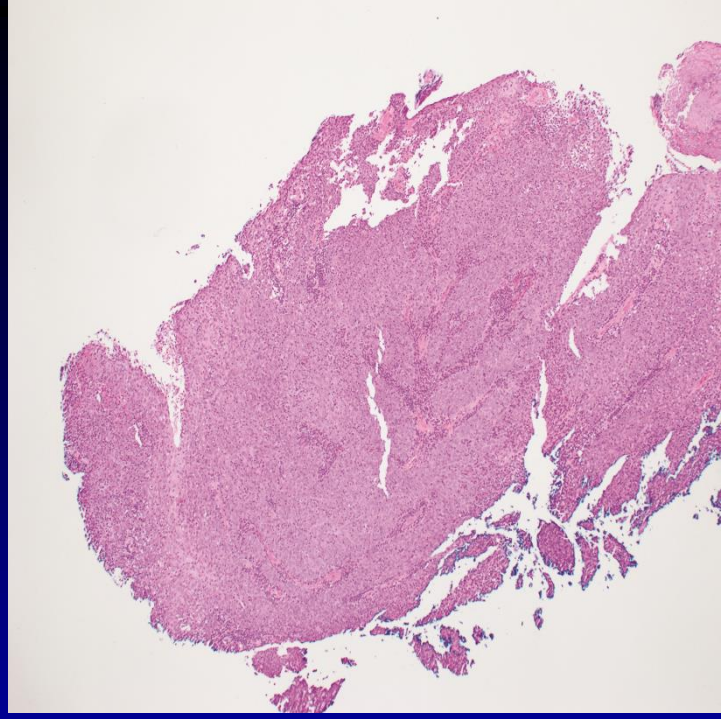
p16

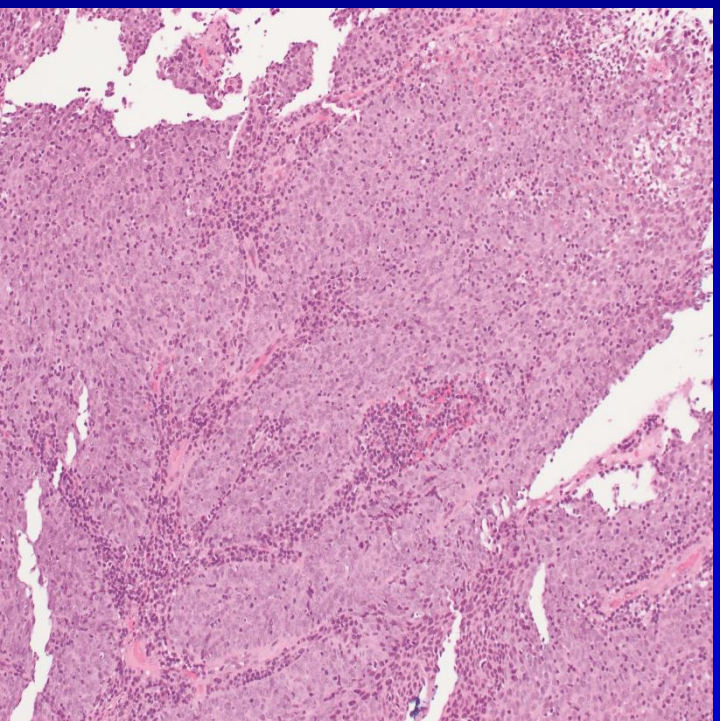
Case Diagnosis

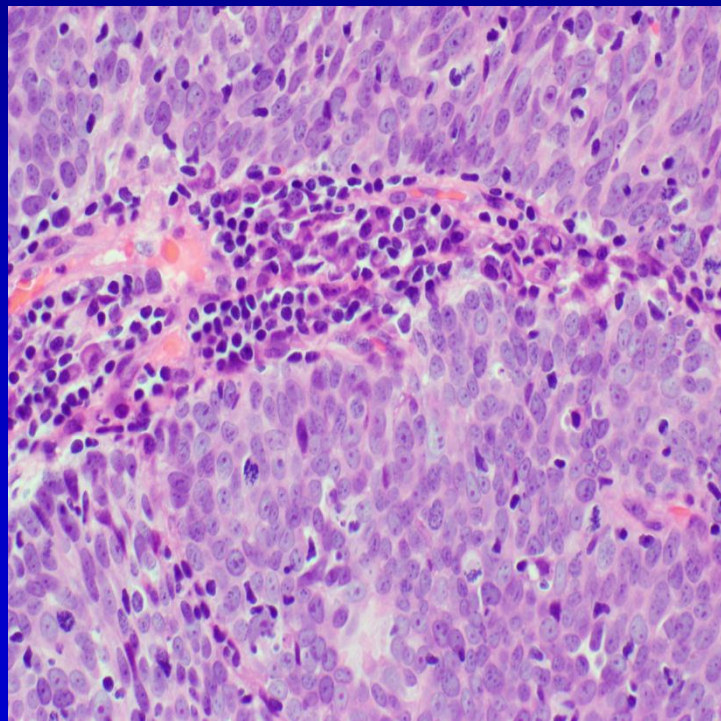
- **Metastatic HPV-associated lymphoepithelial-like carcinoma consistent with oropharyngeal origin**
- **Endoscopic biopsies of UADT sites including oro- and nasopharynx were performed**

Right Tonsil Biopsy

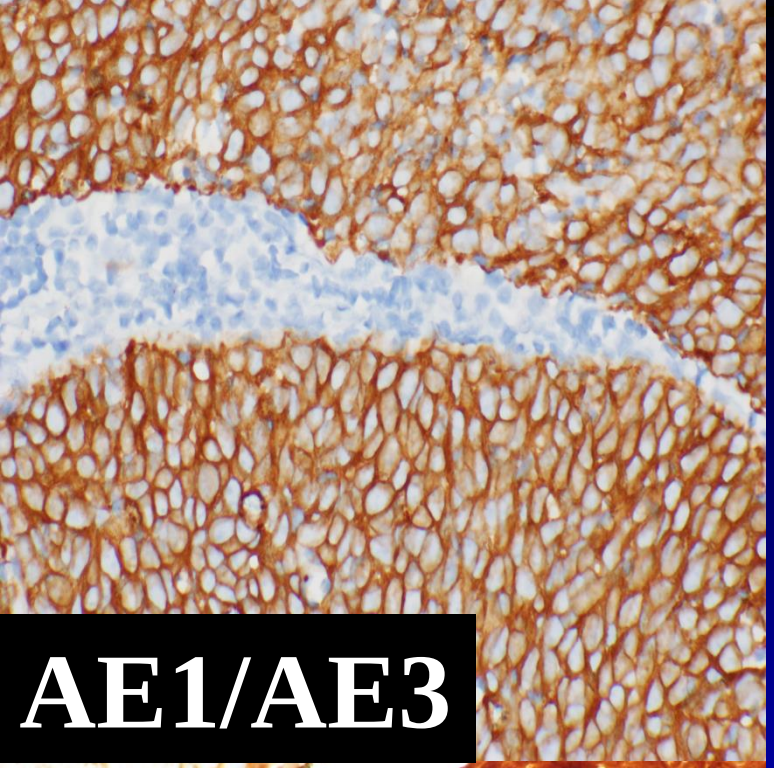


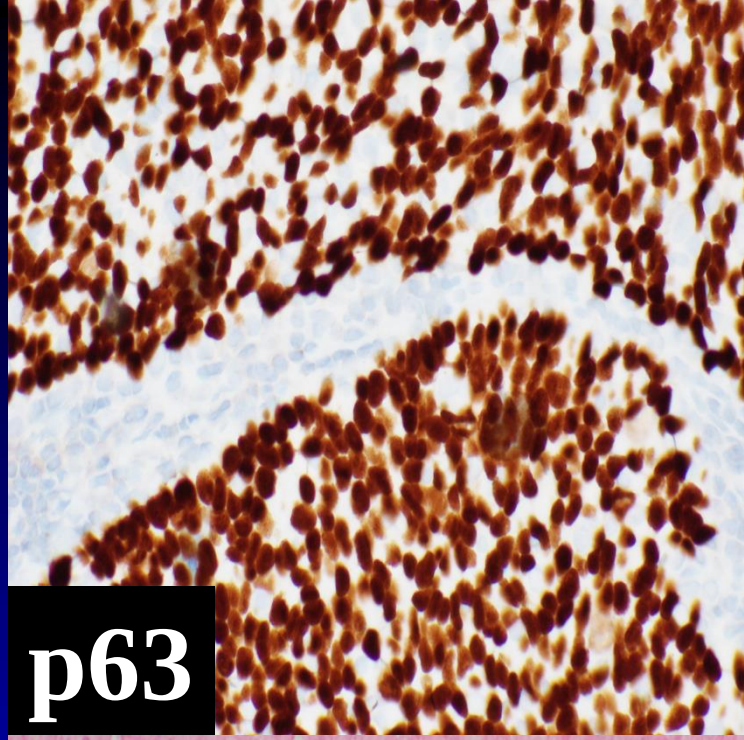


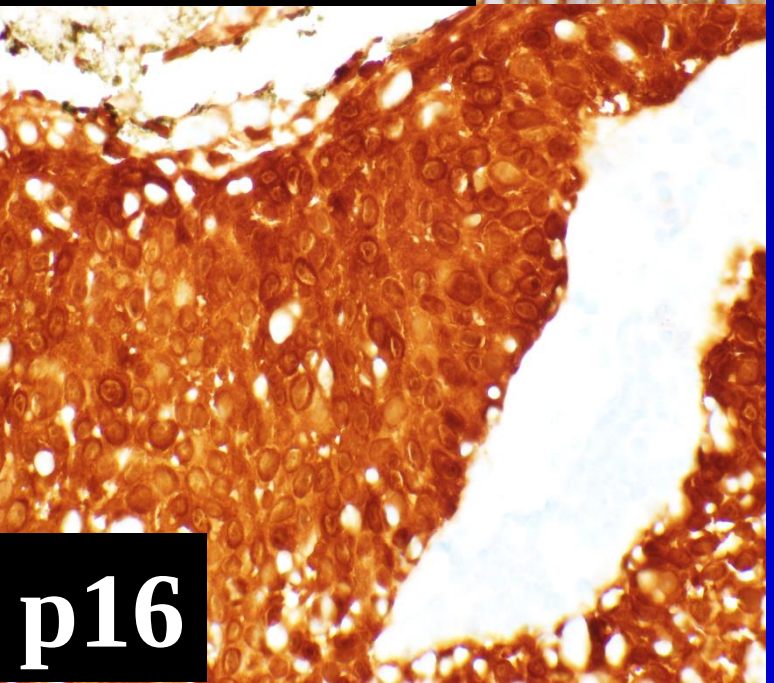


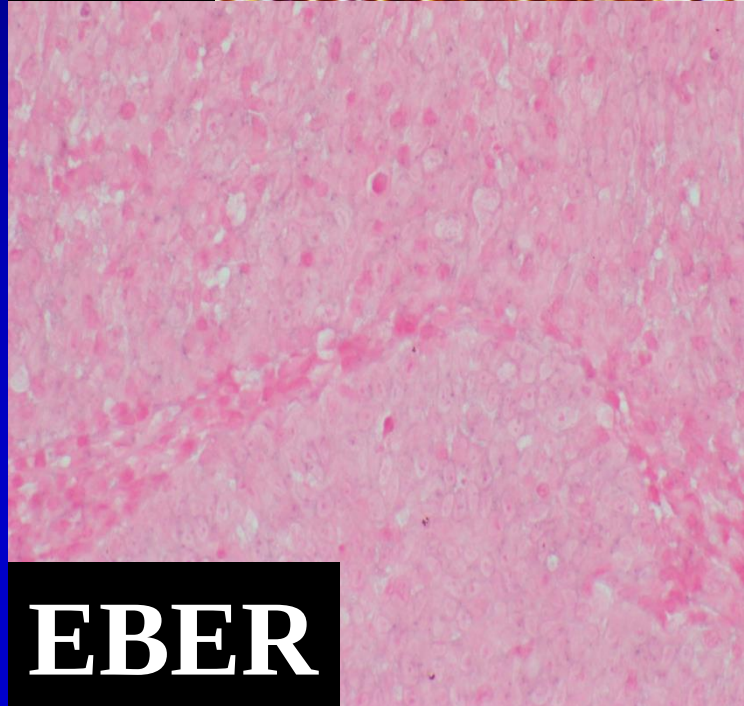


Right Tonsil Biopsy









Lymphoepithelial-like Carcinoma of the Oropharynx: A morphologic variant of HPV-related head and neck carcinoma

Singhi AD, Stelow EB, Mills SE, Westra WH.

Am J Surg Pathol 2010;34:800-805

Viral-Associated HNSCC Summary

- Viral carcinogenesis causally associated with HNSCC
- Classification:
  - SCC, HPV-positive (oropharynx)
  - SCC, EBV-positive (nasopharynx)
- Overall better prognosis than non-viral associated HNSCC
- Overlapping morphology between HPV+ and EBV+ cancers:
  - When confronted with MCCUP, both p16 and EBER should be performed
- No correlation to size of primary neoplasm (millimeters) and size of metastasis (centimeters)
  - tiny foci may give rise to large metastases
- Relative to oropharyngeal cancers concept of CIS is not applicable:
  - lesions that morphologically appear to be CIS may metastasize

AJCC Staging 8th Edition

- **HPV-mediated (p16+) Oropharyngeal Cancer (Chapter 10):**

  - Descriptor "poorly-differentiated" at odds with known improved prognosis so use should be avoided

  - Use of the designation "oropharyngeal SCC, nonkeratinizing type" is recommended

  - Histologic grading is not relevant

  - Presence of keratinization in a p16+/HR HPV+ carcinoma does not exclude using this staging system

  - Cervical lymph node metastases (to level II/III) from unknown primary tumor (pT0) that is p16+ and histology is consistent with HPV-mediated carcinogenesis are staged according to the guidelines in this chapter

  - Diagnosis of malignant transformation of branchial cleft cyst "should be rejected"

AJCC Staging 8th Edition
Unknown Primary Tumor

- Unique to head & neck:
  - Metastatic cervical node with no primary found (T0)
  - Due to anatomic site staging differences
  - Impossible to choose between multiple H&N chapters
- p16+ and EBER required for staging:
  - p16+ staged T0 N-appropriate in HPV+ Oropharynx chapter
  - EBER+ staged T0 N-appropriate in Nasopharynx chapter
  - p16-, EBER-SCC staged in Cervical Node Chapter as T0 N-appropriate +/- ENE
- T0 eliminated from all chapters except:
  - HPV-related oropharynx
  - EBV-related nasopharynx
  - Salivary gland based on histology of lymph node

Viral-Associated HNSCC Summary

- 2017 WHO Classification of H&N PDNEC includes small cell and large cell types
- PDNEC may also metastasize without a known primary particularly of oropharyngeal origin:

  - May be HPV+ (not associated with more favorable prognosis)

Thank You