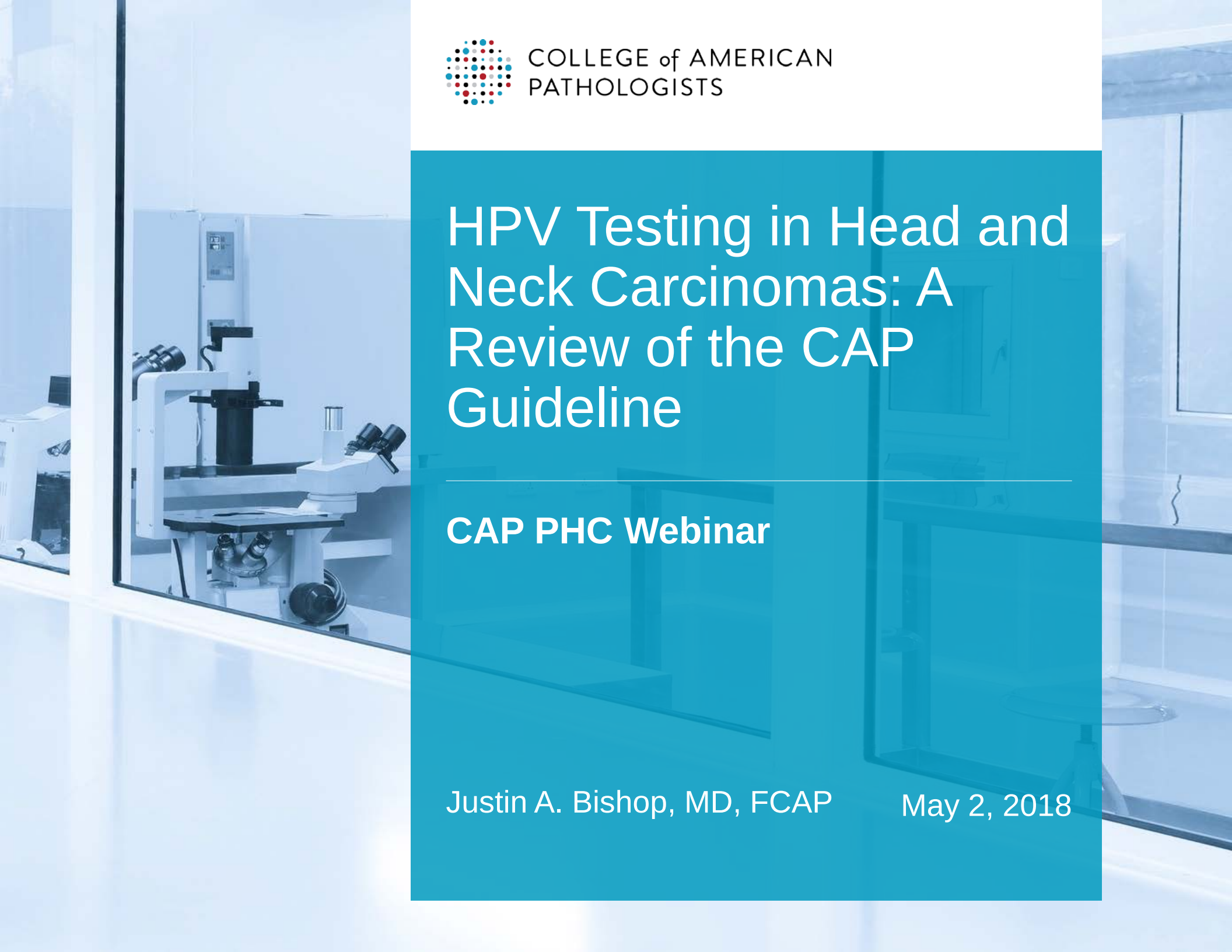

COLLEGE of AMERICAN PATHOLOGISTS

HPV Testing in Head and Neck Carcinomas: A Review of the CAP Guideline

CAP PHC Webinar

Justin A. Bishop, MD, FCAP

May 2, 2018

Webinar Host

- **This series is sponsored by the Personalized Healthcare Committee (PHC)**
- **Today's webinar host is PHC vice chair, Dr. Jordan Laser**

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- **This presentation will be recorded. The recording and PDF will go out to all registrants in one week**
- **All lines are muted during the presentation**
- **Please send in your questions as you think of them via the "Question box" in your control panel**

Justin Bishop, MD, FCAP

- **Associate Professor of Pathology, Director of Surgical Pathology and Head & Neck Pathology, UT Southwestern Medical Center, Dallas, Texas**
- **Expert Panel member of the CAP's Committee on HPV Testing in Head and Neck Squamous Cell Carcinomas**

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Dr. Bishop’s Conflicts of Interest

- **None.**

Introduction

Why HPV?

SEARCH

The New York Times

tensify, a
ffect Grows

Health Care Overhaul Collapses as Two Republican Senators Defect

PERSONAL HEALTH

With Cancer Screening, Better Safe Than Sorry?

In South Asian Social Castes, a Living Lab for Genetic Disease

HEALTH

HPV Vaccine Found to Help With Cancers of Throat

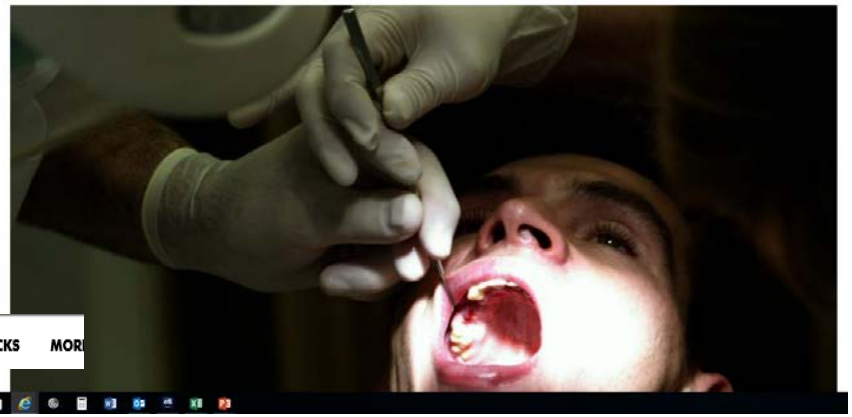
By DONALD G. McNEIL Jr. JULY 18, 2013

A vaccine that protects women against cervical cancer also appears to protect them against throat cancers caused by oral sex, and presumably would protect men as well, according to a study released Thursday.

TECH & SCIENCE

HPV INFECTIONS INCREASE RISK FOR HEAD AND NECK CANCER

BY JESSICA FIRGER ON 1/22/16 AT 2:48 PM



USA TODAY NEWS LIFE MONEY TECH TRAVEL OPINION 88° CROSSWORDS WASHINGTON VIDEO STOCKS MOR

Man speaks out about his HPV-associated throat cancer

ROB ROGERS , The Billings Gazette Published 5:17 p.m. ET April 15, 2017 | Updated 6:25 p.m. ET April 15, 2017

(Photo: Sashkin - Fotolia)

13 CONNECT TWEET LINKEDIN COMMENT EMAIL MORE

BILLINGS, Mont. (AP) — It's not just ladies.

Robert Fox, 42, contracted and survived cancer that developed from an HPV infection, the virus best known for causing cervical cancer in women. And he wants men to know they can get it, too.

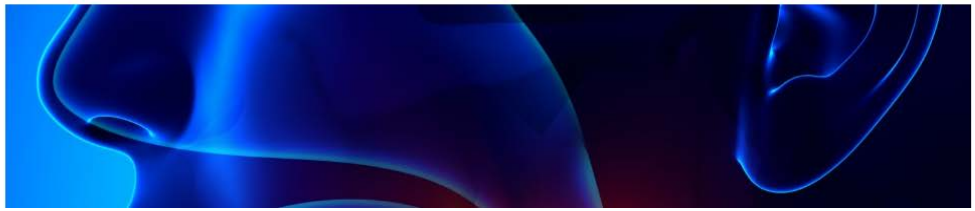
"It was a shock," the Montana man said. "It's a cancer I never thought I'd get."

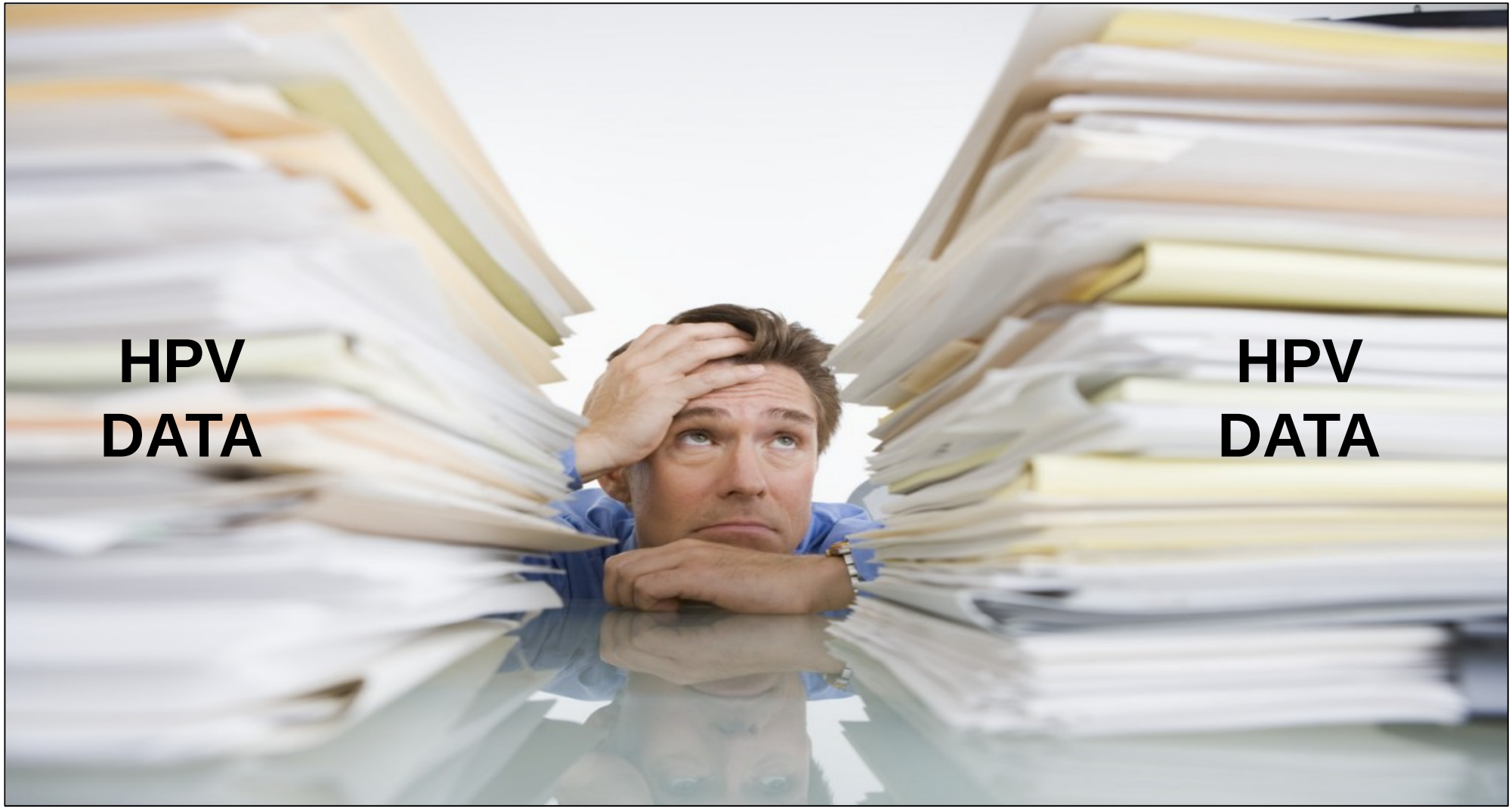
Fox was diagnosed with throat cancer two years ago. He had a really raw sore throat for weeks that showed no signs of abating. He went to his family physician, who

The Washington Post

Health & Science

What men should know about cancer that spreads through oral sex





CAP Pathology and Laboratory Quality Center: Human Papillomavirus Testing in Head and Neck Squamous Cell Carcinomas Expert Panel

Practical
Recommendations

CAP HPV Testing in Head and Neck Cancers Guideline Statements

1. **Pathologists should perform HR-HPV testing on all patients with newly diagnosed oropharyngeal squamous cell carcinoma (OPSCC), including all histologic subtypes. This testing may be performed on the primary tumor or on a regional lymph node metastasis when the clinical findings are consistent with an oropharyngeal primary.**
2. **For oropharyngeal tissue specimens (i.e., non-cytology), 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.**
3. **Pathologists should *not* routinely perform HR-HPV testing on patients with non-squamous carcinomas of the oropharynx.**
4. **Pathologists should *not* routinely perform HR-HPV testing on patients with non-oropharyngeal primary tumors of the head and neck.**
5. **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.**
6. **For tissue specimens (i.e., non-cytology) from patients presenting with metastatic SCC of unknown primary in a cervical upper or mid jugular chain lymph node, pathologists should perform p16 IHC.**
7. **Pathologists should perform HR-HPV testing on head and neck fine needle aspiration (FNA) SCC samples from all patients with known oropharyngeal SCC not previously tested for HR-HPV, with suspected oropharyngeal SCC, 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.**
8. **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**
9. **Pathologists should not routinely perform low-risk HPV testing on patients with head and neck carcinomas.**
10. **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.**
11. **Pathologists should not routinely perform HR-HPV testing on patients with distant metastases if primary tumor HR-HPV status has been established. 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 metastasis or a new primary SCC.**
12. **Pathologists should report primary OPSCCs that test positive for HR-HPV or its surrogate marker p16 as "HPV-positive" and/or "p16-positive."**
13. **Pathologists should not provide a tumor grade or differentiation status for HPV-positive/p16-positive OPSCC.**
14. **Pathologists should not alter HR-HPV testing strategy based on patient smoking history**

Human Papillomavirus Testing in Head and Neck Carcinomas

Guideline From the College of American Pathologists

James S. Lewis Jr, MD; Beth Beadle, MD, PhD; Justin A. Bishop, MD; Rebecca D. Chernock, MD; Carol Colasacco, MLIS, SCT(ASCP); Christina Lacchetti, MHSc; Joel Todd Moncur, MD, PhD; James W. Rocco, MD, PhD; Mary R. Schwartz, MD; Raja R. Seethala, MD; Nicole E. Thomas, MPH, CT(ASCP)^{CM}; William H. Westra, MD; William C. Faquin, MD, PhD

• ***Context.***—**Human papillomavirus (HPV) is a major cause of oropharyngeal squamous cell carcinomas, and HPV (and/or surrogate marker p16) status has emerged as a prognostic marker that significantly impacts clinical management. There is no current consensus on when to test oropharyngeal squamous cell carcinomas for HPV/p16 or on which tests to choose.**

Objective.—**To develop evidence-based recommendations for the testing, application, interpretation, and reporting of HPV and surrogate marker tests in head and neck carcinomas.**

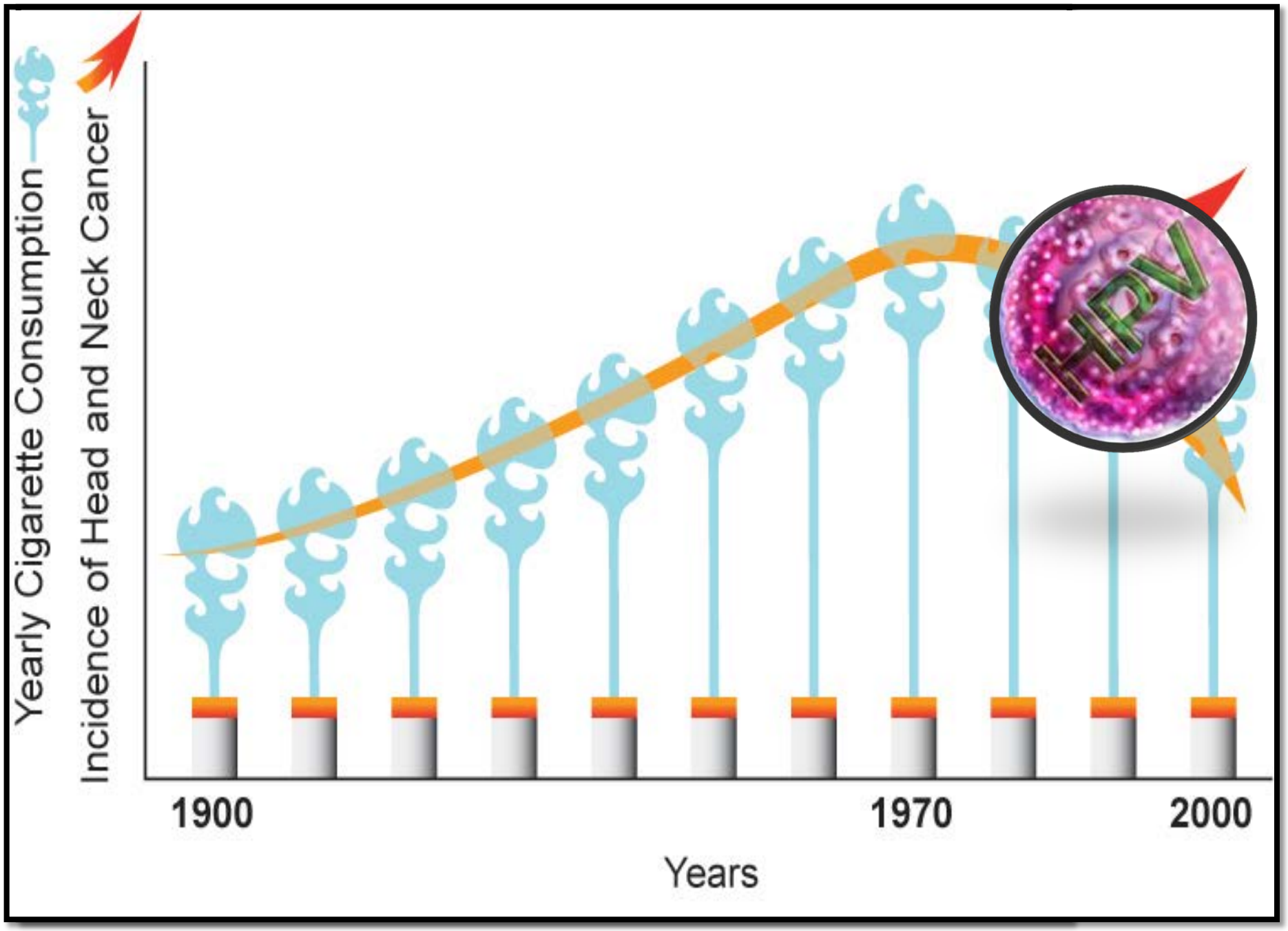
Design.—**The College of American Pathologists convened a panel of experts in head and neck and molecular pathology, as well as surgical, medical, and radiation oncology, to develop recommendations. A systematic review of the literature was conducted to address 6 key questions. Final recommendations were derived from strength of evidence, open comment period feedback, and expert panel consensus.**

Results.—**The major recommendations include (1) testing newly diagnosed oropharyngeal squamous cell carcinoma patients for high-risk HPV, either from the primary tumor or from cervical nodal metastases, using p16 immunohistochemistry with a 70% nuclear and cytoplasmic staining cutoff, and (2) not routinely testing nonsquamous oropharyngeal carcinomas or nonoropharyngeal carcinomas for HPV. Pathologists are to report tumors as HPV positive or p16 positive. Guidelines are provided for testing cytologic samples and handling of locoregional and distant recurrence specimens.**

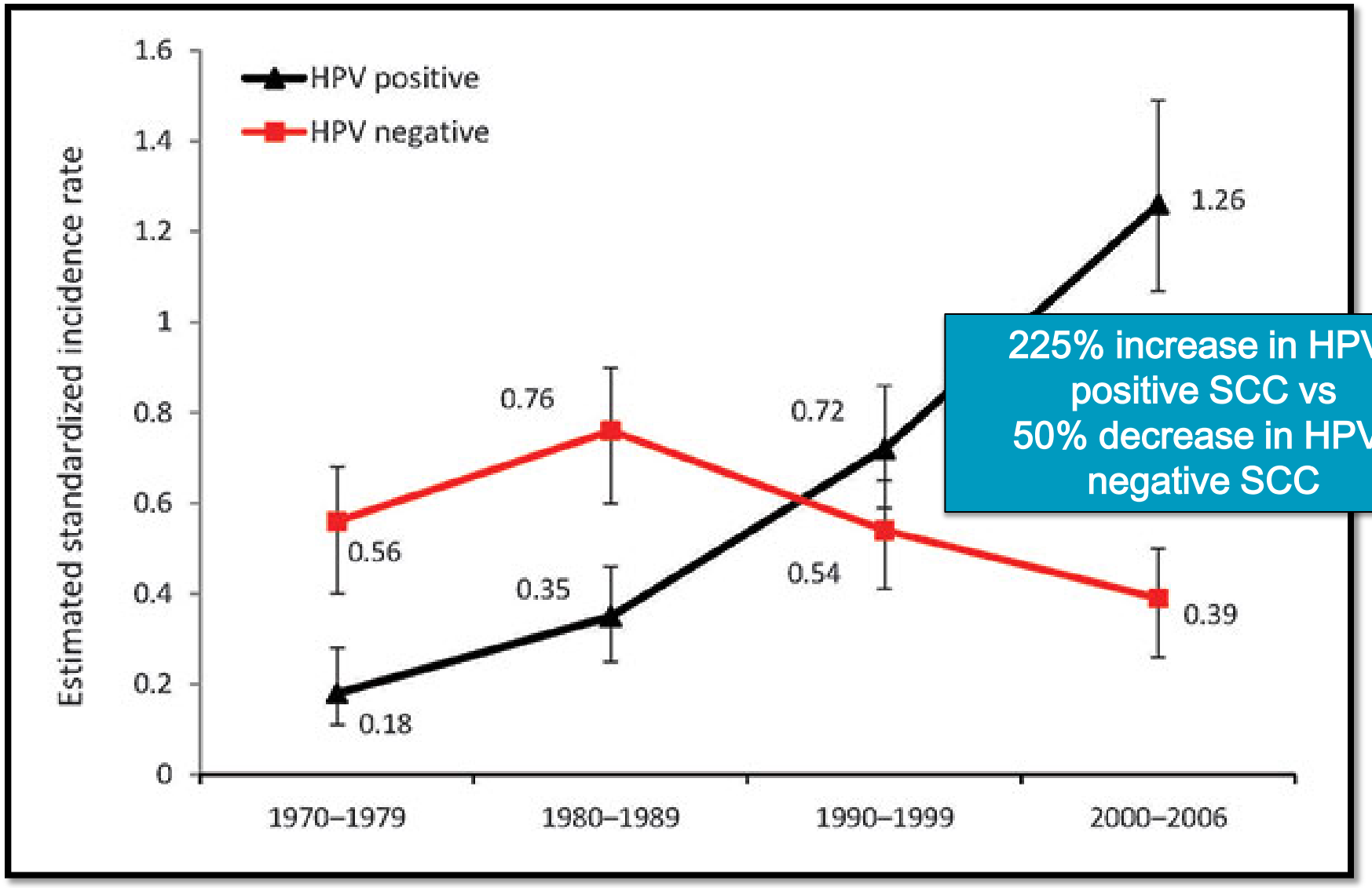
Conclusions.—**Based on the systematic review and on expert panel consensus, high-risk HPV testing is recommended for all new oropharyngeal squamous cell carcinoma patients, but not routinely recommended for other head and neck carcinomas.**

(*Arch Pathol Lab Med.* 2018;142:559–597; doi: 10.5858/arpa.2017-0286-CP)

Accepted for publication October 23, 2017.
Published as an Early Online Release December 18, 2017.

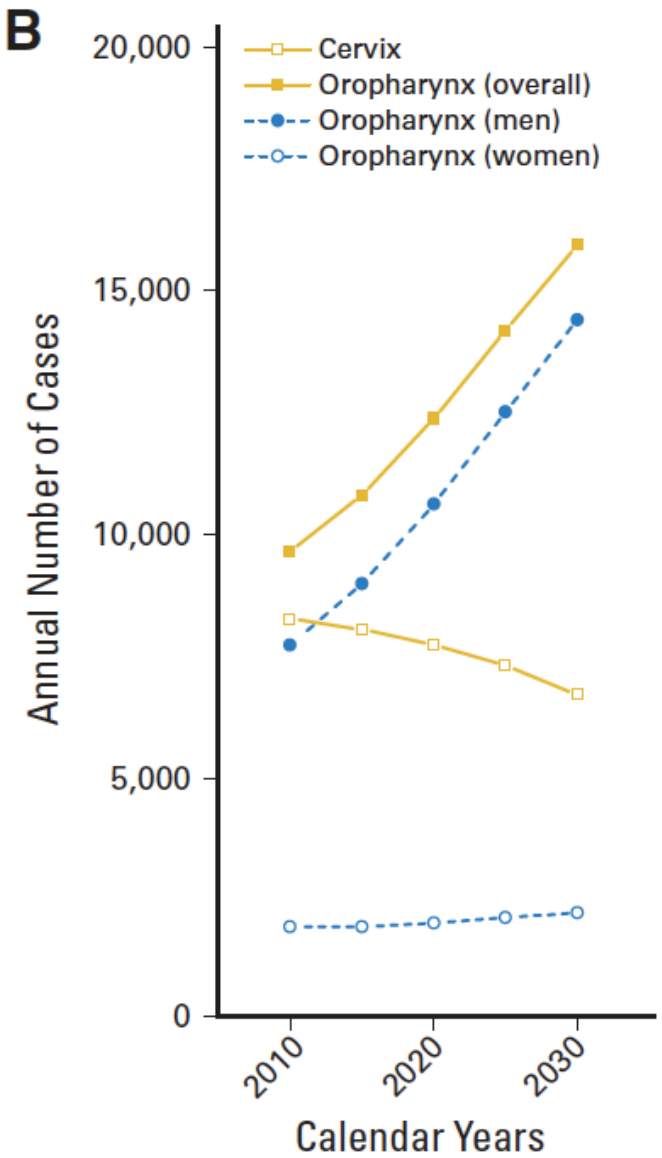


HPV and Head and Neck Cancer



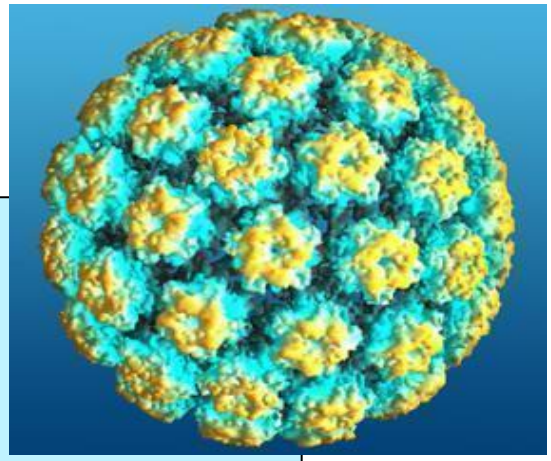
Nasman A, et al. Int J Cancer. 2009; 125:362–6.

Incidence of OPSCC in the USA: Has surpassed cervical carcinoma



Chaturvedi, SEER data from 1984-2004

Human Papillomavirus



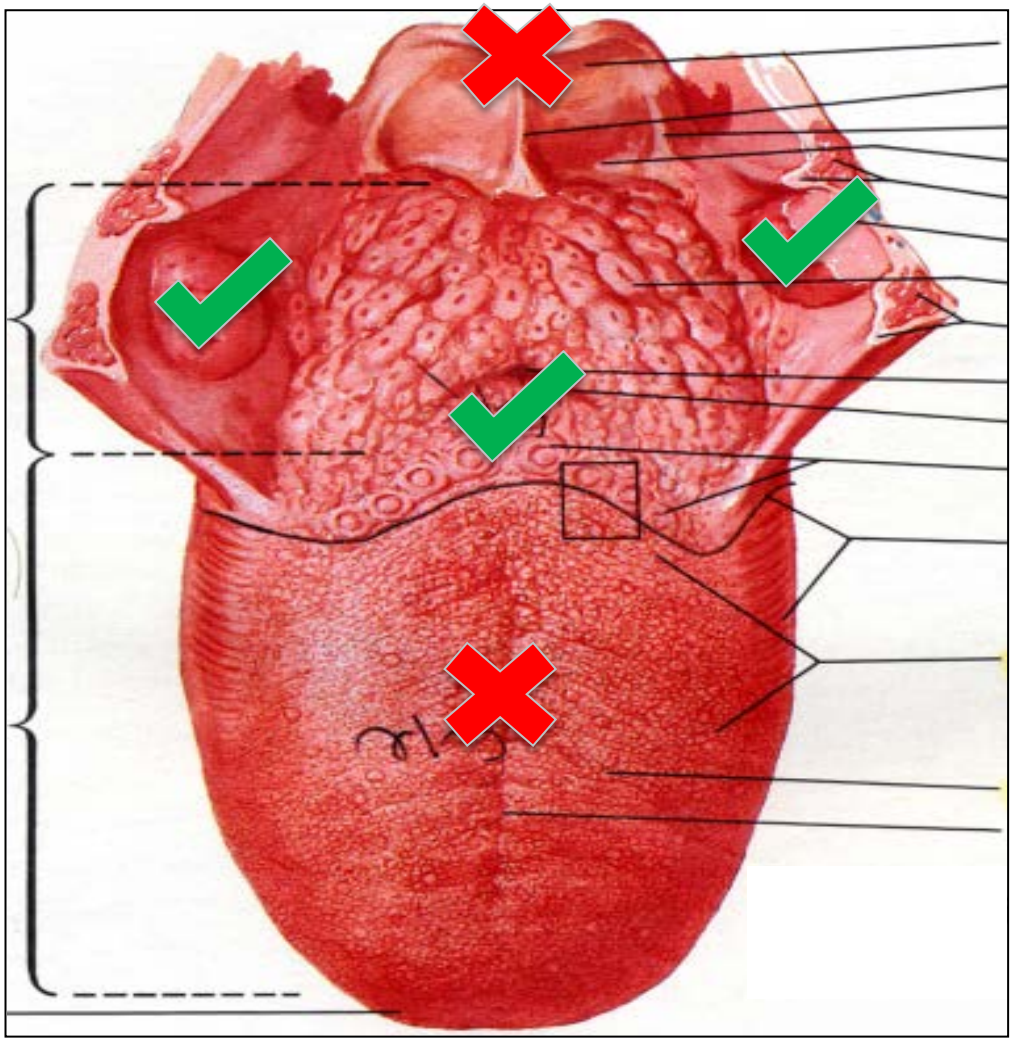
- **Papovaviridae family**
- **>100 genotypes**
  - **30 sexually transmitted**
    - **80% genital infection rate in adults!**
- **Structural**
  - **Early and late proteins (7E and 2L)**
    - **E6**
      - **Binds and degrades p53**
    - **E7**
      - **Binds and degrades Rb**
- **Classification**
  - **Alpha/beta papillomaviruses**
  - **Alpha - High risk (16, 18, 31, 33, 35…)**
  - **Alpha - Low risk (6, 11)**

Low-risk vs. High-risk HPV

- **Low-risk → papillomas, warts**
- **High-risk → cancer**

HPV 16

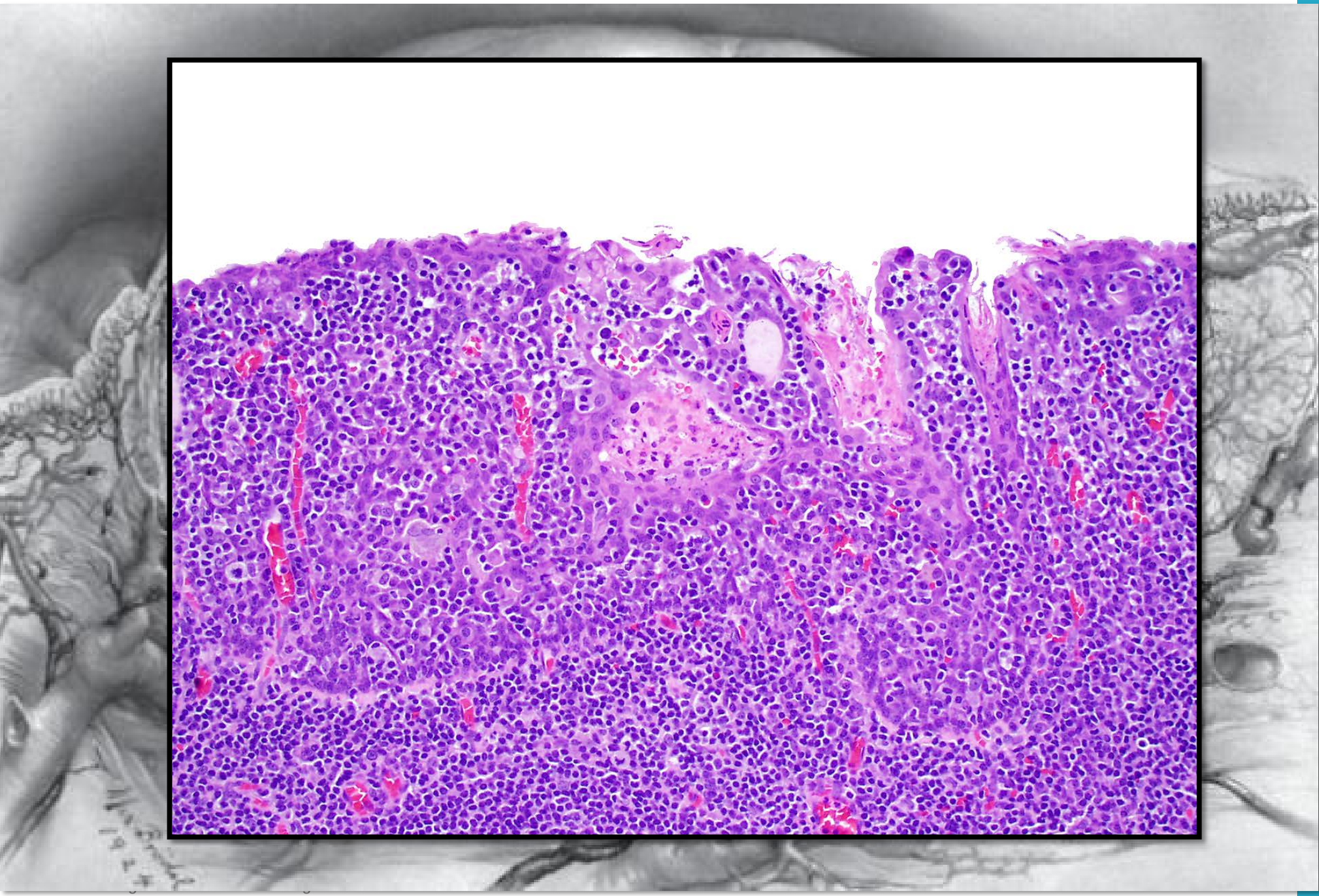
Oropharynx and HPV

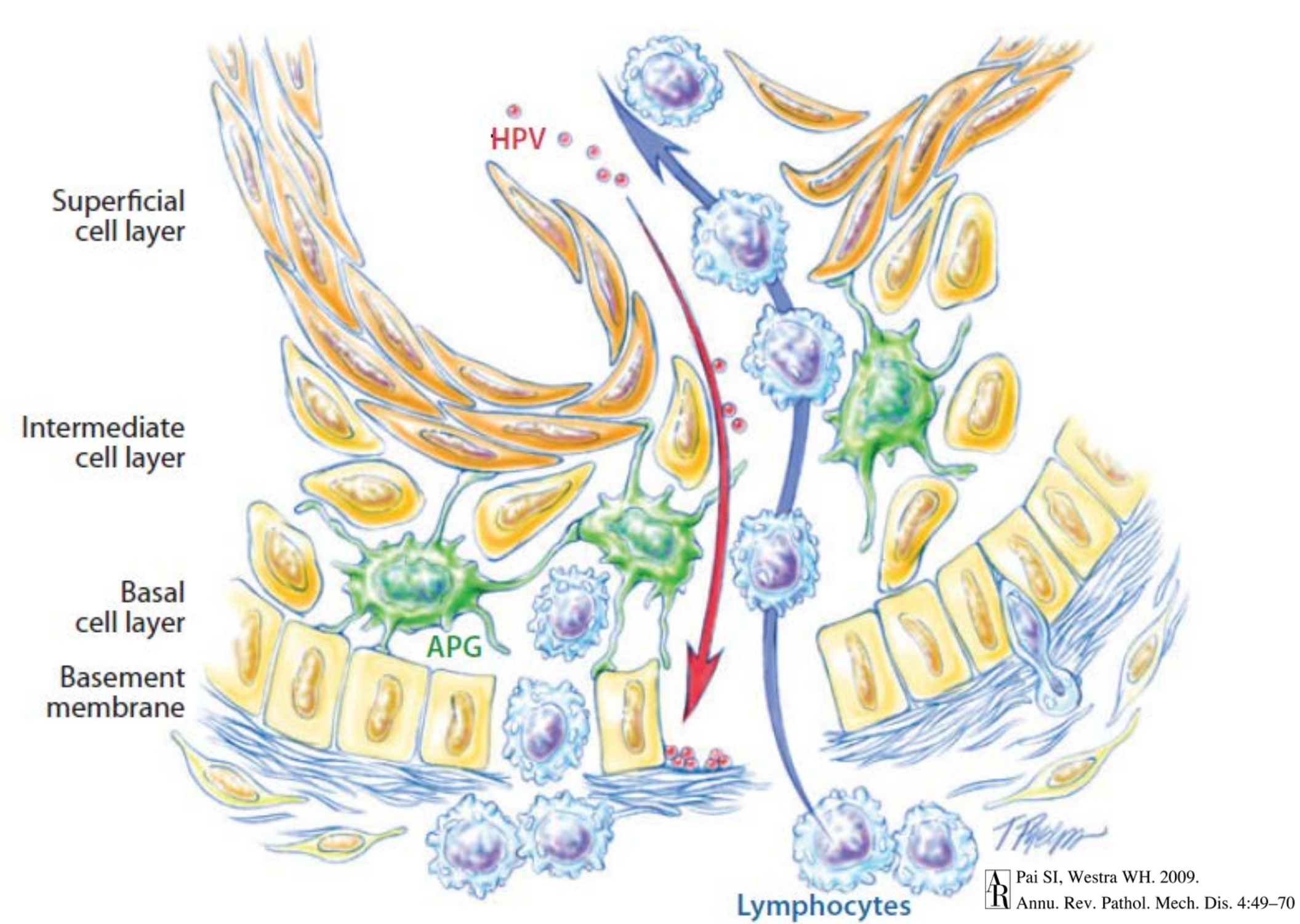


Oropharynx

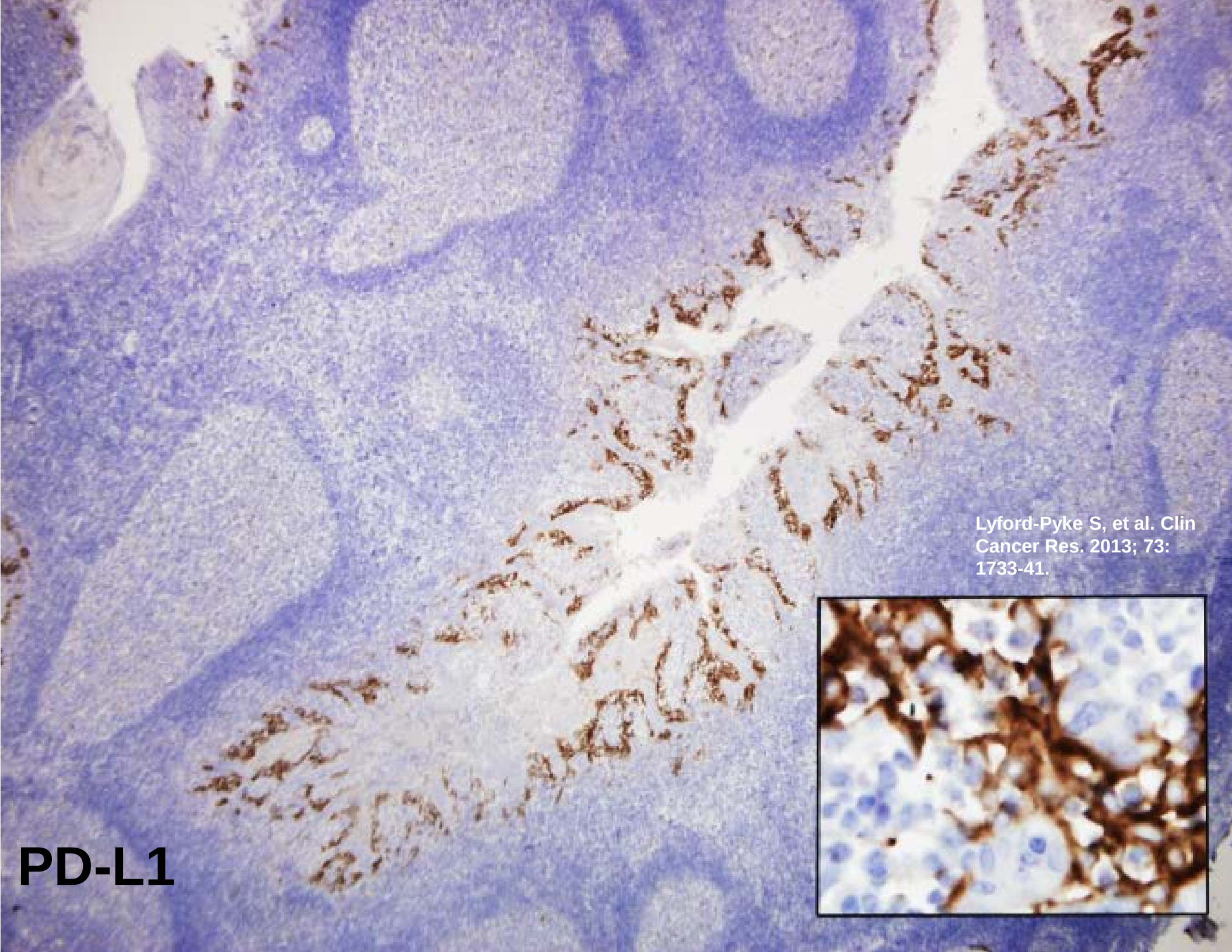
=

Tonsils and Base of Tongue





Pai SI, Westra WH. 2009.
Annu. Rev. Pathol. Mech. Dis. 4:49–70


PD-L1
Lyford-Pyke S, et al. Clin Cancer Res. 2013; 73: 1733-41.

WHO

2005

WHO classification of tumours of the oral cavity and oropharynx

Malignant epithelial tumours		Myoepithelial carcinoma	8982/3
Squamous cell carcinoma	8070/3	Carcinoma ex pleomorphic adenoma	8941/3
Verrucous carcinoma	8051/3	Salivary gland adenomas	
Basaloid squamous cell carcinoma	8083/3	Pleomorphic adenoma	8940/0
Papillary squamous cell carcinoma	8052/3	Myoepithelioma	8982/0
Spindle cell carcinoma	8074/3	Basal cell adenoma	8147/0
Acantholytic squamous cell carcinoma	8075/3	Canalicular adenoma	8149/0
Adenosquamous carcinoma	8560/3	Duct papilloma	8503/0
Carcinoma cuniculatum	8051/3	Cystadenoma	8440/0
Lymphoepithelial carcinoma	8082/3		
		Soft tissue tumours	
Epithelial precursor lesions		Kaposi sarcoma	9140/3
		Lymphangioma	9170/0
Benign epithelial tumours		Ectomesenchymal chondromyxoid tumour	
Papillomas	8050/0	Focal oral mucinosis	
Squamous cell papilloma and verruca vulgaris		Congenital granular cell epulis	
Condyloma acuminatum			
Focal epithelial hyperplasia		**Haematolymphoid tumours**	
Granular cell tumour	9580/0	Diffuse large B-cell lymphoma (DLBCL)	9680/3
Keratoacanthoma	8071/1	Mantle cell lymphoma	9673/3
		Follicular lymphoma	9690/3
Salivary gland tumours		Extranodal marginal zone B-cell lymphoma of MALT type	9699/3
Salivary gland carcinomas		Burkitt lymphoma	9687/3
Acinic cell carcinoma	8550/3	T-cell lymphoma (including anaplastic large cell lymphoma	9714/3
Mucoepidermoid carcinoma	8430/3	Extramedullary plasmacytoma	9734/3
Adenoid cystic carcinoma	8200/3	Langerhans cell histiocytosis	9751/1
Polymorphous low-grade adenocarcinoma	8525/3	Extramedullary myeloid sarcoma	9930/3
Basal cell adenocarcinoma	8147/3	Follicular dendritic cell sarcoma / tumour	9758/3
Epithelial-myoepithelial carcinoma	8562/3		
Clear cell carcinoma, not otherwise specified	8310/3	**Mucosal malignant melanoma**	8720/3
Cystadenocarcinoma	8450/3		
Mucinous adenocarcinoma	8480/3	**Secondary tumours**	
Oncocytic carcinoma	8290/3		
Salivary duct carcinoma	8500/3		

[1] Morphology code of the International Classification of Diseases for Oncology (ICD-O) (821) 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.

2017

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

Squamous cell carcinoma, HPV positive	8085/3	Burkitt lymphoma	9687/3
Squamous cell carcinoma, HPV negative	8070/3	Follicular lymphoma	9690/3
Squamous cell carcinoma, (non-kreatinizing)	8072/3	Mantle cell lymphoma	9673/3
Pleomorphic adenoma	8940/0	T-lymphoblastic lymphoma / leukemia	9837/3
Adenoid cystic carcinoma	8200/3	Follicular dendritic sarcoma	9758/3
Polymorphous adenocarcinoma	8525/3		
Haematolymphoid neoplasms		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*.	
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		

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

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

Oropharynx has its own section in the 2017 WHO classification

2017

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

Squamous cell carcinoma, HPV positive	8085/3
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Mantle cell lymphoma	9673/3
T-lymphoblastic lymphoma / leukemia	9837/3
Follicular dendritic sarcoma	9758/3

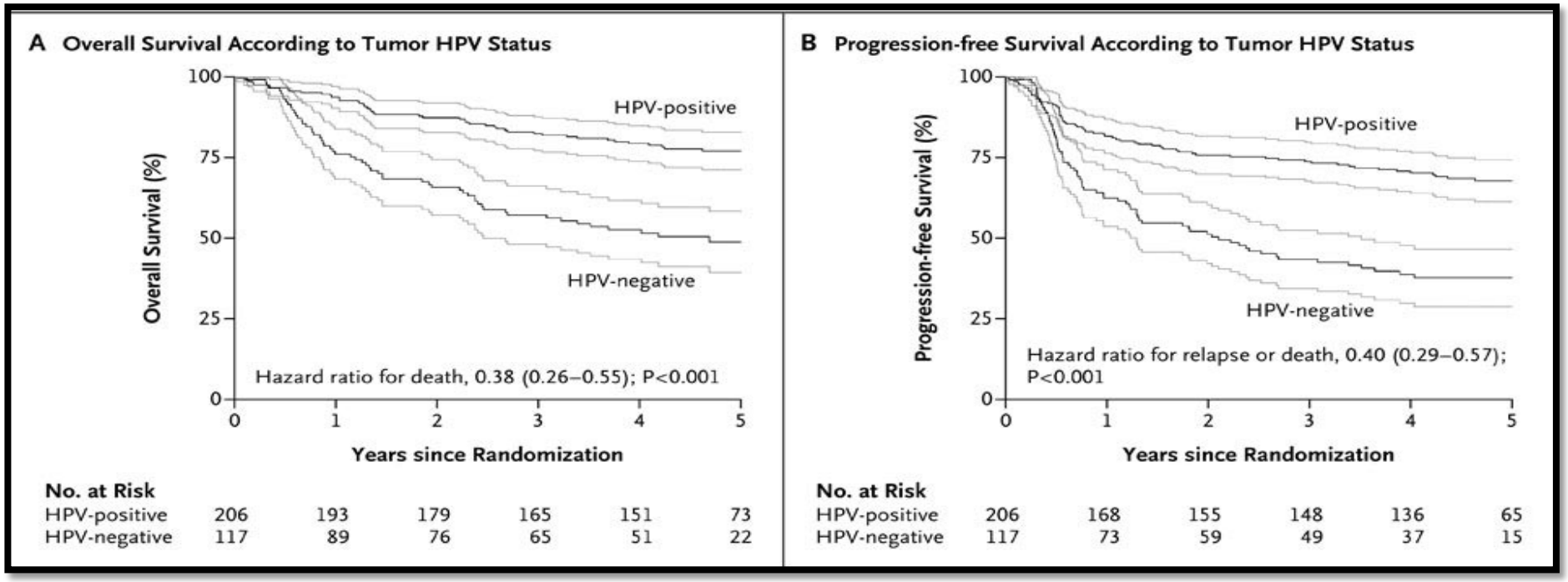
The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) [742A]. Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours. The 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*.

Oropharyngeal SCCs are now Sub-classified by HPV status

HPV+ vs. HPV– OPSCC

	HPV-	HPV+
Incidence	Falling	Rising
Age	Older	Younger
Socio-economic status	Low	High
Risk factors	Tobacco, alcohol	Sexual behavior
Survival	Worse	Better

HPV+ vs. HPV– OPSCC



Ang K et al. N Engl J Med 2010; 363(1):24-35.

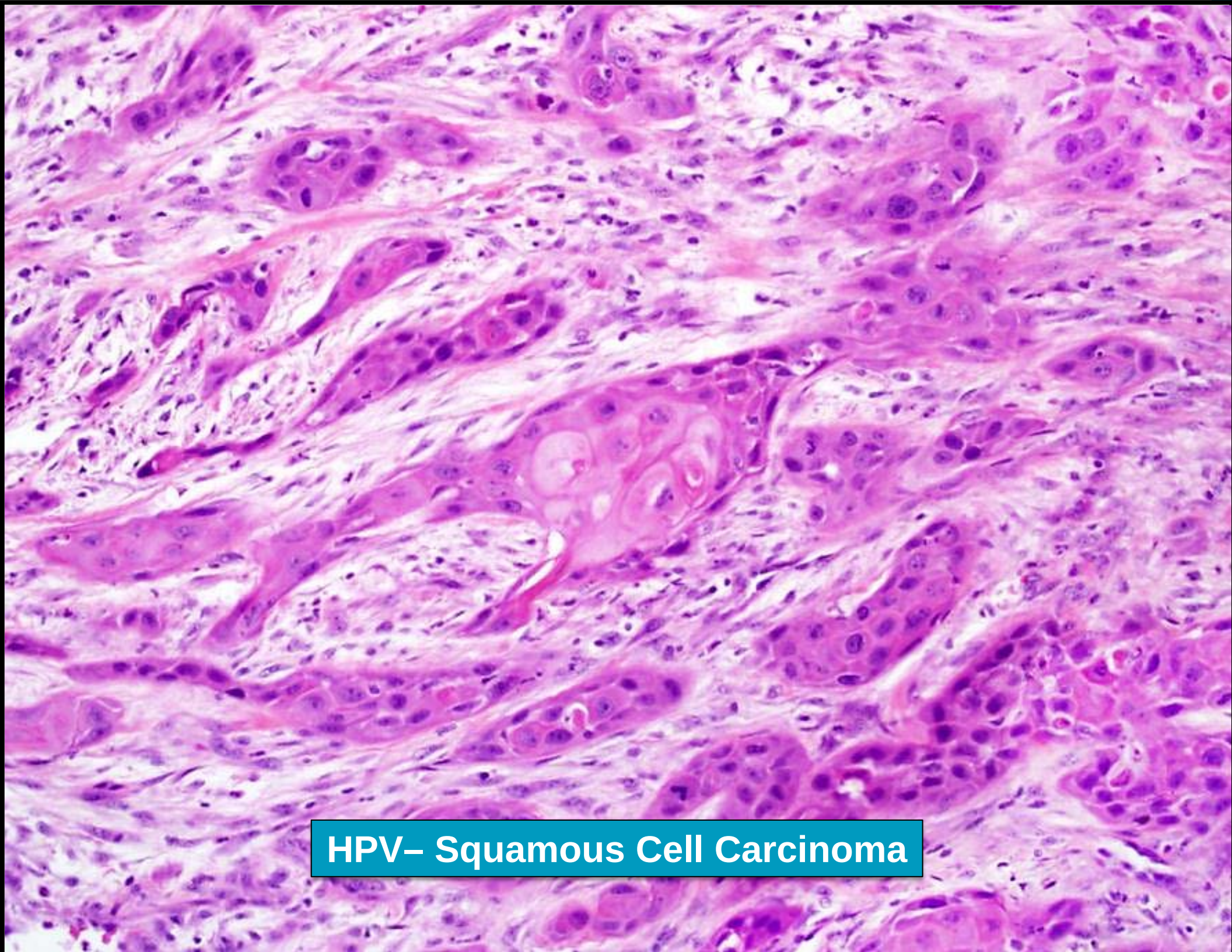
Nodal metastases are present at presentation in ~85-90%+ of all HPV-related oropharyngeal squamous cell carcinomas

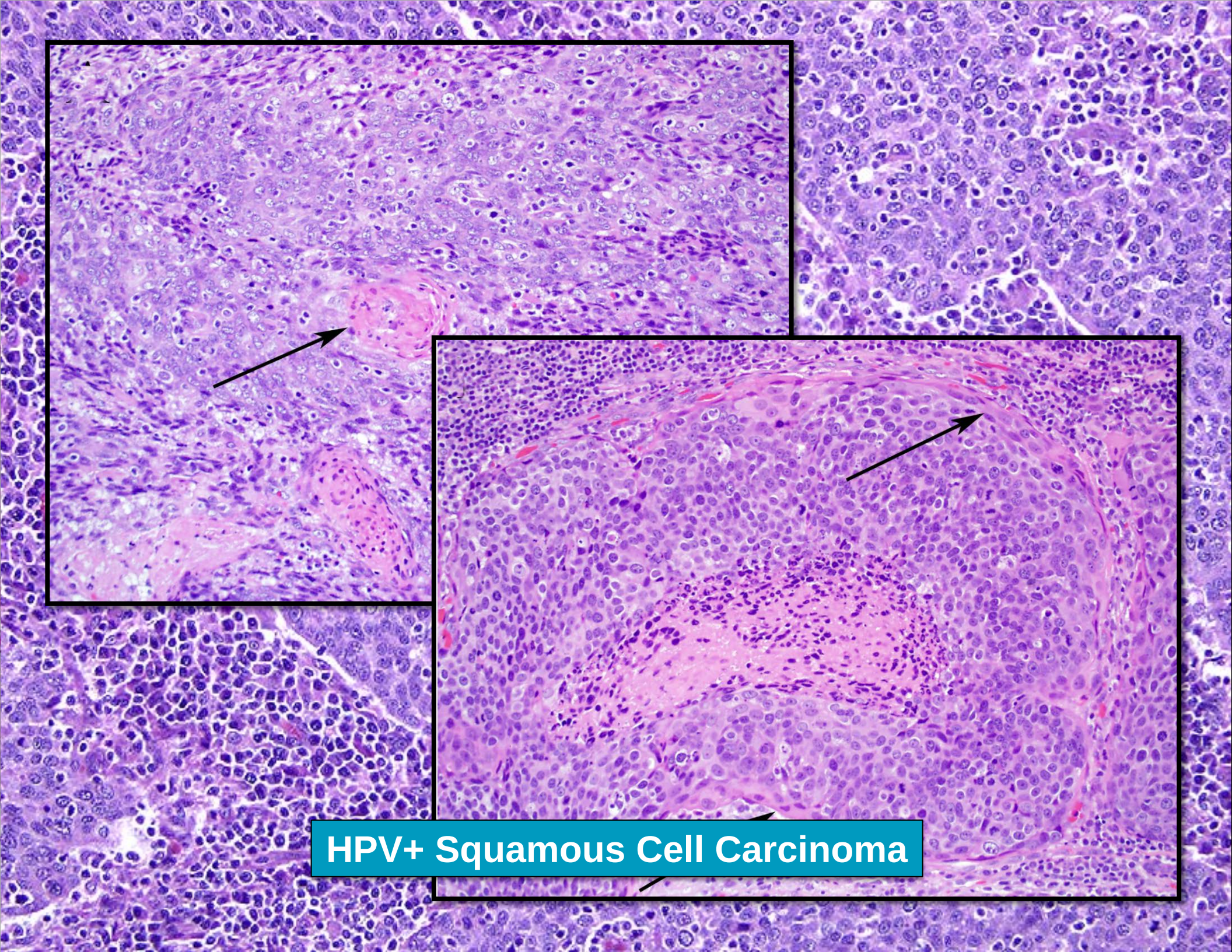
Ang et al. *NEJM* 2010; 363: 24.
Jordan et al. *Am J Surg Pathol* 2012; 36: 945.
Lewis Jr. et al. Am J Surg Pathol 2010; 1044:38.
O'Sullivan et al. Lancet Oncol 2016; 17: 440.

~50% of HPV+ OPSCC Patients Present with Neck Symptoms

(vs ~20% in HPV-)

McIlwain et al. JAMA Otolaryngol Head Neck Surg 2014; 140: 441.

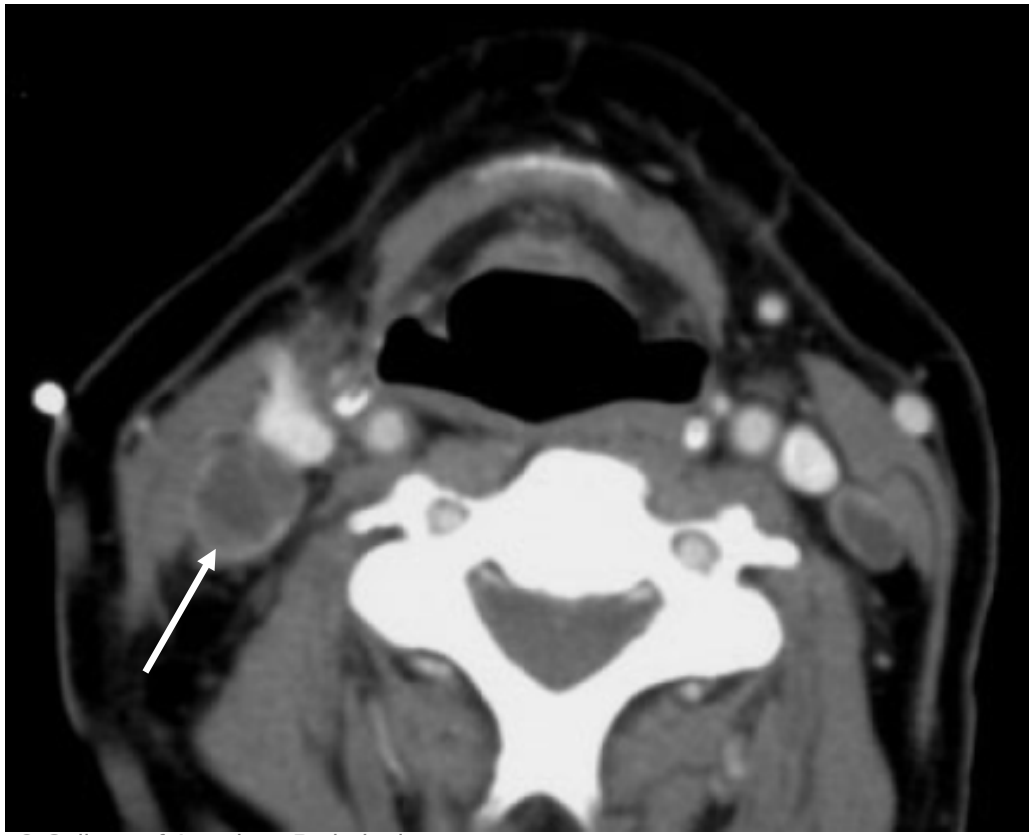

HPV– Squamous Cell Carcinoma


HPV+ Squamous Cell Carcinoma

CYSTIC LYMPH NODE METASTASIS IN PATIENTS WITH HEAD AND NECK CANCER: AN HPV-ASSOCIATED PHENOMENON

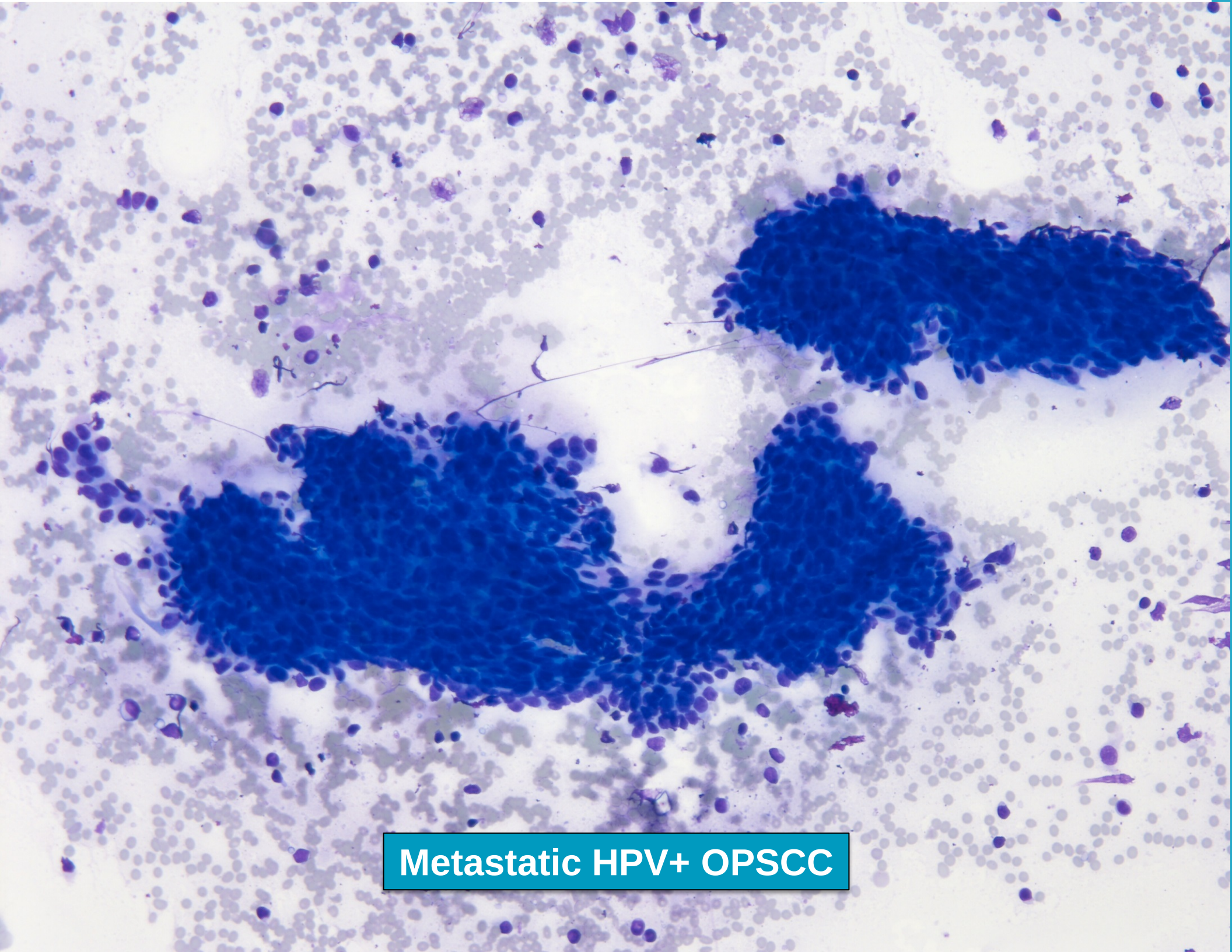
David Goldenberg, MD,[1] Shahnaz Begum, MD, PhD,[2] William H. Westra, MD,[2]
Zubair Khan, MD,[3] James Sciubba, DMD, PhD,[3] Sara I. Pai, MD, PhD,[3]
Joseph A. Califano, MD,[3] Ralph P. Tufano, MD,[3] Wayne M. Koch, MD[3]

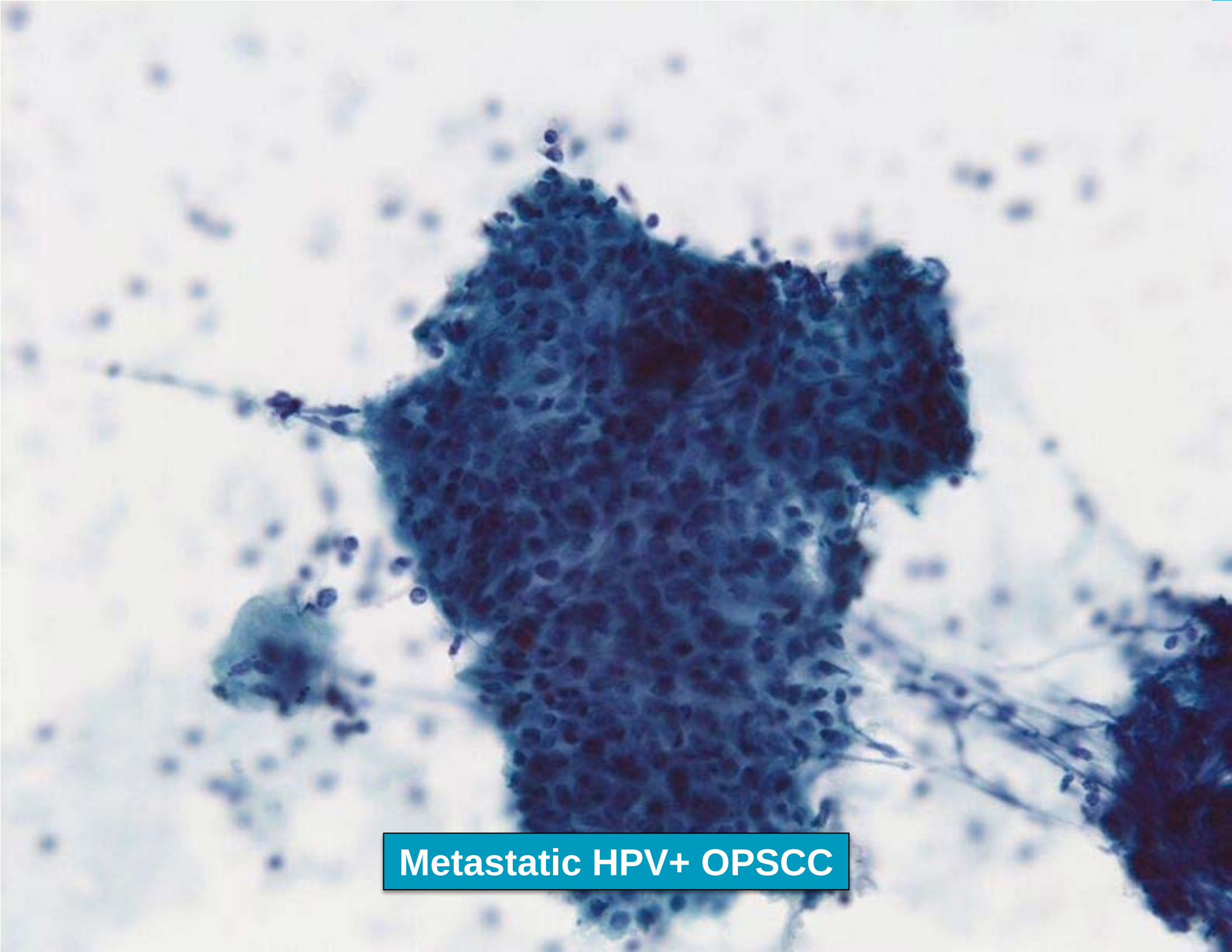
Head Neck 2008; 30:898-903

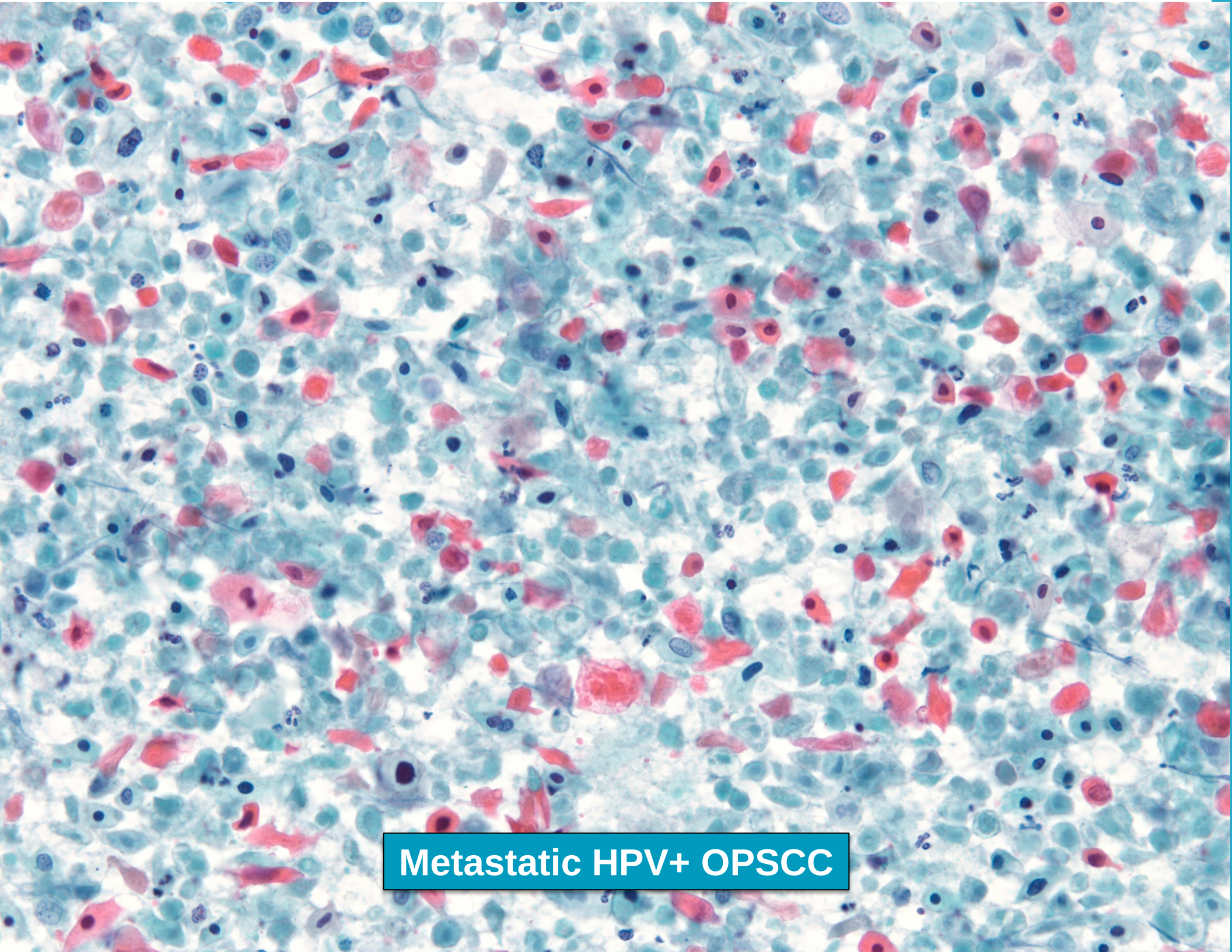


90% were HPV+


Metastatic HPV+ OPSCC


Metastatic HPV+ OPSCC


Metastatic HPV+ OPSCC

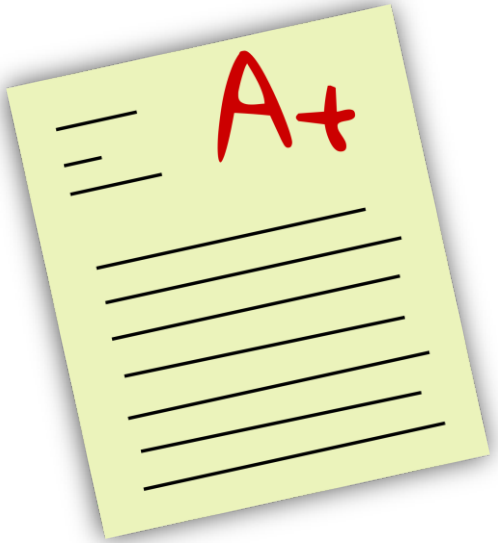

Metastatic HPV+ OPSCC

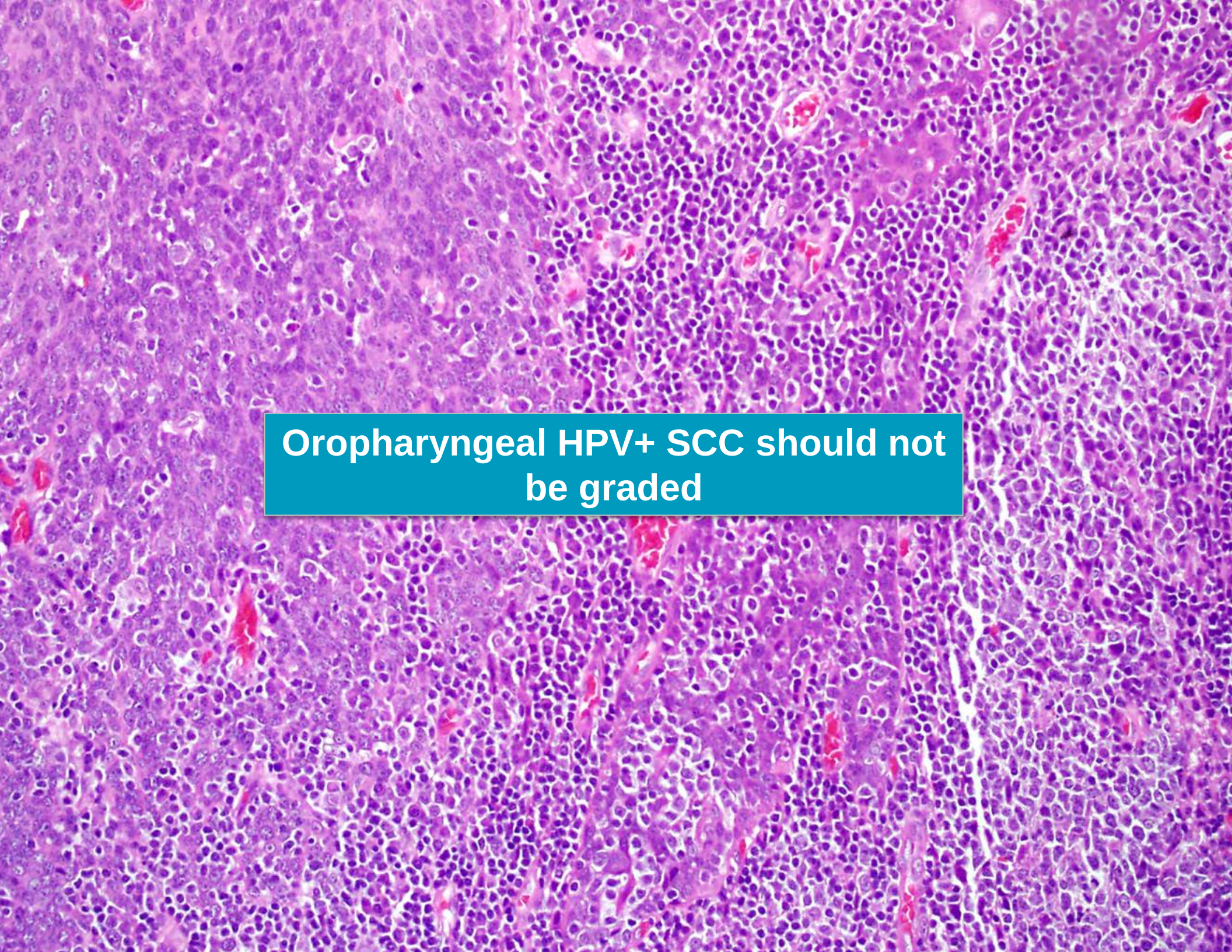
Issues Unique to HPV+ OPSCC

- **Grading**
- **Terminology**
- **Invasion**

Tumor Grading

- **Semi-quantitative measurement of differentiation, expressed as the degree to which a tumor resembles the normal tissue from which it arises**
  - **Well differentiated**
  - **Moderately differentiated**
  - **Poorly differentiated**
  - **Undifferentiated**
- **Correlates with tumor behavior**

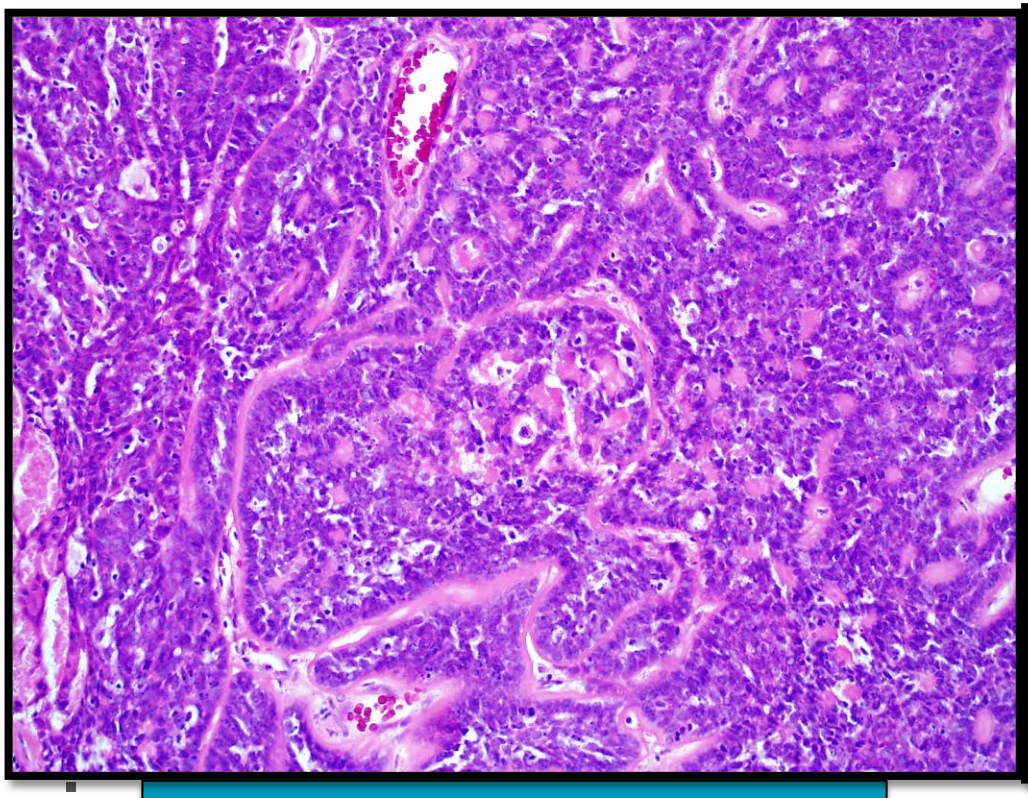



Oropharyngeal HPV+ SCC should not be graded

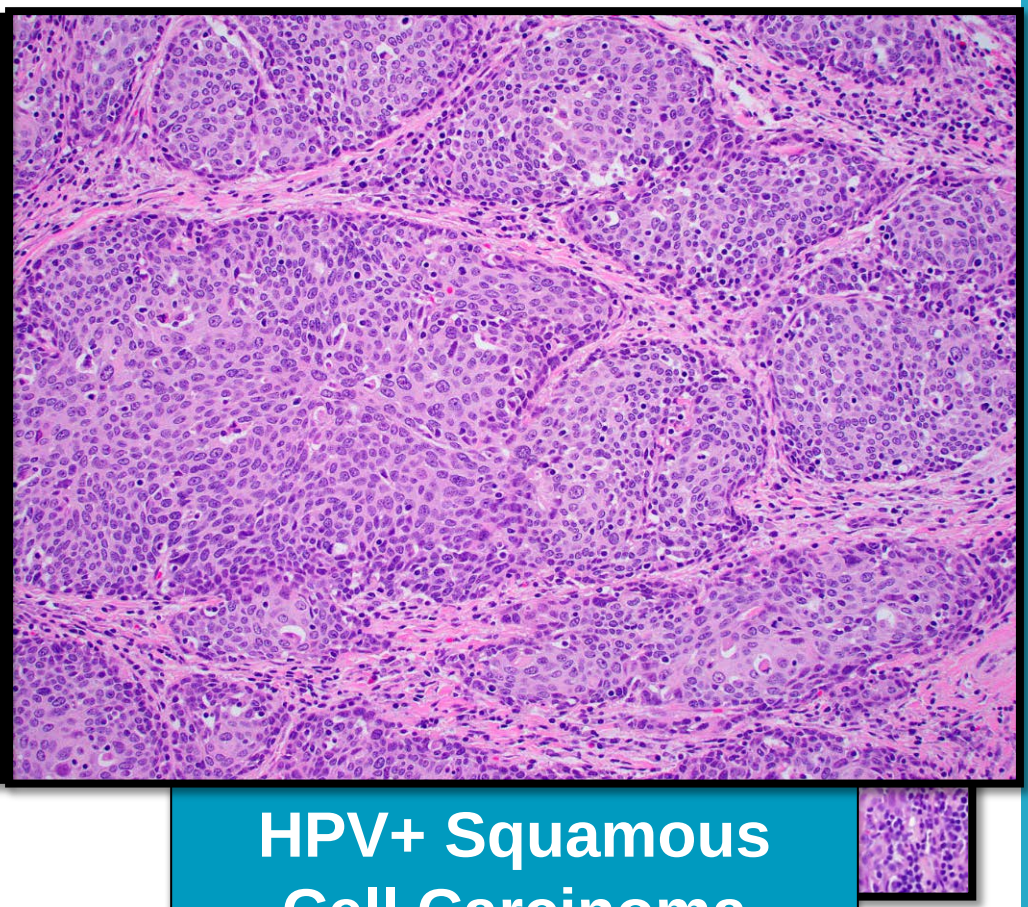
CAP guideline

13. Pathologists should not provide a tumor grade or differentiation status for HPV-positive/p16-positive OPSCC.

Diagnostic Terminology



Basaloid Squamous Cell Carcinoma

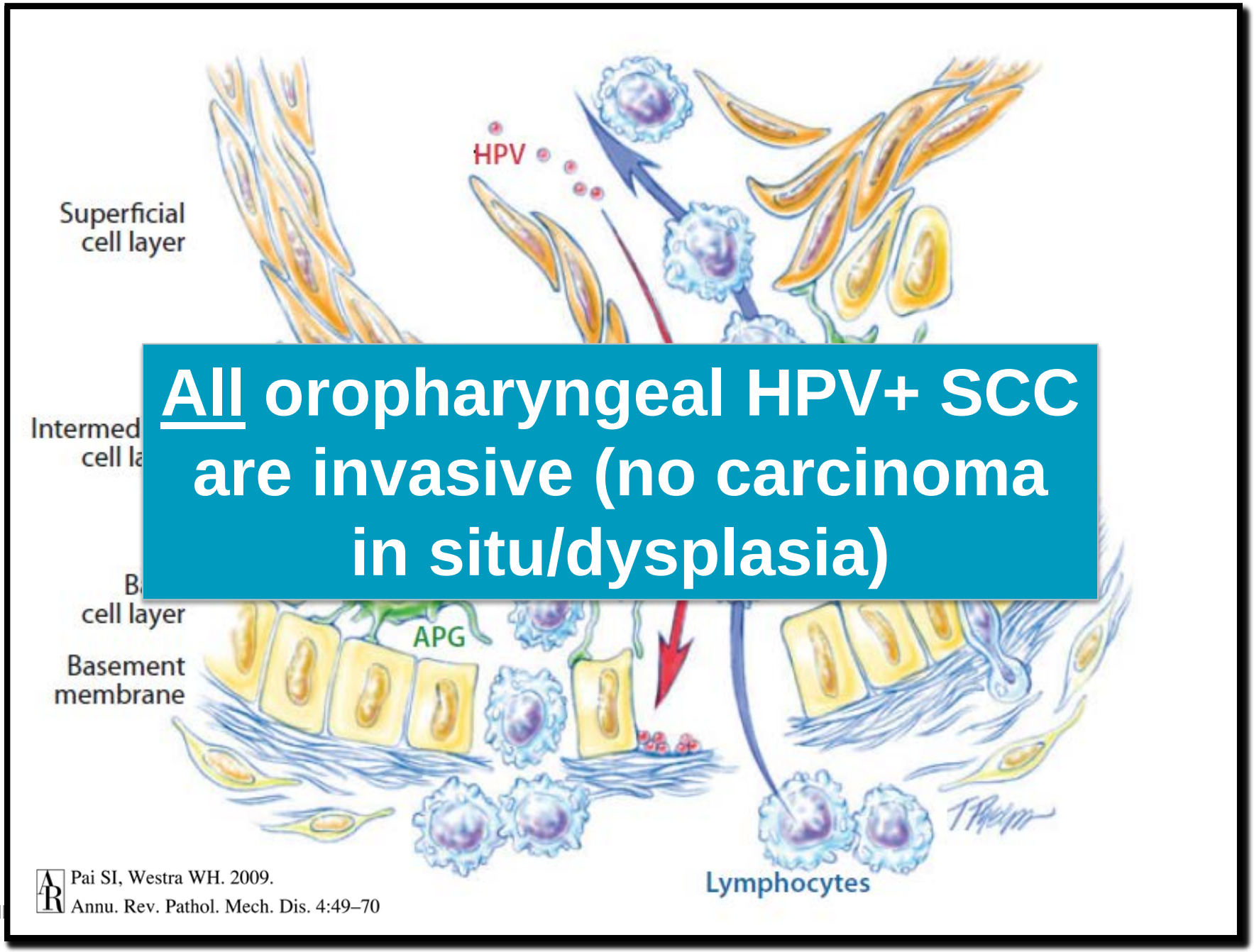


HPV+ Squamous Cell Carcinoma

CAP guideline

12. Pathologists should report primary OPSCCs that test positive for HR-HPV or its surrogate marker p16 as “HPV-positive” and/or “p16-positive.”

Invasive?



All oropharyngeal HPV+ SCC are invasive (no carcinoma in situ/dysplasia)

HPV Testing

- **Why?**
  - **Tumor classification/diagnosis**
    - **New WHO: HPV+ vs. HPV- OPSCC**
  - **Prognosis**
    - **Separate staging in new AJCC**
  - **Treatment? – not yet routinely, But…**
    - **Eligibility for clinical trials**

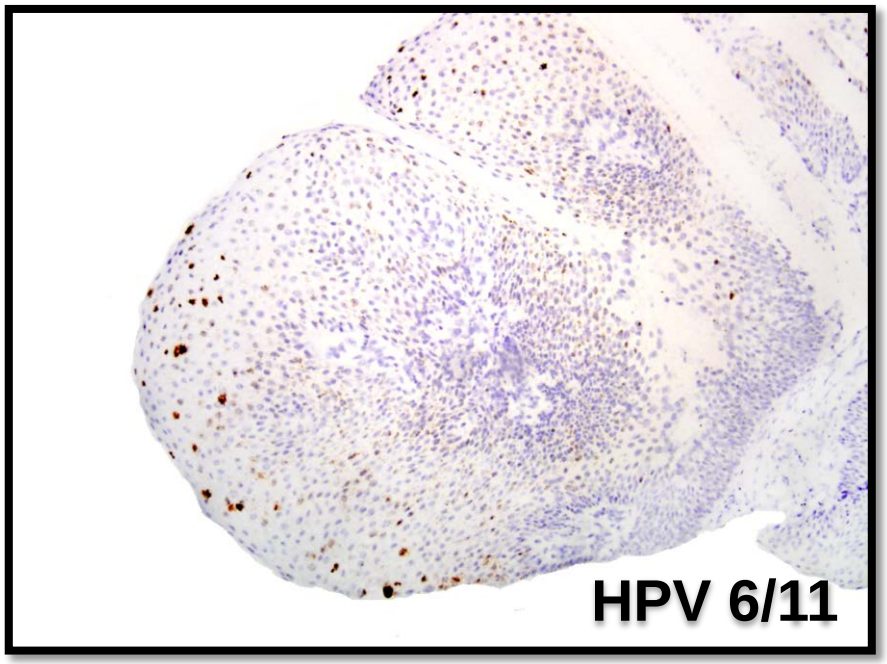
When to test for HPV

1. **Pathologists should perform HR-HPV testing on all patients with newly diagnosed oropharyngeal squamous cell carcinoma, including all histologic subtypes.**

This testing may be performed on the primary tumor or on a regional lymph node metastasis when the clinical findings are consistent with an oropharyngeal primary.

How to test for HPV?

- **High-risk types only.**
  - **16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, and 82**
- **HPV types 6 and 11 are low-risk.**
  - **Cause papillomas and warts.**
  - **Can cause morbidity (e.g., laryngeal papillomatosis) but not a significant cause of HPV+ OPSCC**



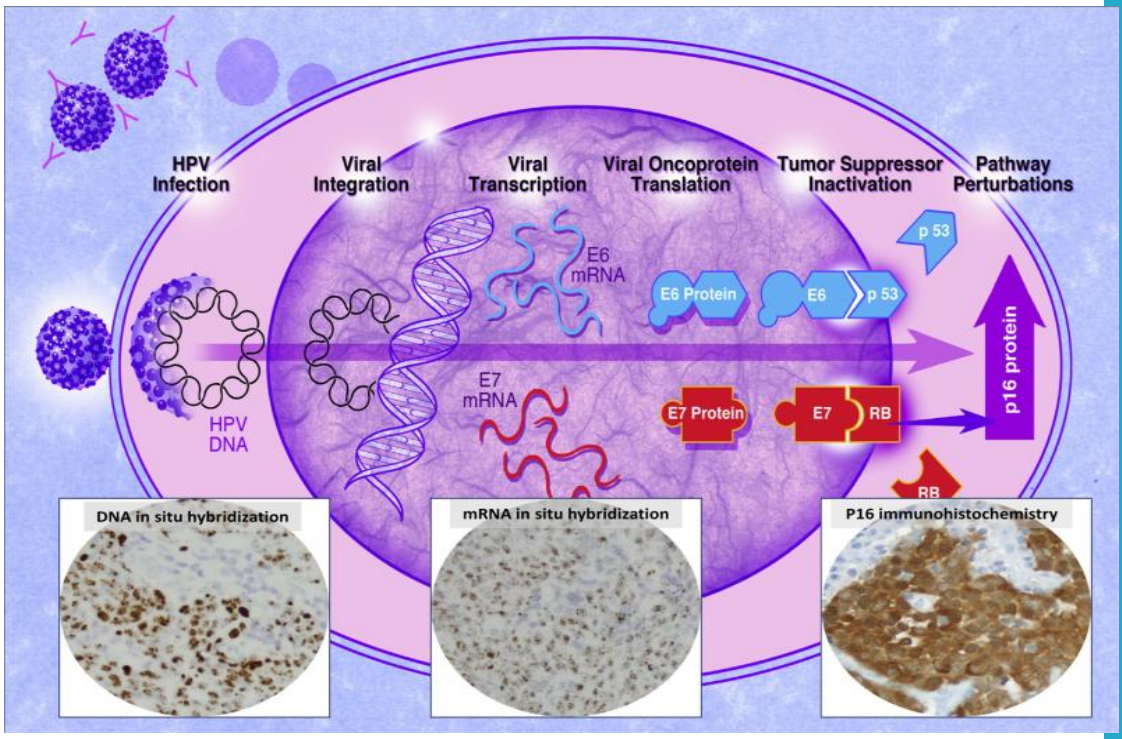
CAP guideline

9. Pathologists should not routinely perform low-risk HPV testing on patients with head and neck carcinomas.

How to test for HPV?

Methods:

- **PCR for HPV DNA**
- **PCR for HPV E6/E7 mRNA**
- **p16 immunohistochemistry**
- **DNA in situ hybridization**
- **RNA in situ hybridization**
- **Cytology-based techniques**
- **Combinations/algorithms**



PCR Detection of HR-HPV DNA

Moderate technical complexity, TAT, and variable cost

Simultaneous identification of multiple HPV types– allows for genotyping

Very high sensitivity

Cross-contamination problem (false positive)

Does not distinguish “driver” virus from “passenger” virus

RT PCR – quantitative approach to measure viral load

p16 Immunohistochemistry

Widely available, easy to perform

Highly sensitive

~80% specific in oropharynx

Diffuse (>70%), strong, nuclear and cytoplasmic

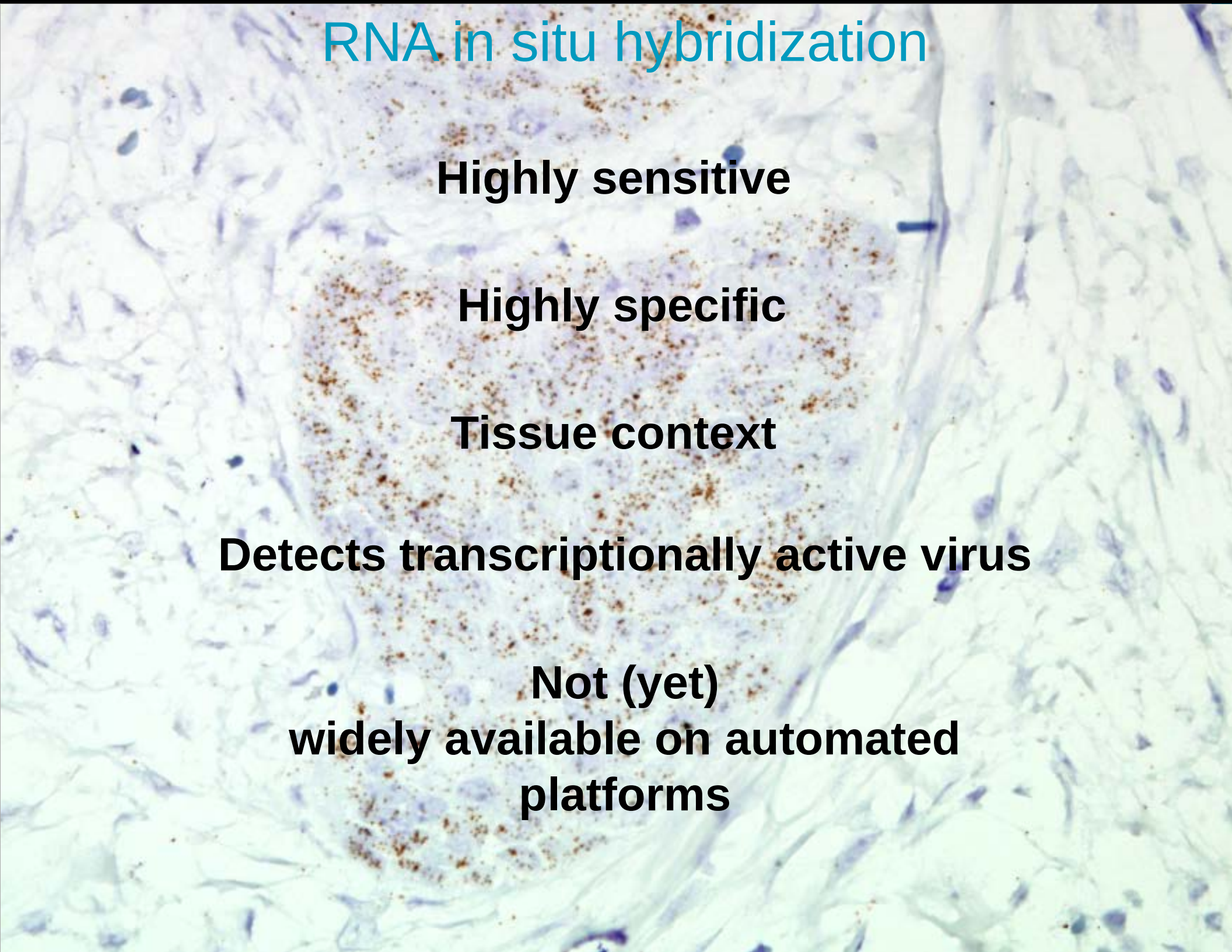
Poor surrogate outside of oropharynx

Rautava J and Syrjanen S. Head Neck Pathol. 2012;6(1s):3-15.

p16 Immunohistochemistry

- 3 to 4 Major Commercial Antibodies Used
  - Most Use E6H4 Predilute
  - But no current evidence favoring one over another

RNA in situ hybridization



Highly sensitive

Highly specific

Tissue context

Detects transcriptionally active virus

Not (yet)
widely available on automated platforms

CAP Guidelines

2. For oropharyngeal tissue specimens (i.e., non-cytology), 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.

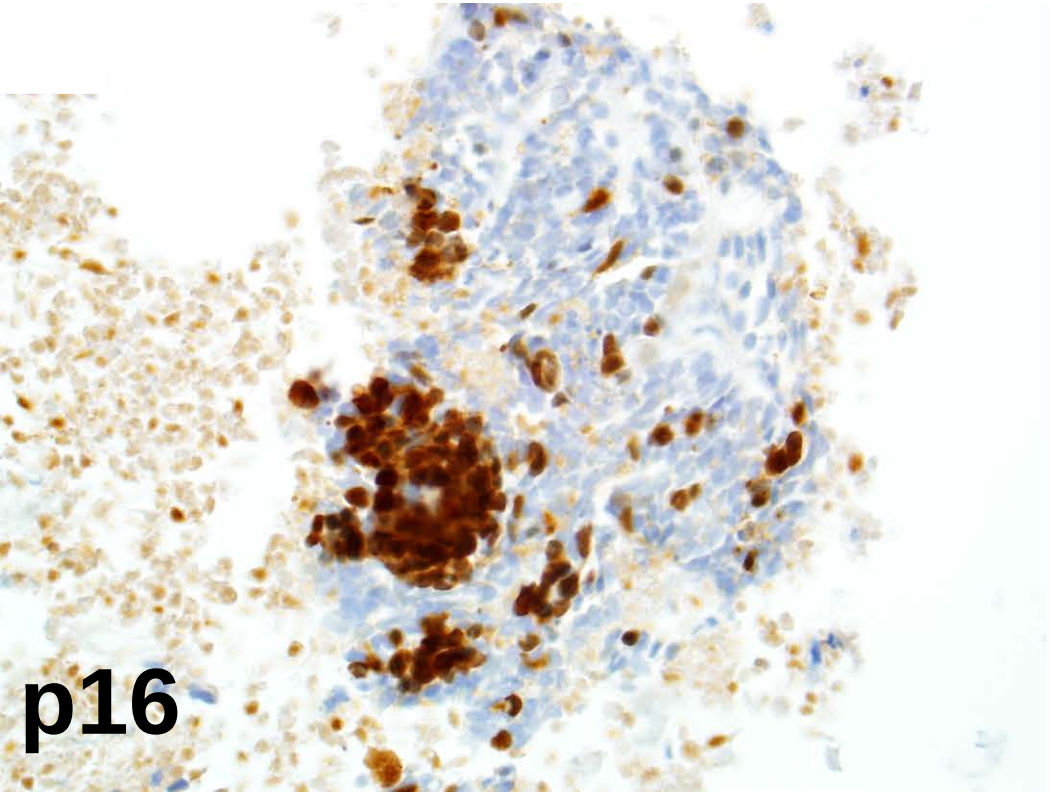
6. For tissue specimens (i.e., non-cytology) from patients with metastatic SCC of unknown primary in a cervical upper or mid jugular chain lymph node, pathologists should perform p16 IHC

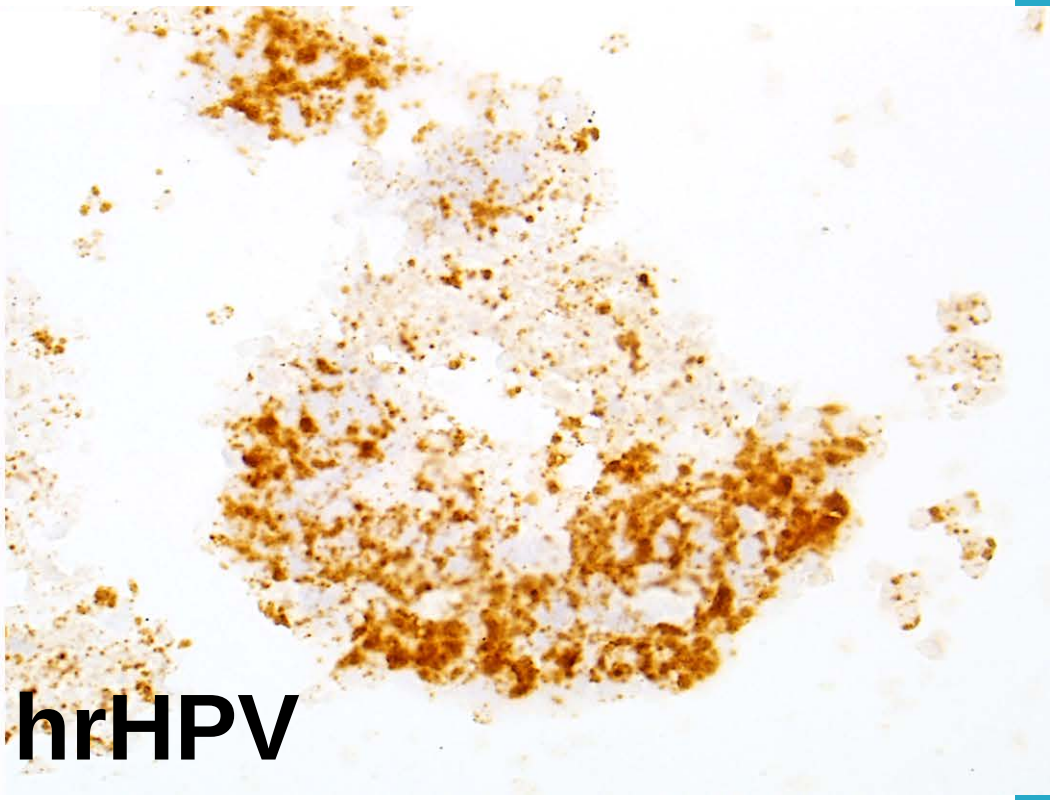
CAP Guidelines

8. 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

HPV testing on cyto material

- **Often the first material available.**
- **All of the tissue-based testing methods can be done on cell blocks.**
- **BUT… p16 is often more patchy in FNA material than it is in tissue.**
  - **Threshold not standardized.**
  - **% difficult to determine.**

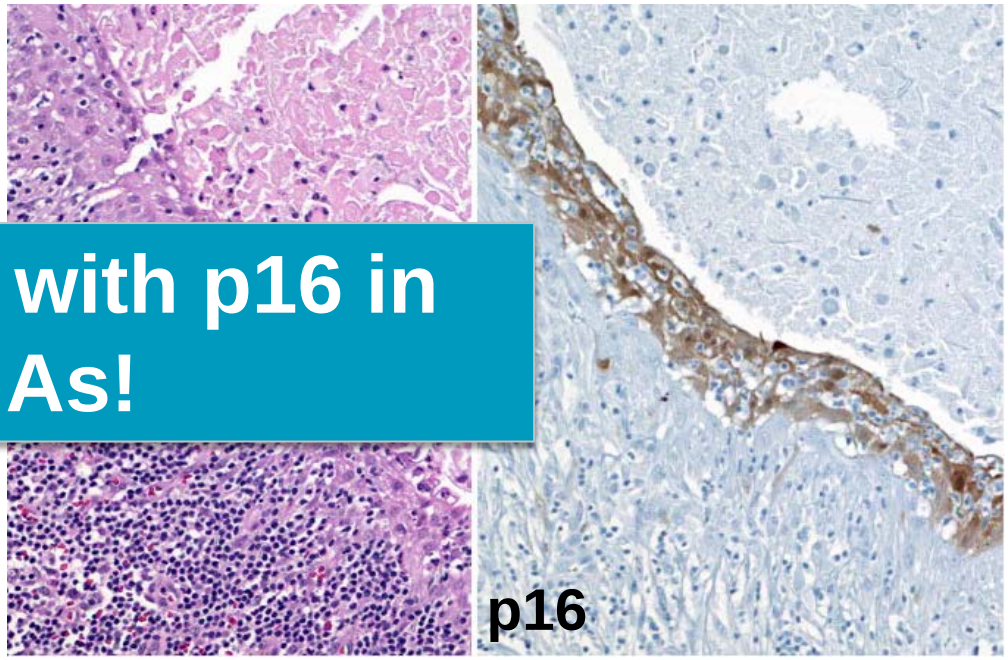




Also…

- **p16 often positive in branchial cleft cysts, lung and skin SC**
- **More speci methods often needed.**

Be careful with p16 in FNAs!



Liquid phase assays

- **Hybrid Capture II, Cervista™ HPV HR, Roche Cobas® HPV test, and APTIMA® HPV assay.**
- **Already in wide use for cervical cytology.**
- **Obviates the need for creating a cell block.**
- **Provides a quantitative result with clear-cut scoring.**
- **A few studies with promising results**
- **Widespread clinical validation still needed before these assays can be routinely used**

CAP Guidelines

7. Pathologists should perform HR-HPV testing on head and neck fine needle aspiration (FNA) SCC samples from all patients with known oropharyngeal SCC not previously tested for HR-HPV, with suspected oropharyngeal SCC, or with metastatic SCC of unknown primary.

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 repeated on tissue if it becomes available.

Variants of HPV+ Oropharyngeal Carcinoma

Lymphoepithelial-like

Papillary

Adenosquamous

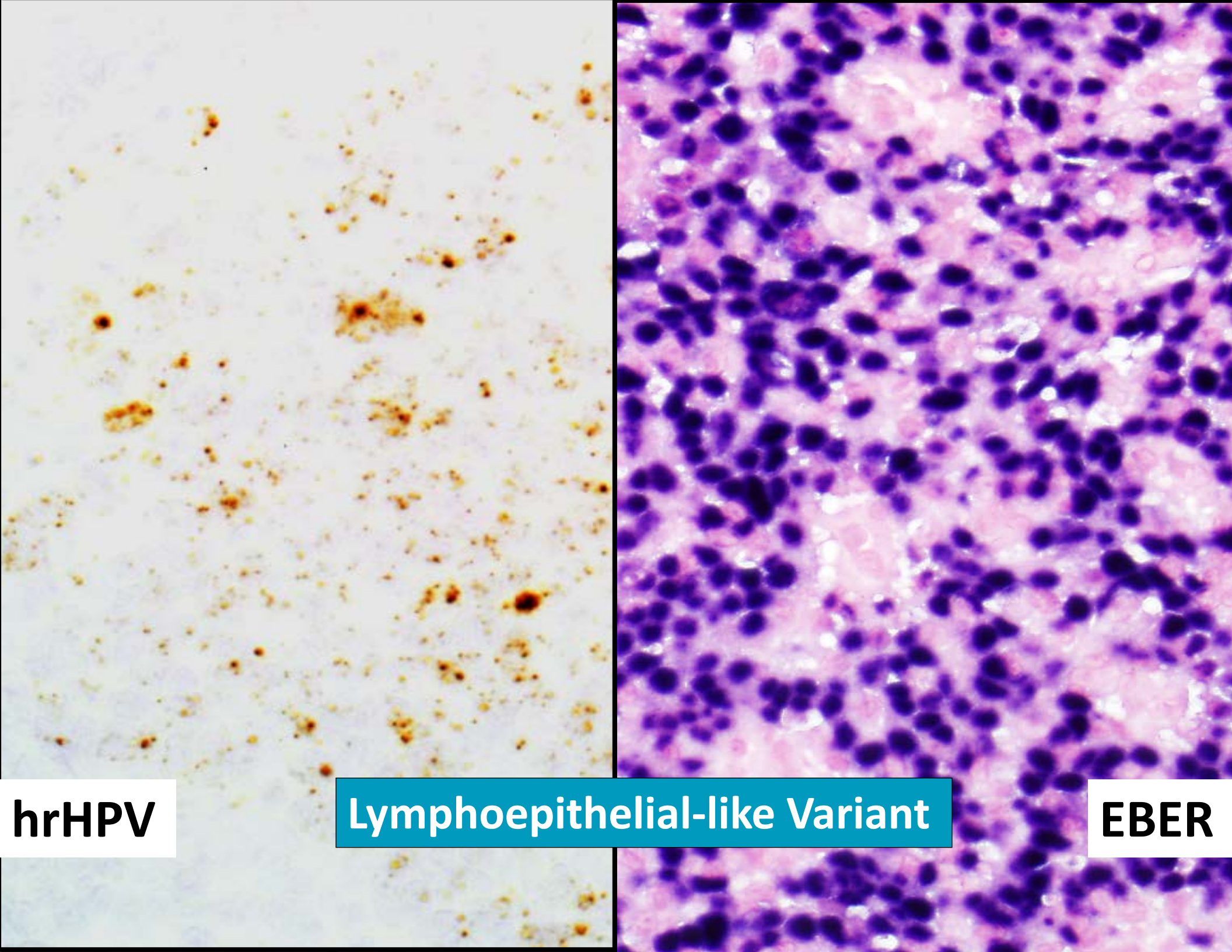
Adenocarcinoma, NOS

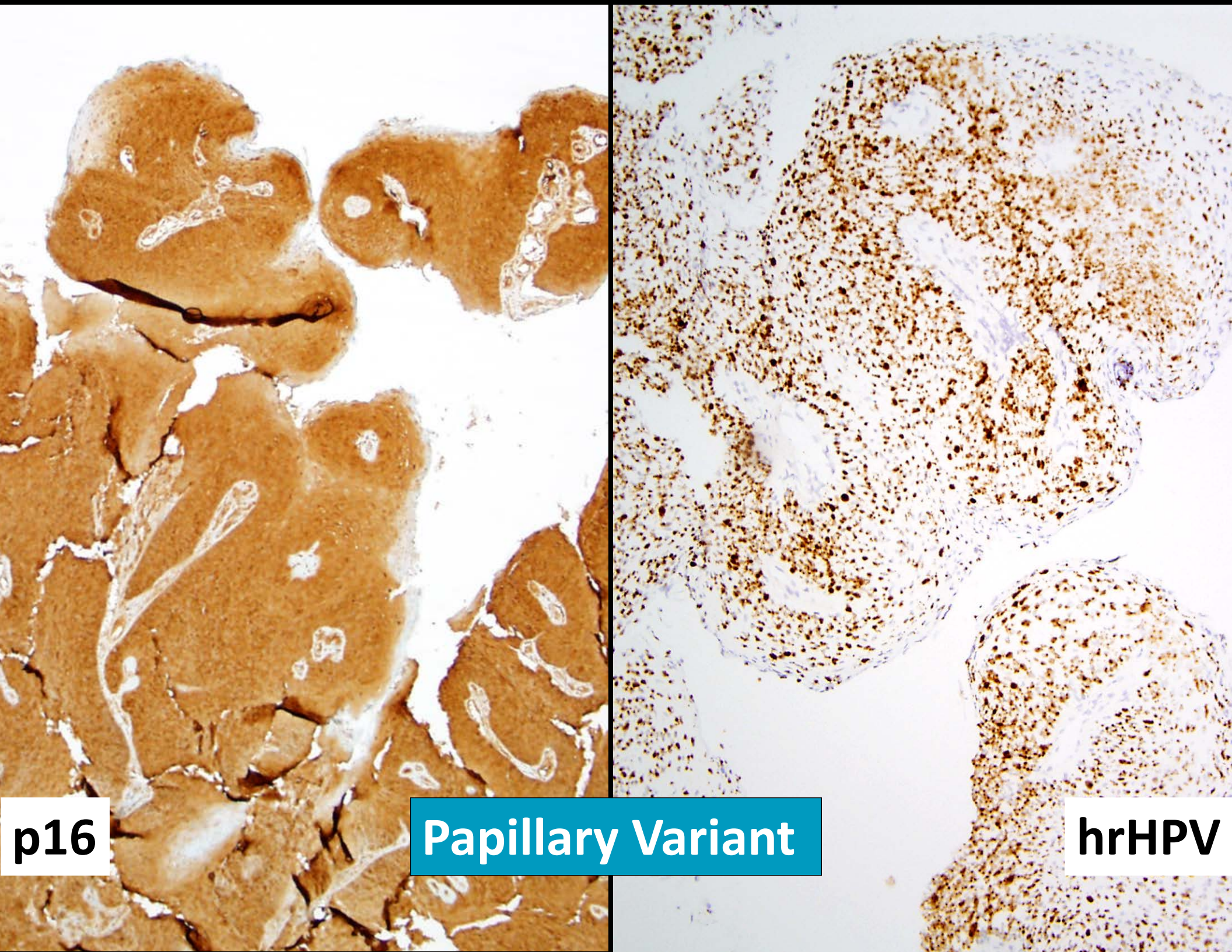
Sarcomatoid

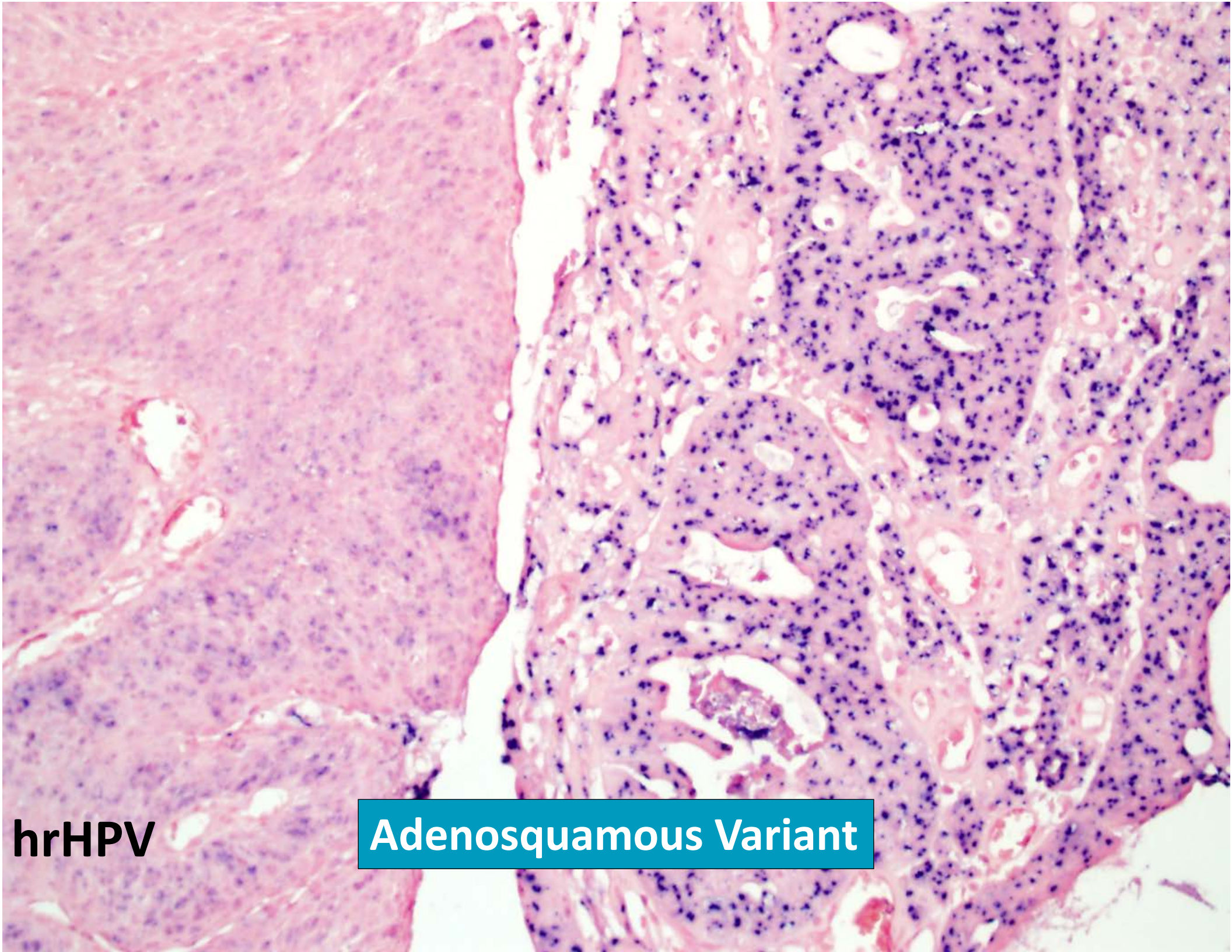
Neuroendocrine carcinoma

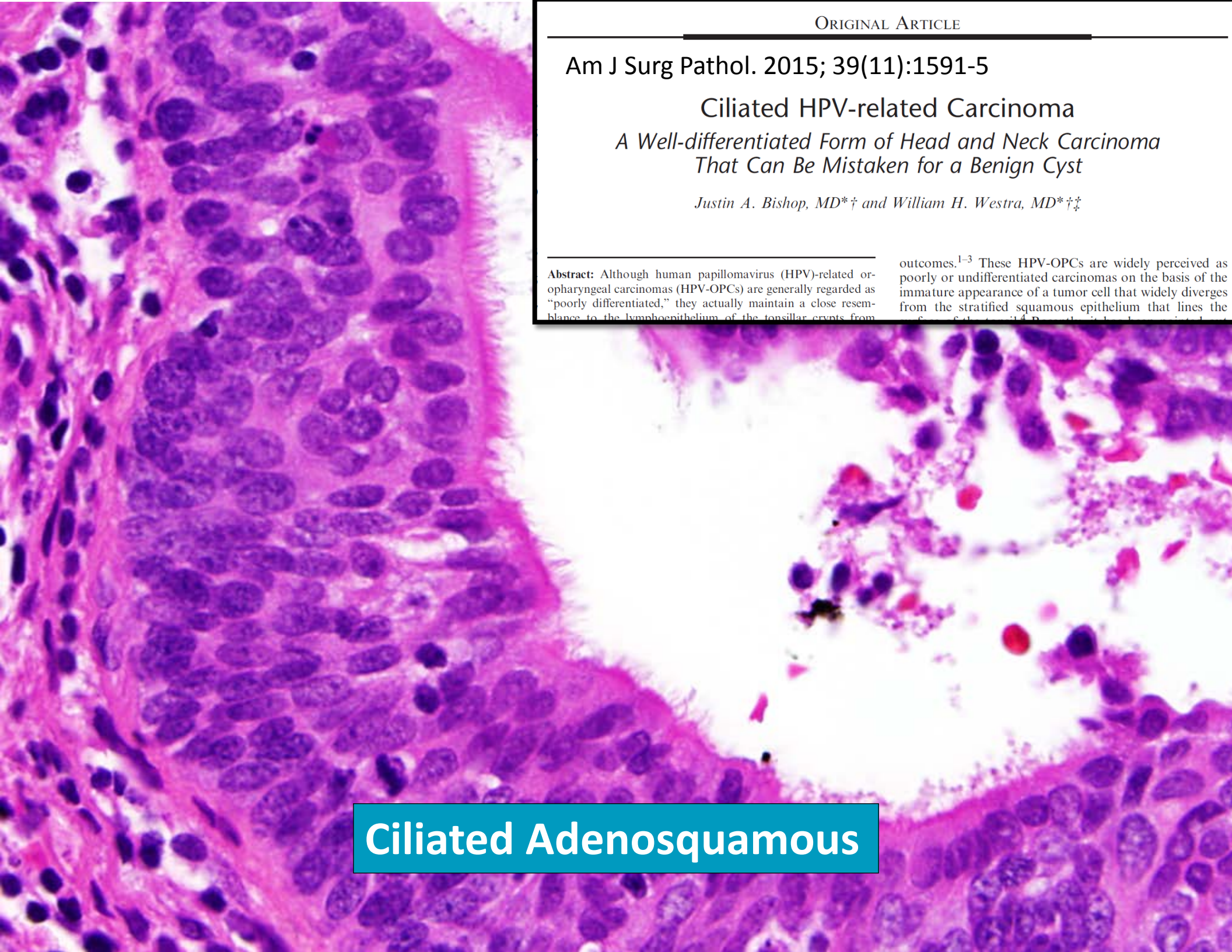
Small cell

Large cell neuroendocrine


hrHPV
Lymphoepithelial-like Variant
EBER


p16
Papillary Variant
hrHPV


hrHPV
Adenosquamous Variant



ORIGINAL ARTICLE

Am J Surg Pathol. 2015; 39(11):1591-5

Ciliated HPV-related Carcinoma

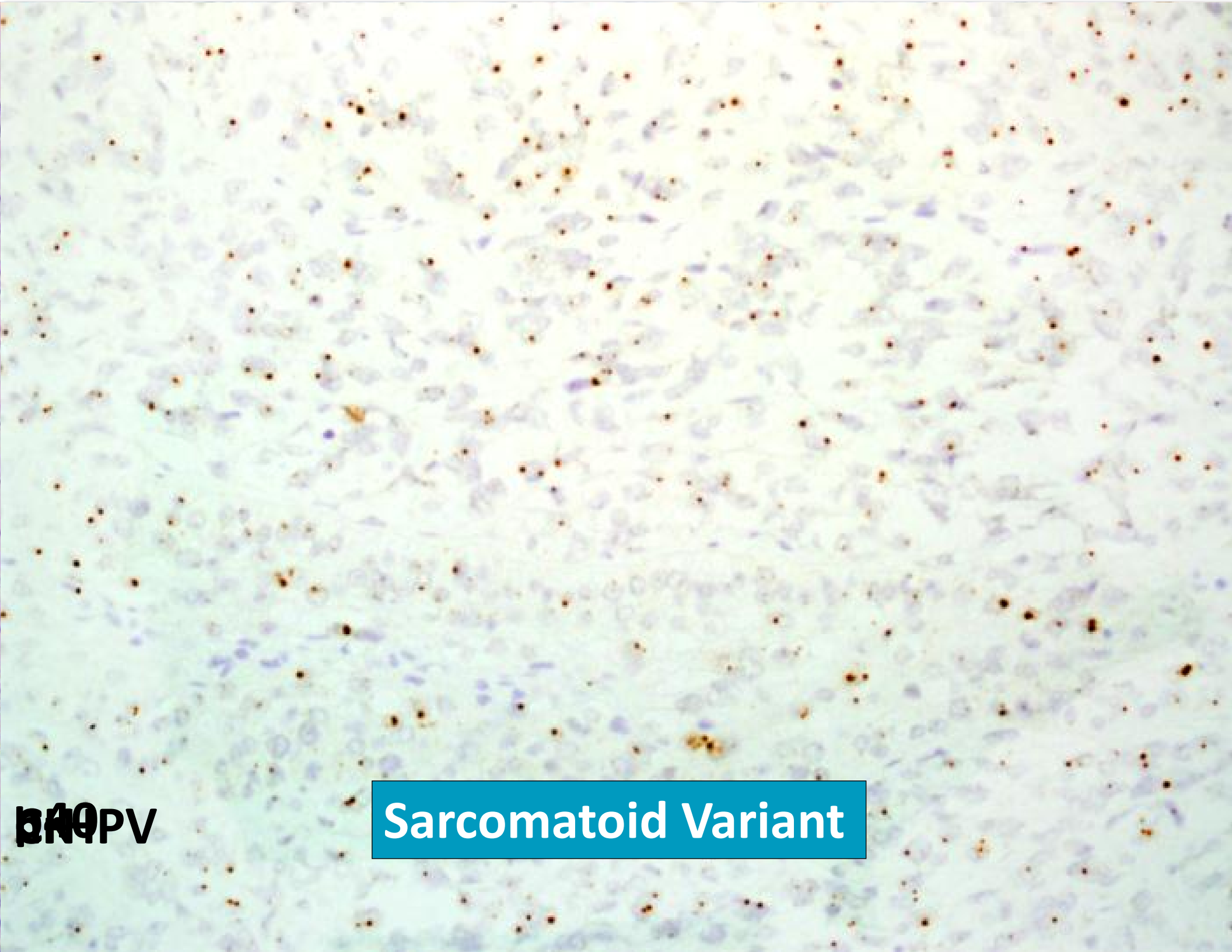
A Well-differentiated Form of Head and Neck Carcinoma That Can Be Mistaken for a Benign Cyst

Justin A. Bishop, MD† and William H. Westra, MD*†‡*

Abstract: Although human papillomavirus (HPV)-related oropharyngeal carcinomas (HPV-OPCs) are generally regarded as "poorly differentiated," they actually maintain a close resemblance to the lymphoepithelium of the tonsillar crypts from

outcomes.[1–3] These HPV-OPCs are widely perceived as poorly or undifferentiated carcinomas on the basis of the immature appearance of a tumor cell that widely diverges from the stratified squamous epithelium that lines the

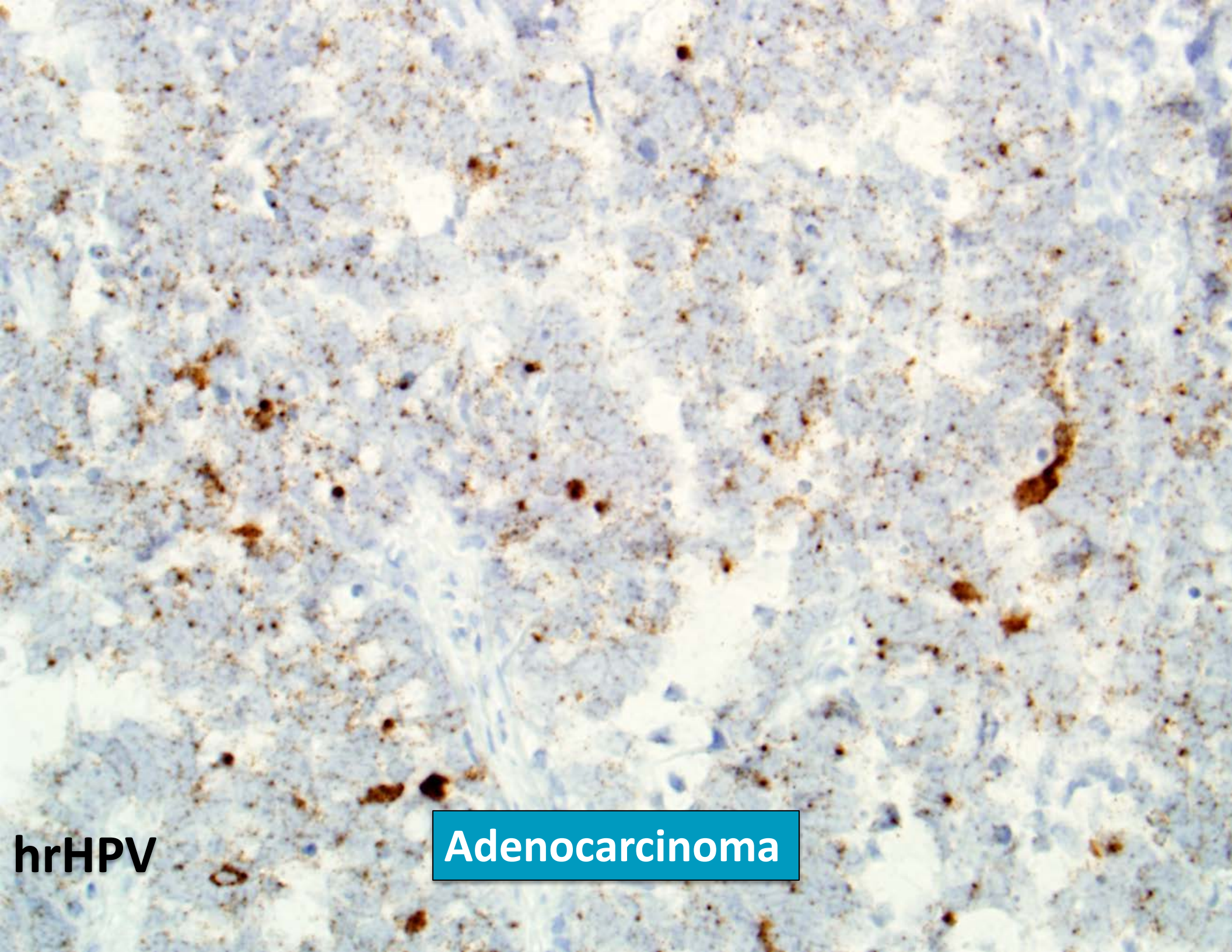
Ciliated Adenosquamous

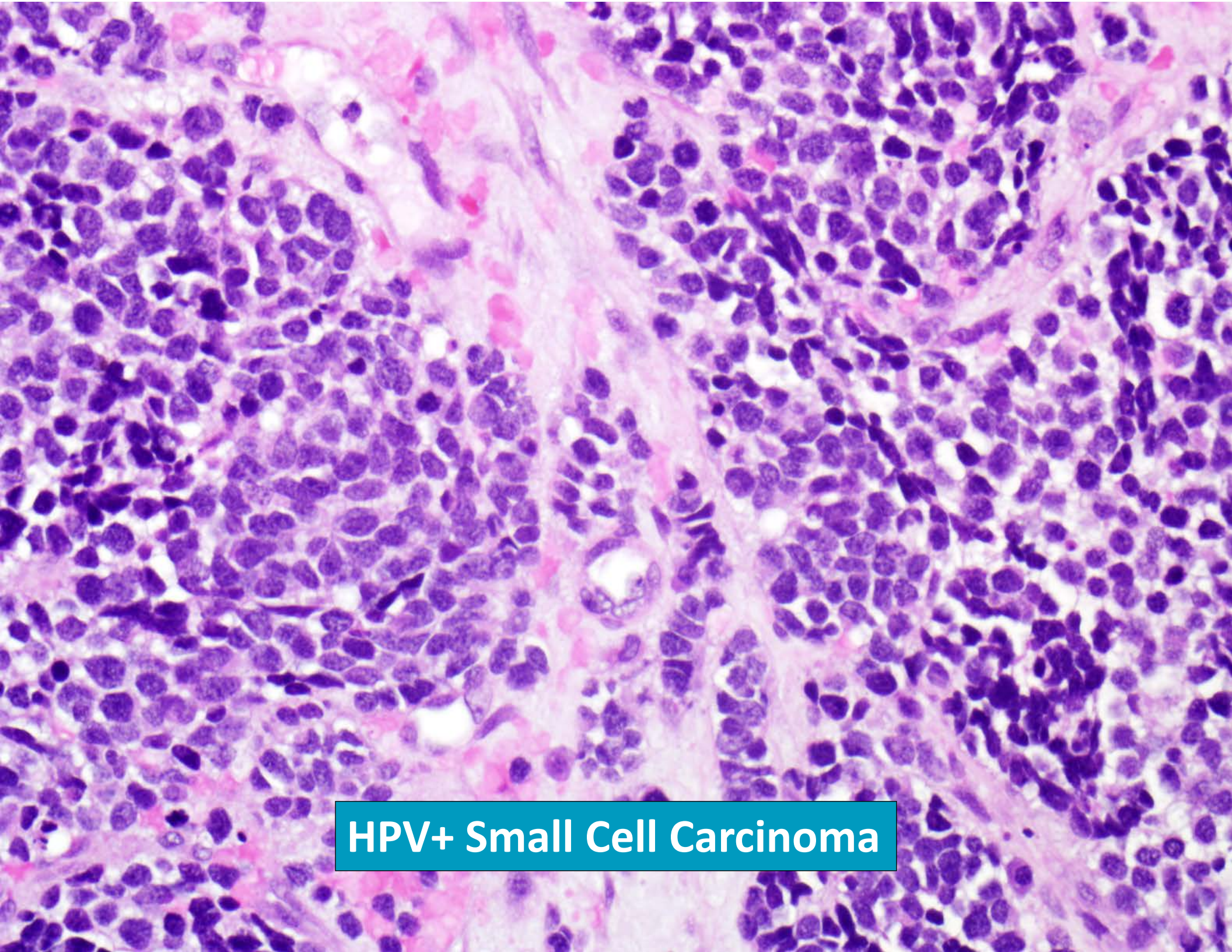

p40
HPV
Sarcomatoid Variant

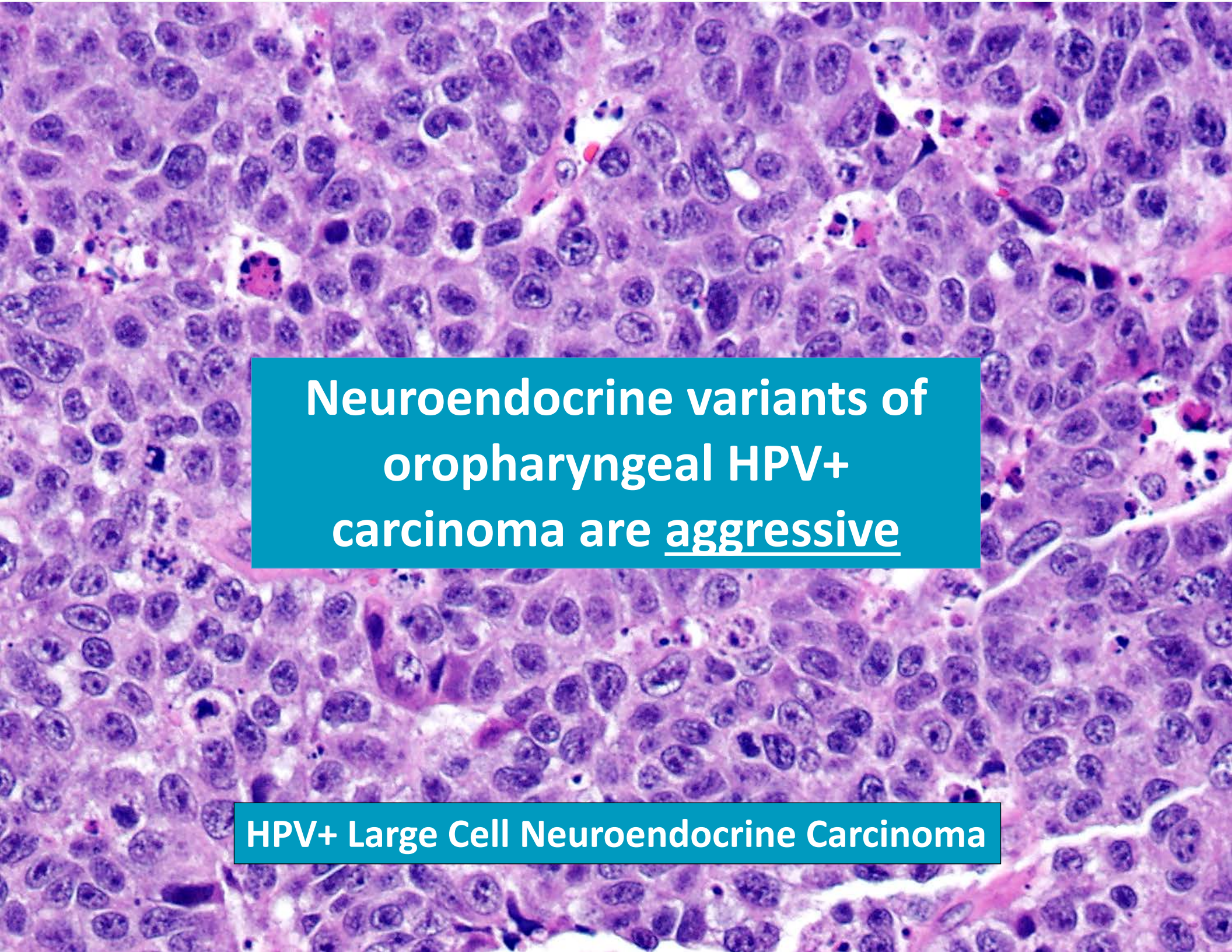
When to test for HPV

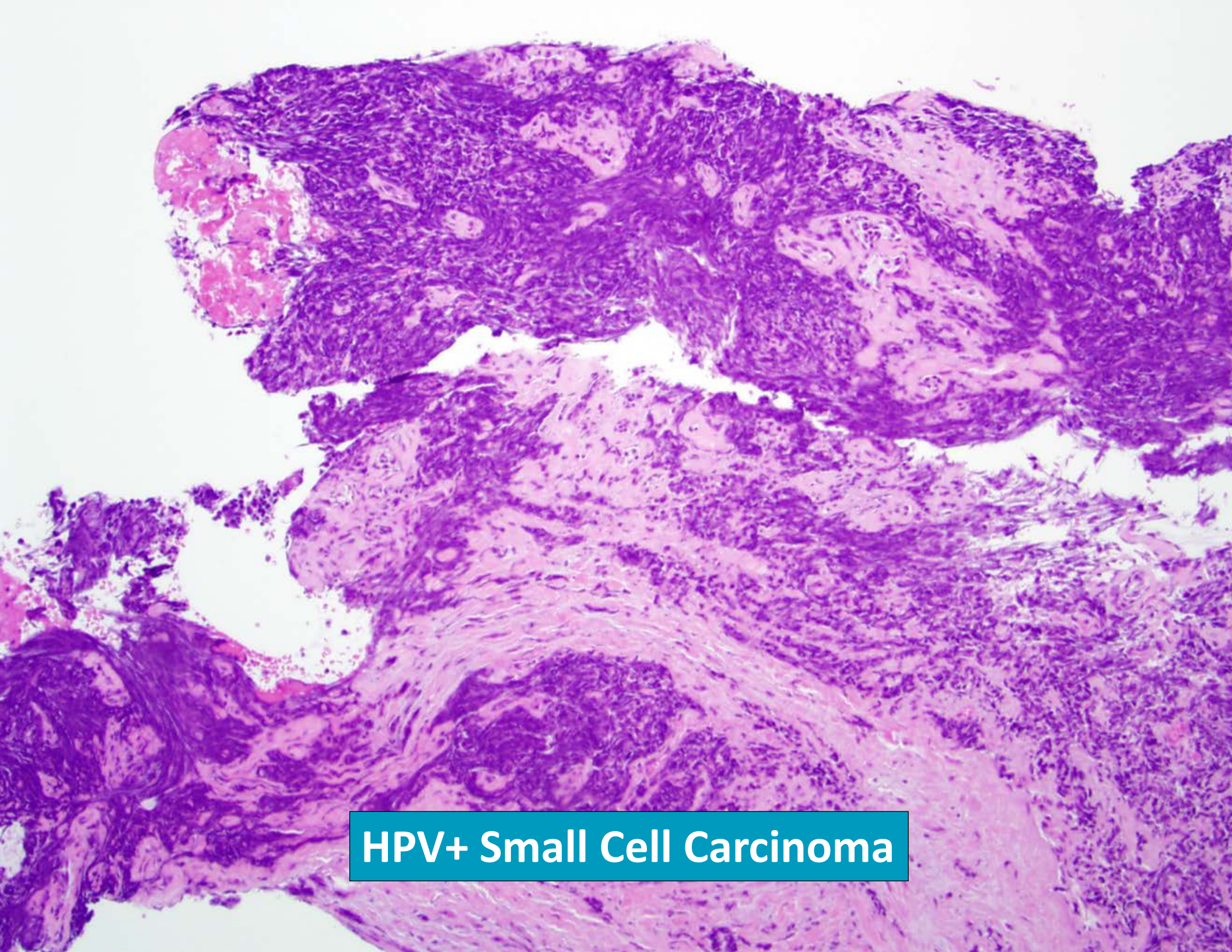
1. Pathologists should perform HR-HPV testing on all patients with newly diagnosed oropharyngeal squamous cell carcinoma, *including all histologic subtypes.*

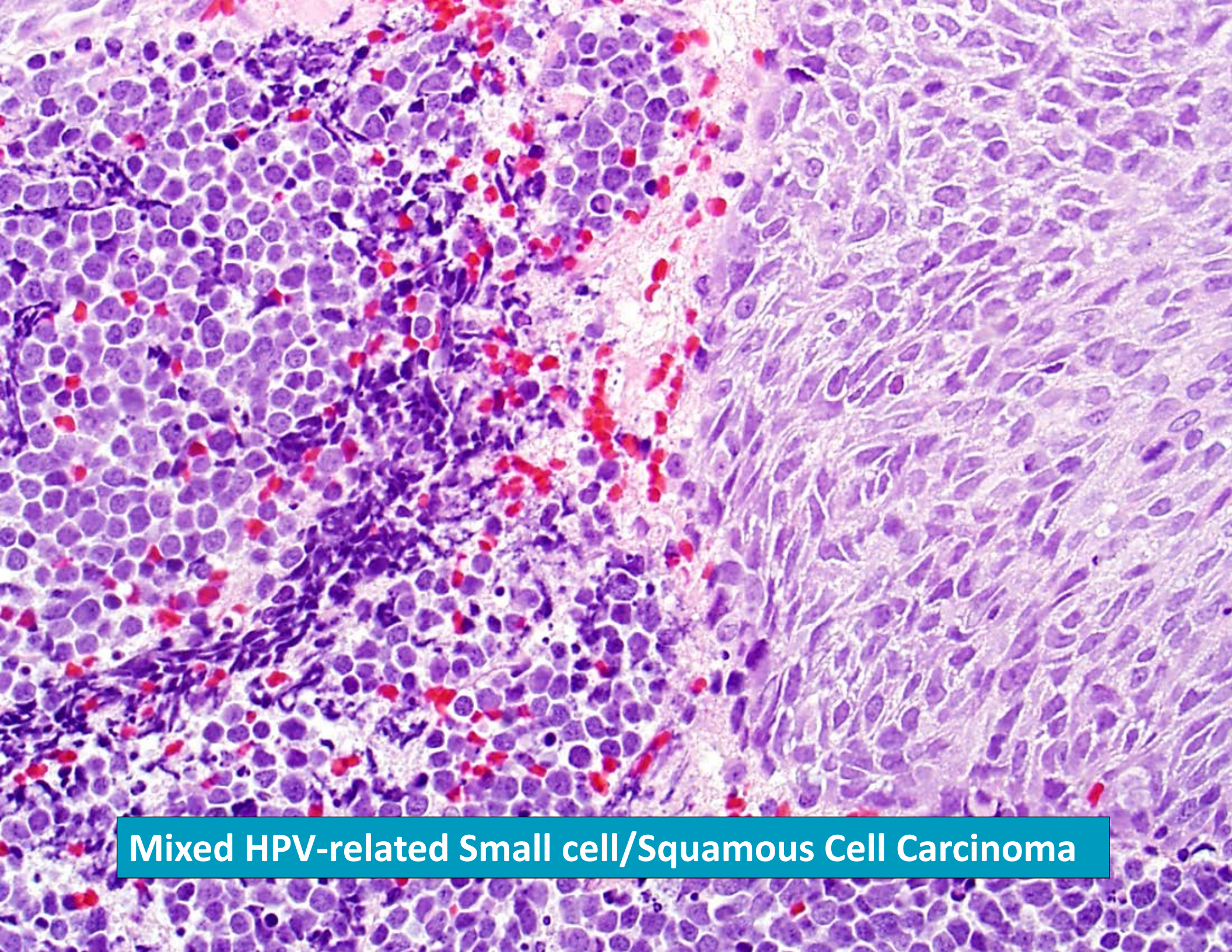
This testing may be performed on the primary tumor or on a regional lymph node metastasis when the clinical findings are consistent with an oropharyngeal primary.


hrHPV
Adenocarcinoma

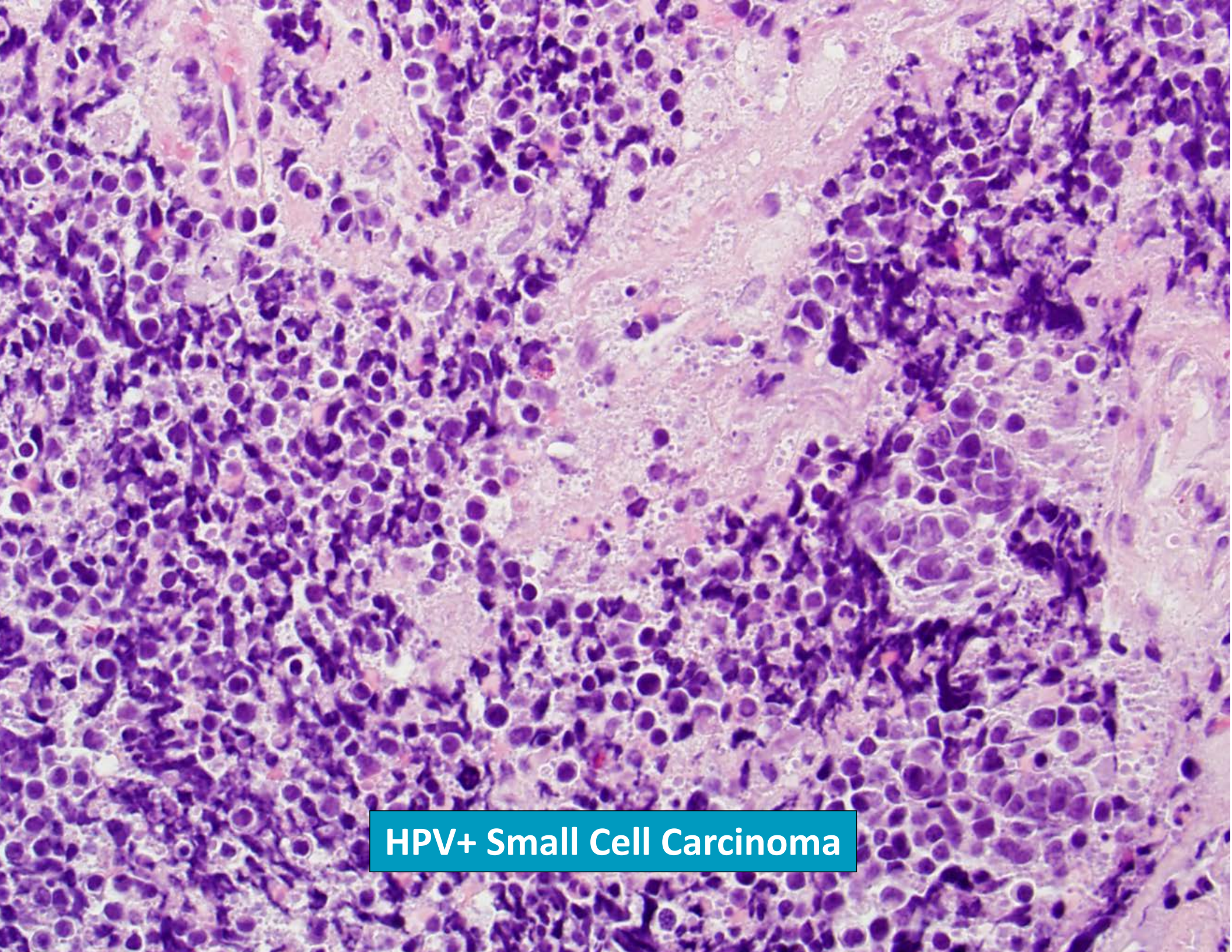

HPV+ Small Cell Carcinoma

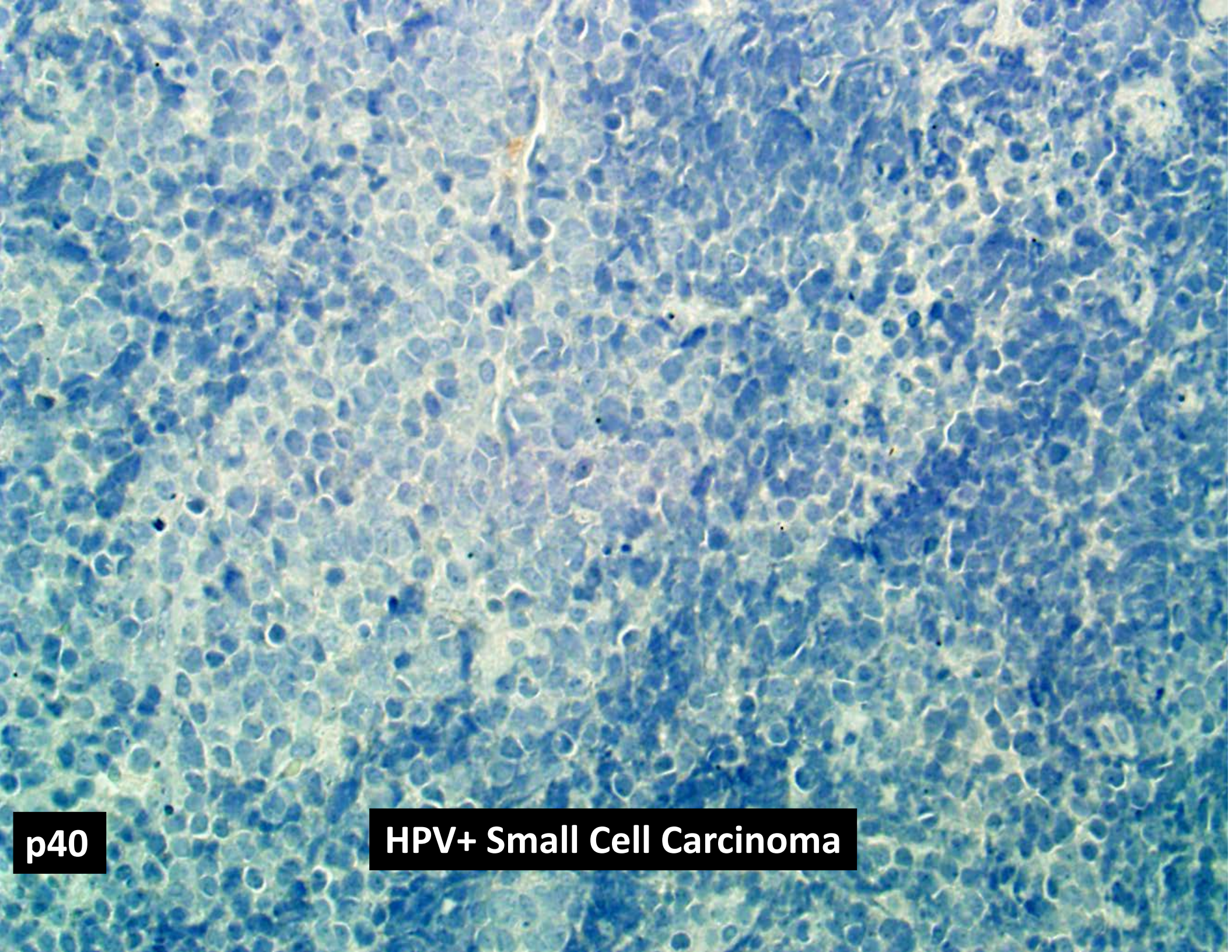

Neuroendocrine variants of oropharyngeal HPV+ carcinoma are aggressive
HPV+ Large Cell Neuroendocrine Carcinoma

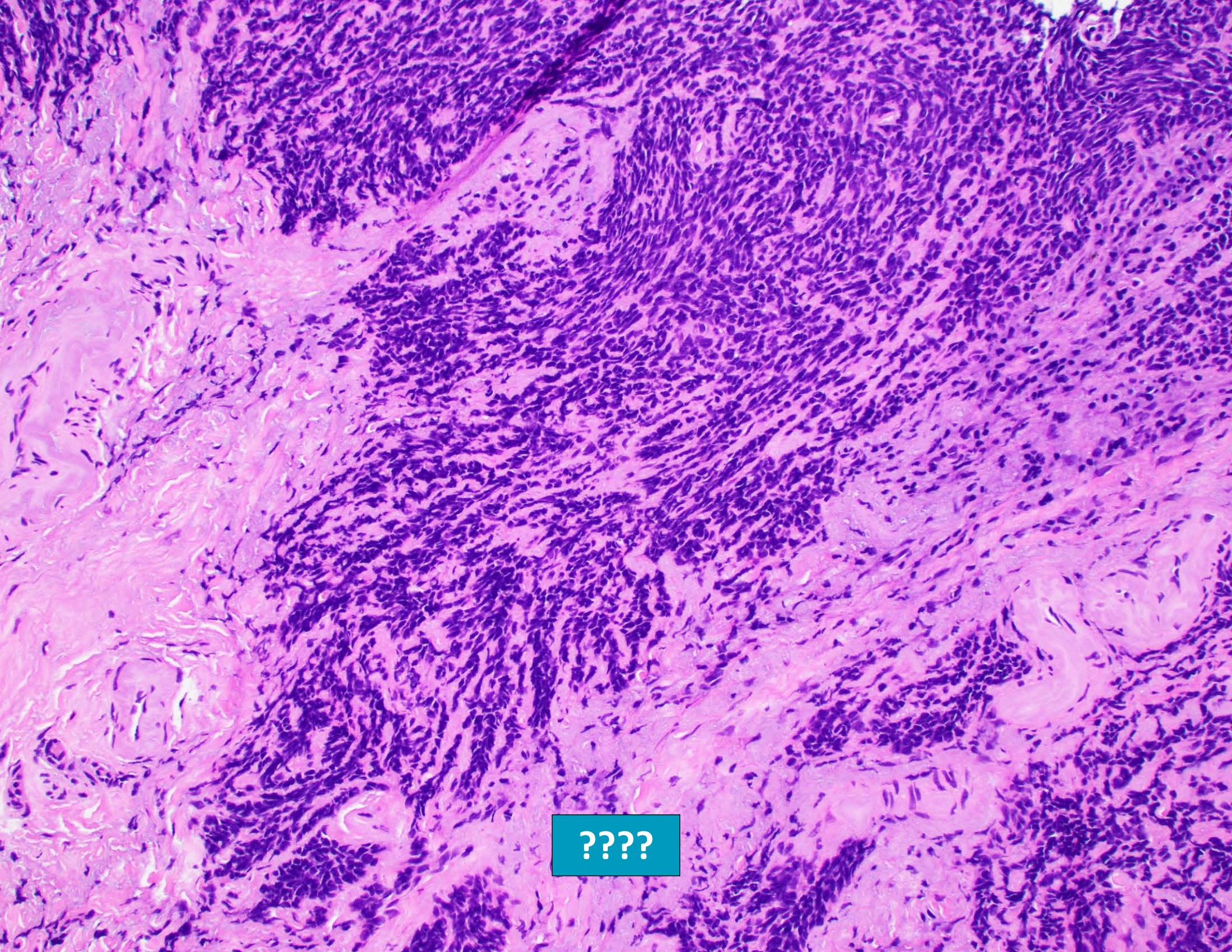

HPV+ Small Cell Carcinoma

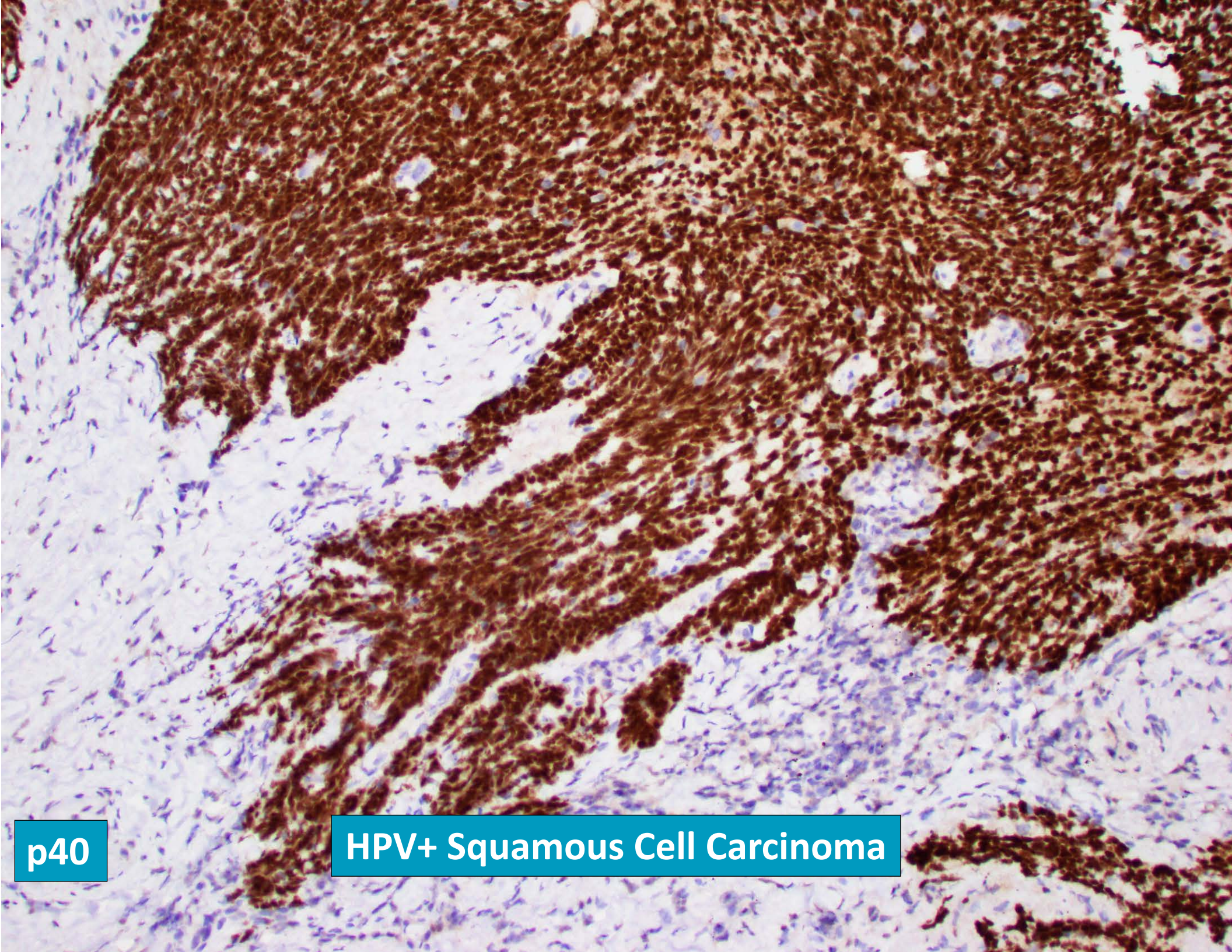

Mixed HPV-related Small cell/Squamous Cell Carcinoma

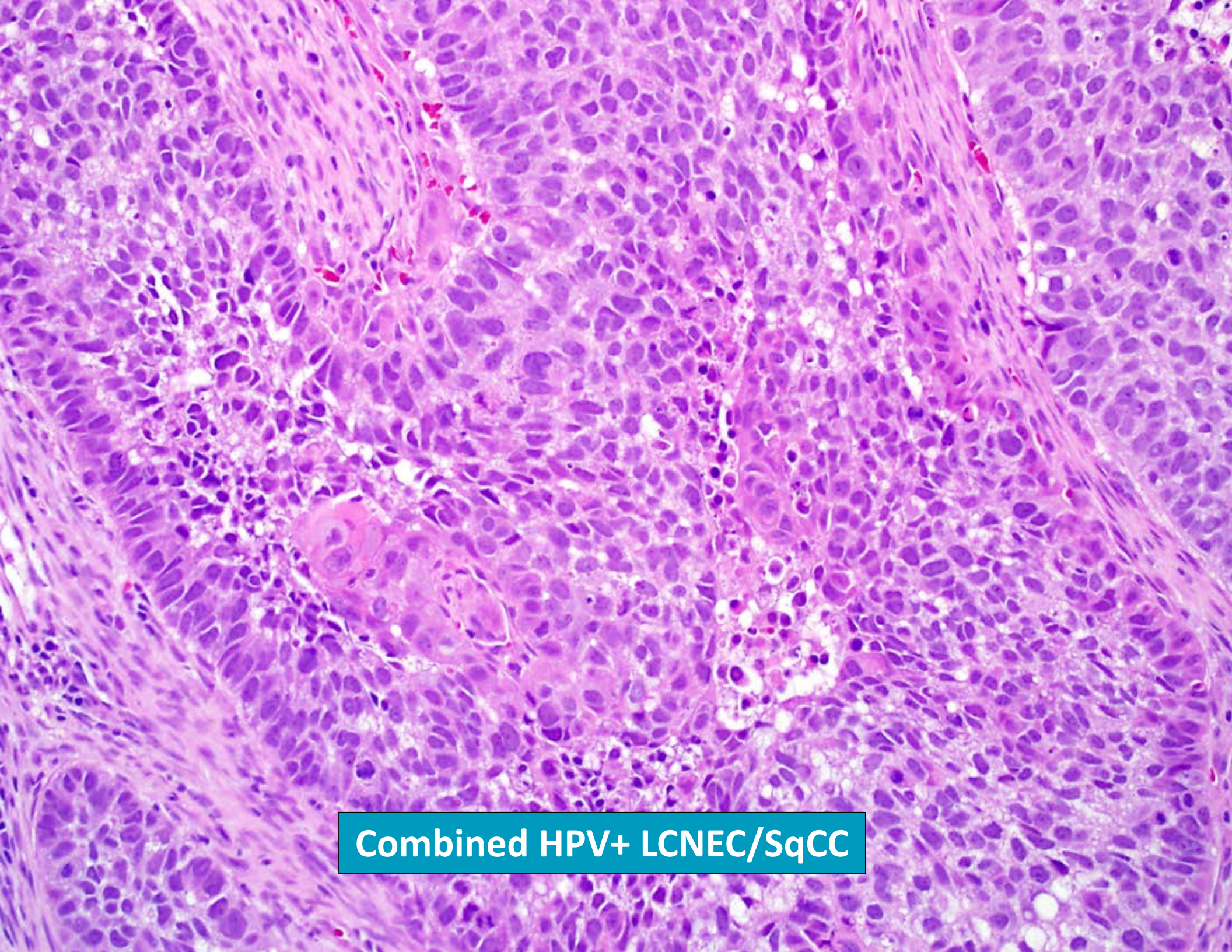
If you have any suspicion for a neuroendocrine carcinoma component, do a p40 (or p63)

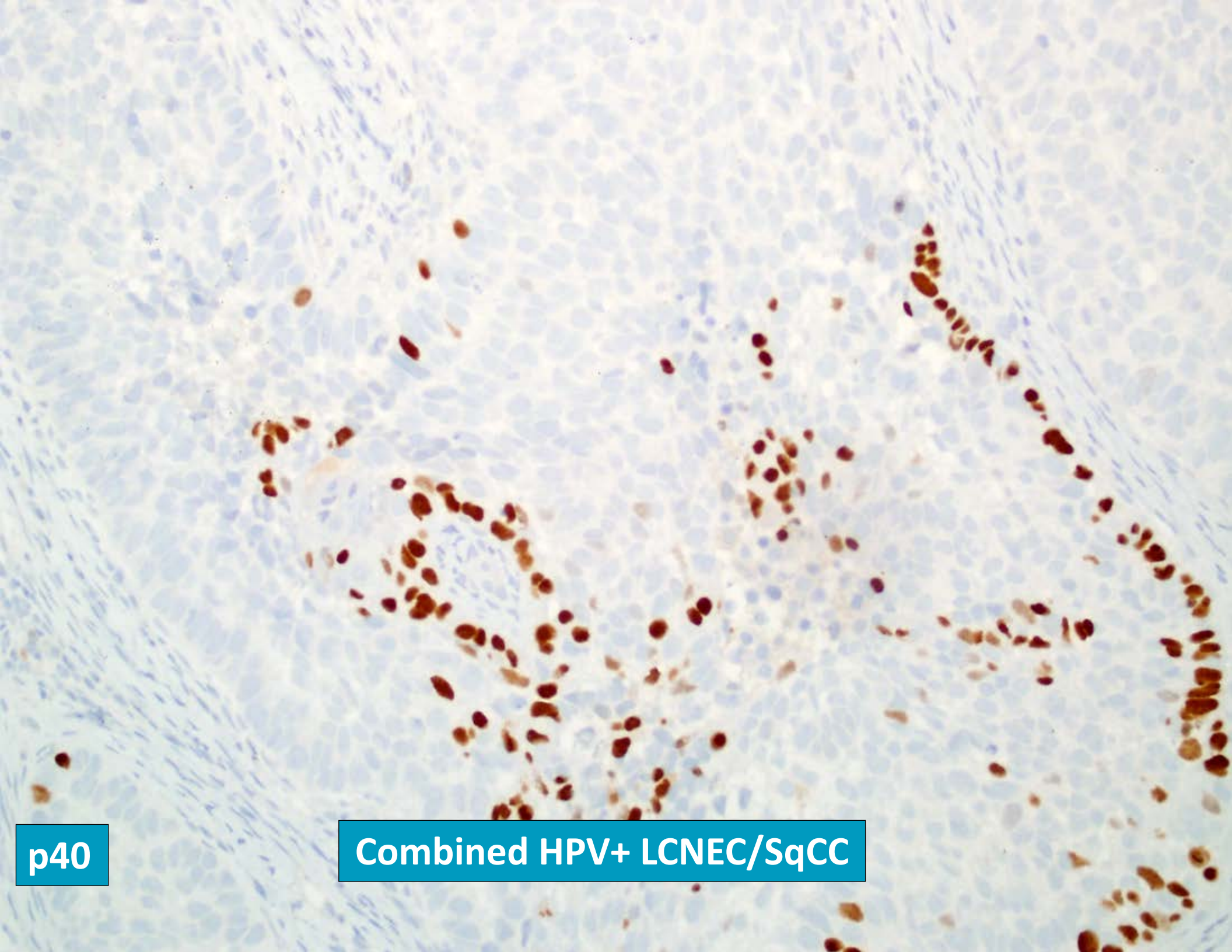

HPV+ Small Cell Carcinoma

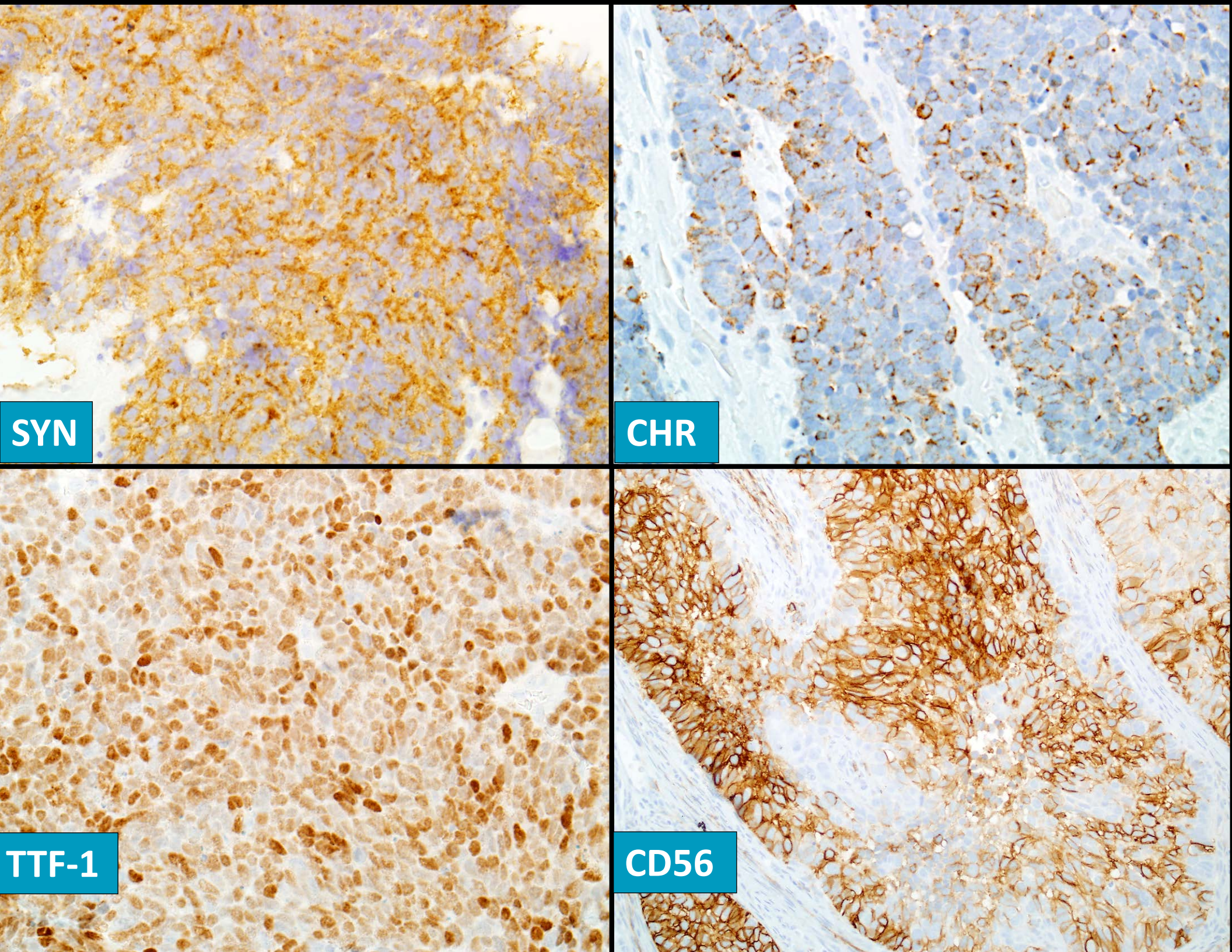

p40
HPV+ Small Cell Carcinoma




p40
HPV+ Squamous Cell Carcinoma


Combined HPV+ LCNEC/SqCC


p40
Combined HPV+ LCNEC/SqCC


SYN
CHR
TTF-1
CD56

Salivary-Type Adenocarcinomas

- **Virtually all can involve the oropharynx.**
- **Evidence almost universally says that they are HPV-unrelated.**
  - **One outlier study (Isayeva, et al, 2013) on mucoepidermoid carcinoma that has not be replicated.**

Non-Squamous Carcinomas of Oropharynx

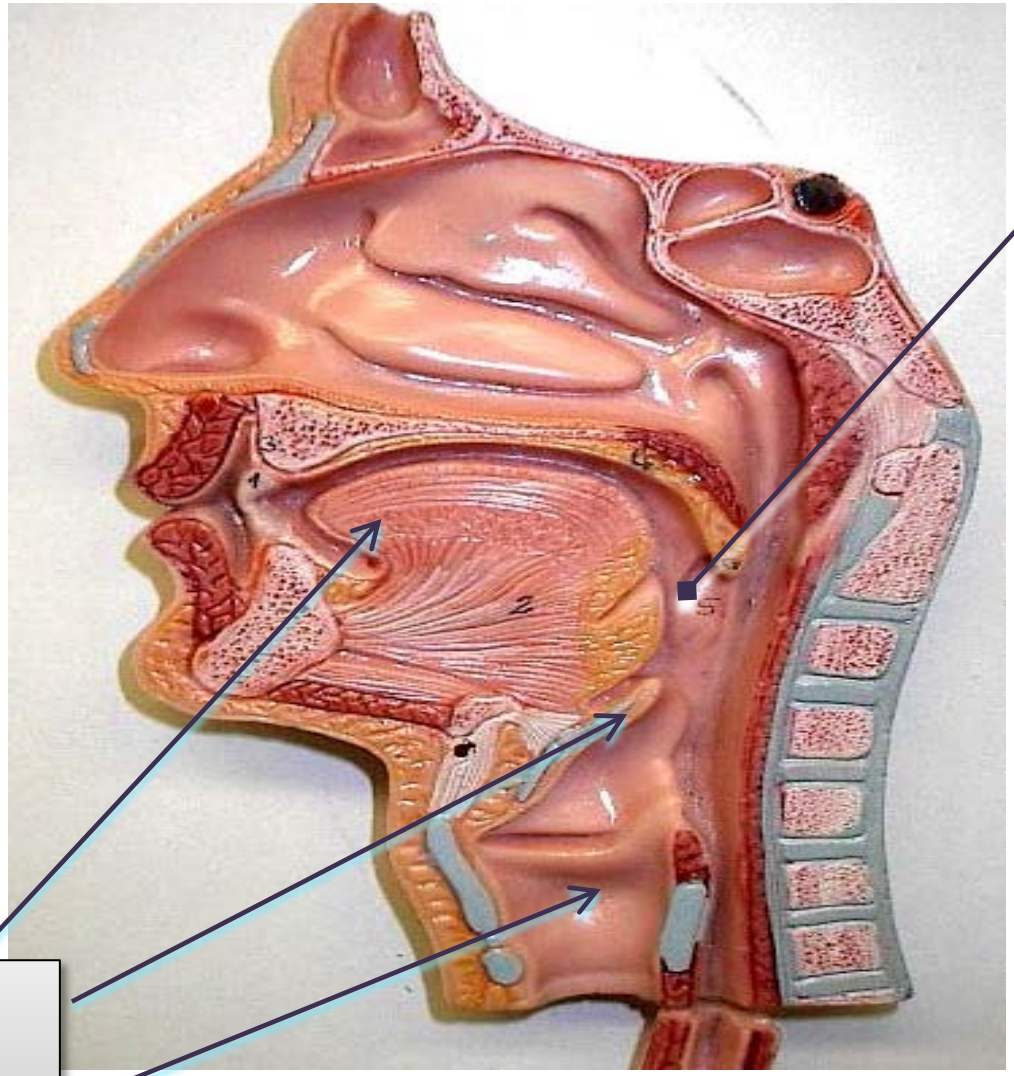
- **Salivary-type → HPV unrelated**
- **HPV+ adenocarcinoma → unknown significance**
- **HPV+ small cell and large cell neuroendocrine carcinoma → aggressive *regardless* of HPV status**

CAP Guideline

3. Pathologists should *not* routinely perform HR-HPV testing on patients with *non-squamous* carcinomas of the oropharynx.

HPV-related carcinomas outside of the oropharynx

Anatomic distribution of HPV-HNSCC



Oropharynx
80%

Larynx/
Hypoharynx/
Oral Cavity
???

Larynx/hypopharynx

Author	Year	Country	Method, primers, amplicon detection	Number of cancers HPV+	Total cancers studied	Cancers HPV+ (%)
Almadori	2001	Italy	PCR, MY09/MY11, enzyme immune assay typing	15	42	35.7
Anderson	2007	Scotland	PCR, GP5/GP6, real time quantitative PCR	2	64	3.1
Badaracco	2007	Italy	PCR, MY09/MY11, GP5/GP6	4	30	13.3
Baez	2004	Puerto Rico	PCR, HPV16E6/E7 ORF	24	52	46.2
Baumann	2009	USA	PCR, GP5/GP6, enzyme immune assay typing	6	38	15.8
Boscolo-Rizzo	2009	Italy	PCR, HPV16 specific primers	1	38	2.6
Deng	2011	Japan	PCR, MY09/MY11, GP5/GP6, E1 consensus primers	2	16	74.6
Duray	2011	Belgium	PCR, GP5/GP6, type specific primers and real time quantitative PCR	44	59	
El-Mofty	2003	USA	PCR, SPF10, INNO-LiPA line probe	2	7	
Fakhry	2008	USA	PCR, MY09/MY11, Roche Molecular systems probe array	0	34	0.0
Fischer	2003	Germany	PCR, L1 consensus primers	13	34	
Furniss	2007	USA	PCR, SPF1A, SPF2B, HPV16E6 specific primers	14	45	31.1
Gillison	2000	USA	PCR, MY09/MY11, HPV16/18E7 specific primers	16	86	18.6
Gudleviciene	2009	Lithuania	PCR, HPV16/18 specific primers, gel	6	18	33.3
Guvenc	2008	Turkey	PCR, nested MY09/MY11, GP5/GP6	7	50	14.0
Hassumi	2012	Brazil	PCR, GP5/GP6	7	53	13.2
Kleist	2004	Germany	PCR, MY09/MY11, types specific primers, polyacrylamide gels, sequencing	6	38	15.8
Klussmann	2001	Germany	PCR, consensus primers, HPV16 specific primers	1	14	7.1
Koppikar	2005	India	PCR, probably MY09/MY11	0	2	0.0
Koskinen	2007	Scandinavia	PCR, MY09/MY11, GP5/GP6, SPF10, INNO-LiPA line probe	3	69	4.3
Liu	2010	China	PCR, GP5/6, HPV16/18 specific primers, agarose gel	29	84	34.5
Major	2005	Hungary	PCR, MY09/MY11, GP5/GP6, HPV 6/11/16 type specific primers, agarose gel	8	16	50.0
Manjarrez	2006	Mexico	PCR, L1C1/L1C2, typing by restriction fragment length polymorphism	2	16	12.5

Isayeva, et al. Head Neck Pathol. 2012;Suppl 1:S104-20.

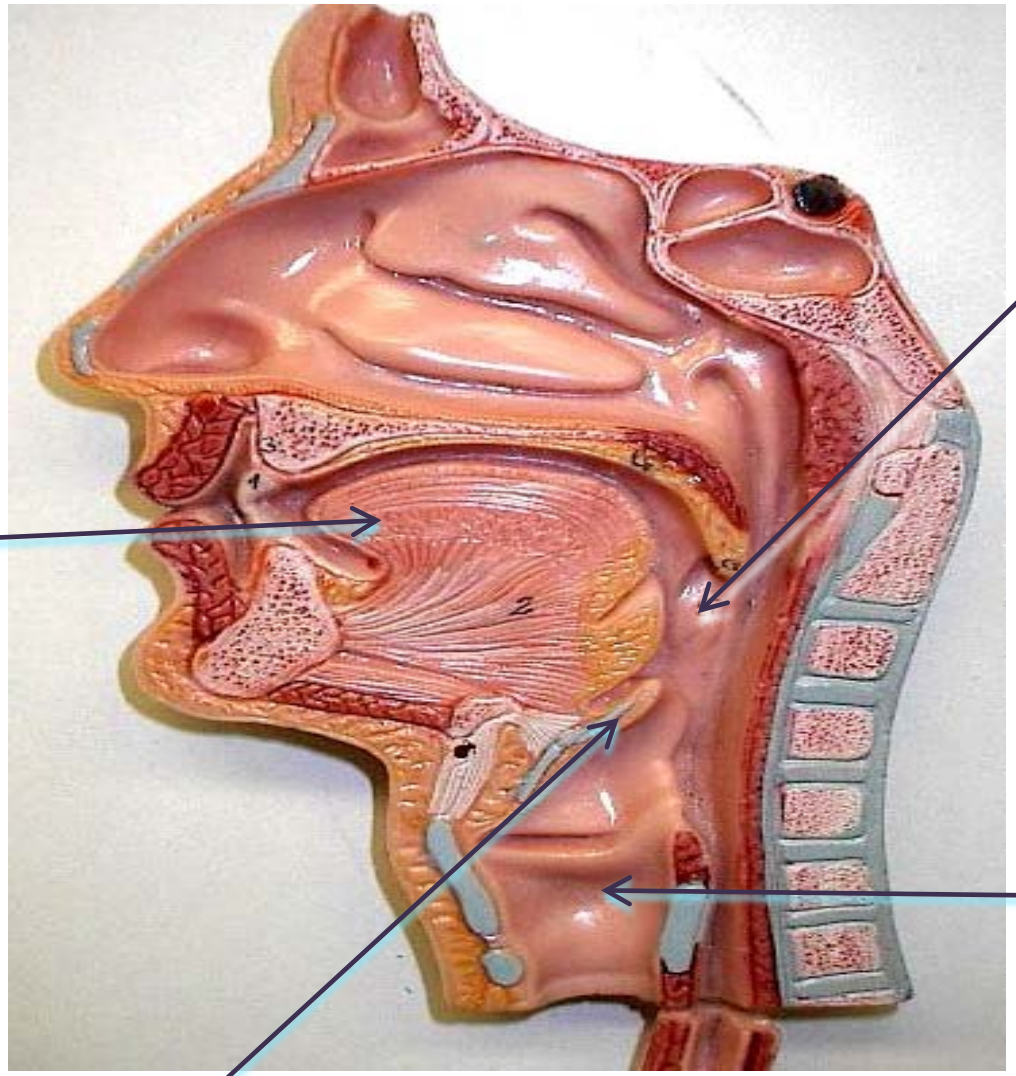
Author	Year	Country	Method, primers, amplicon detection	Number of cancers HPV+	Total cancers studied	Cancers HPV+ (%)
Mork	2001	Scandinavia	PCR, GP5/GP6, CpI, CpII, HPV16 type specific primers	1	32	3.1
Morshed	2010	Poland	PCR, SPF10, agarose gel, enzyme immune assay typing, INNO-LiPA genotyping	33	93	35.5
Oliveira	2006	Brazil	PCR, GP5/GP6, HPV type specific primers	41	11	100
Reidy	2004	USA	PCR, HPV type specific primers, agarose gel	6		
Ringstrom	2002	USA	PCR, MY09/MY11, agarose gel, typing by restriction fragment length polymorphism	1	10	
Schlecht	2011	USA	PCR, MY09/11, dot blot	8	32	25.0
Sethi	2011	USA	PCR, SPF10, INNO-LiPA line probe	26	111	23.4
Slebos	2006	USA	PCR, MY09/MY11, sequenced	1	9	11.1
Smith	2008	USA	PCR, MY09/MY11	4	40	
Smith	2000	USA	PCR, MY09/MY11, agarose gel, sequenced	11	44	0.0
Snietura	2011	Poland	PCR (Abbott Molecular Real Time High-Risk HPV)	0	65	
Stephen	2012	USA	PCR, HPV6 specific primers, real time quantitative PCR	21	77	
Szladek	2005	Hungary	PCR, MY09/MY11, GP5/GP6, then typed	12	25	48.0
Torrente	2005	Chile	PCR, MY09/MY11, E2 for integration, typing by restriction fragment length polymorphism	10	31	32.3
Van Houten	2001	Netherlands	PCR, GP5/GP6, enzyme immune assay typing	0	5	0.0
Van Monsjou	2012	Netherlands	PCR, INNO-LiPA line probe	0	2	0.0
Venuti	2000	Italy	PCR, MY09/MY11, E2 for integration, typing by restriction fragment length polymorphism	13	25	52.0
Vlachtsis	2005	Greece	PCR, "consensus primers"	36	90	40.0
				436	1,712	

- **Non-quantitative PCR-based methods cannot distinguish causative vs. incidental HPV infections!**

Transcriptionally active HPV in larynx/hypopharynx SCC

- **RNA ISH or DNA ISH + p16:**
  - **Lewis, et al. *Histopathology*, 60:982-91, 2012:**
    - **2 of 31 (6%)**
    - **One had involvement of oropharynx.**
  - **Bishop, et al. *Am J Surg Pathol*, 36: 1874-82, 2012:**
    - **1 of 84 (1%)**
  - **Chernock, et al. *Mod Pathol*, 26(2):223-13, 2013:**
    - **4 of 60 (7%)**
  - **Young, et al. Br J Cancer, 112(6):1098-104, 2015.**
    - **7 of 307 (2%)**

Transcriptionally active HR-HPV in HNSCC



Oropharynx 80%

Oral cavity <1%

Larynx <5%

Hypopharynx <5%

Transciptionally active HPV in non-oropharyngeal HNSCC

- **Quite rare.**
- **Clinical significance is unclear.**
  - **Does not appear to have the marked prognostic significance as it does in the oropharynx**
- **Routine HPV testing is NOT indicated.**

CAP Guideline

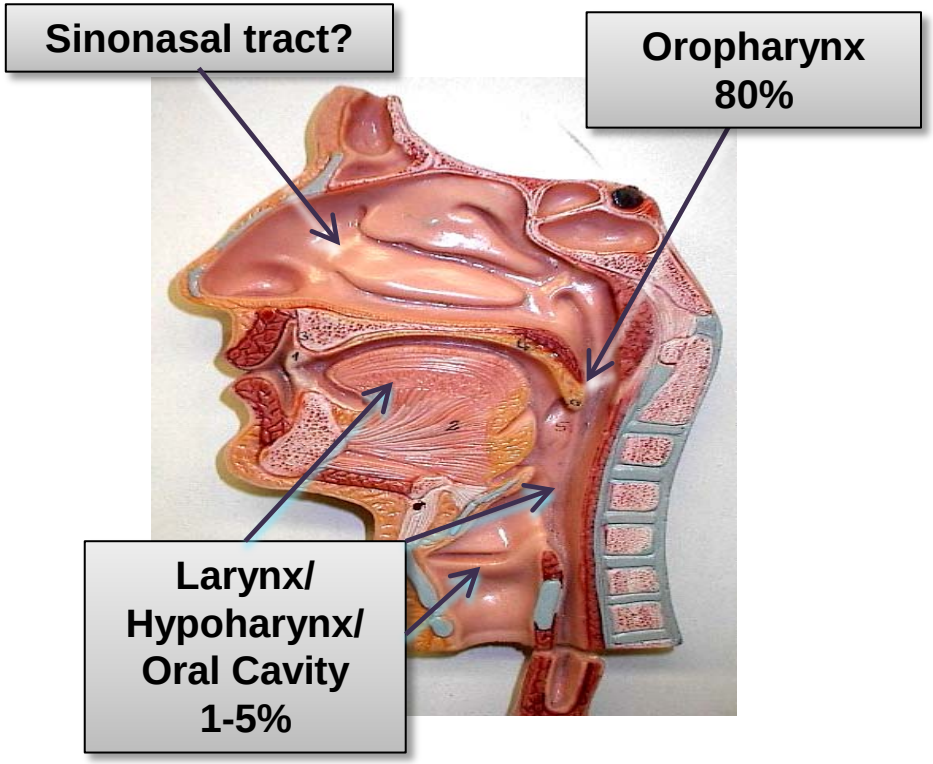
4. Pathologists should *not* routinely perform HR-HPV testing on patients with non-oropharyngeal primary tumors of the head and neck.

How about p16 outside of oropharynx?

- **High sensitivity (approaching 100%). But...**
- **Positive predictive value depends on prevalence of condition**
  - **High in oropharynx, cervical lymph node metastases**
  - **Low everywhere else**
- **Outside of the oropharynx and cervical lymph node metastases, p16 positivity much more likely to be a false positive**
  - **p16 upregulation due to other mechanisms**
  - **If you're going to do it (rare circumstances), do not use p16 by itself**

HPV in Sinonasal Carcinomas

- **Many reports of HPV, but overall incidence and clinicopathologic profile were unclear.**
- **At JHH, 161 consecutive primary sinonasal cancers tested with p16 immunohistochemistry + HPV in situ hybridization.**
  - **34 (21%) positive.**



Transcriptionally active HPV in sinonasal carcinomas

UTILIZING DNA ISH + P16 OR RNA ISH

Head and Neck Pathol (2014) 8:241–249
DOI 10.1007/s12105-013-0514-4

REVIEW PAPER

The Sinonasal Tract: Another Potential "Hot Spot" for Carcinomas with Transcriptionally-Active Human Papillomavirus

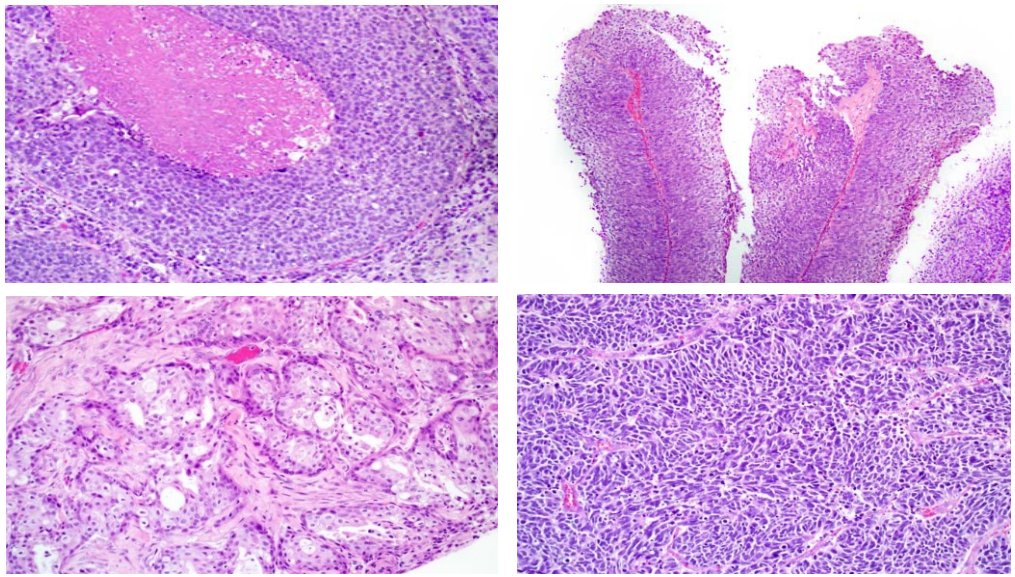
James S. Lewis Jr. · William H. Westra · Lester D. R. Thompson · Leon Barnes · Antonio Cardesa · Jennifer L. Hunt · Michelle D. Williams · Pieter J. Slootweg · Asterios Triantafyllou · Julia A. Woolgar · Kenneth O. Devaney · Alessandra Rinaldo · Alfio Ferlito

Received: 21 October 2013 / Accepted: 3 December 2013 / Published online: 14 December 2013

Abstract While high risk human papillomavirus (HPV) is well established as causative and clinically important for squamous cell carcinoma (SCC) of the oropharynx, its role in non-oropharyngeal head and neck SCC is much less clearly elucidated. In the sinonasal region, in particular, current literature on HPV in sinonasal carcinomas, attempts to more clearly demonstrate what tumors have it and how this relates to possible precursor lesions like inverted papilloma, and discusses the possible clinical ramifications of the presence of the virus.

Transcriptionally active HPV in sinonasal carcinomas

- **Usually (82%) non-keratinizing squamous morphology.**
- **Variants that have been seen in oropharynx: adenosquamous, small cell, basaloid, papillary.**
- **Some cases closely resembled salivary gland tumors, especially adenoid cystic carcinoma.**



Bishop JA, et al. Am. J. Surg. Pathol. 2013. 37(2):185-92.

HPV-related Multiphenotypic Sinonasal Carcinoma

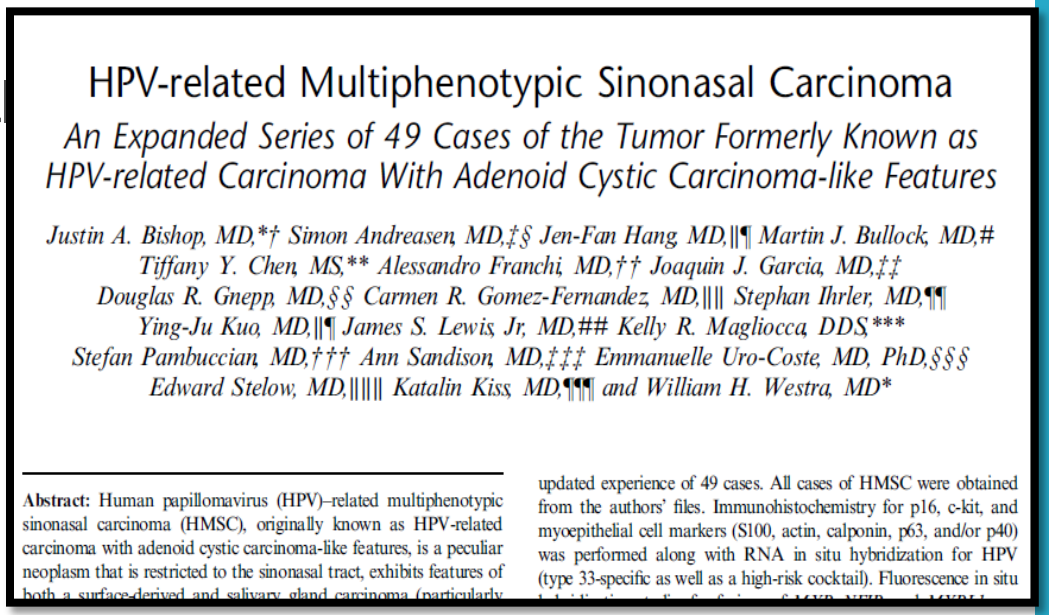
- **Formerly "HPV-related carcinoma with adenoid cystic like features"**
- **Included as a provisional tumor type (under NKSCC) in the 2017 WHO classification.**
- **Additional cases needed to justify inclusion as a full-fledged tumor entity.**

The newly recognized sinonasal tract HPV-related carcinoma with adenoid cystic–like features is a distinctive HPV-related carcinoma of the sinonasal tract, with histological and immunophenotypic features of both surface-derived and salivary gland carcinoma – the latter showing the appearance of a high-grade adenoid cystic carcinoma. Among the few cases of HPV-related carcinoma with adenoid cystic–like features that have been reported to date, the female-to-male ratio is 7:2 and the patient age range is 40–75 years [199,202,1065]. The presence of a high-risk HPV type suggests a viral etiology [202,1065]. Most cases present with nasal obstruction and/or epistaxis, with a tan-white, fleshy mass undermining normal-looking mucosa. The tumour consists of highly cellular proliferations of basaloid cells growing in various sizes, separated by thin collageni
bands. The growth pattern
nantly solid, but cribriform st
frequently encountered. Th
cells align around cylindroma
cystic spaces and have hyp
and slightly angulated nuclei
N:C ratio. True ductal cells a
sent (although less conspic
surrounded by a peripheral
saloid to clear myoepithelial

WHO

HPV-related Multiphenotypic Sinonasal Carcinoma

- 49 cases identified.
  - 28 women, 21 men.
  - 28-90 years (mean, 54).
- All cases arose from the sinonasal tract.
- 40 cases had staging information:
  - T1-2: 23
  - T3-4: 17
- Tumor size known in 40 cases:
  - 0.7 – 8.5 cm (mean, 3.9 cm).
- Presented most often with obstruction/stenosis (n=26) and/or epistaxis (n=20).



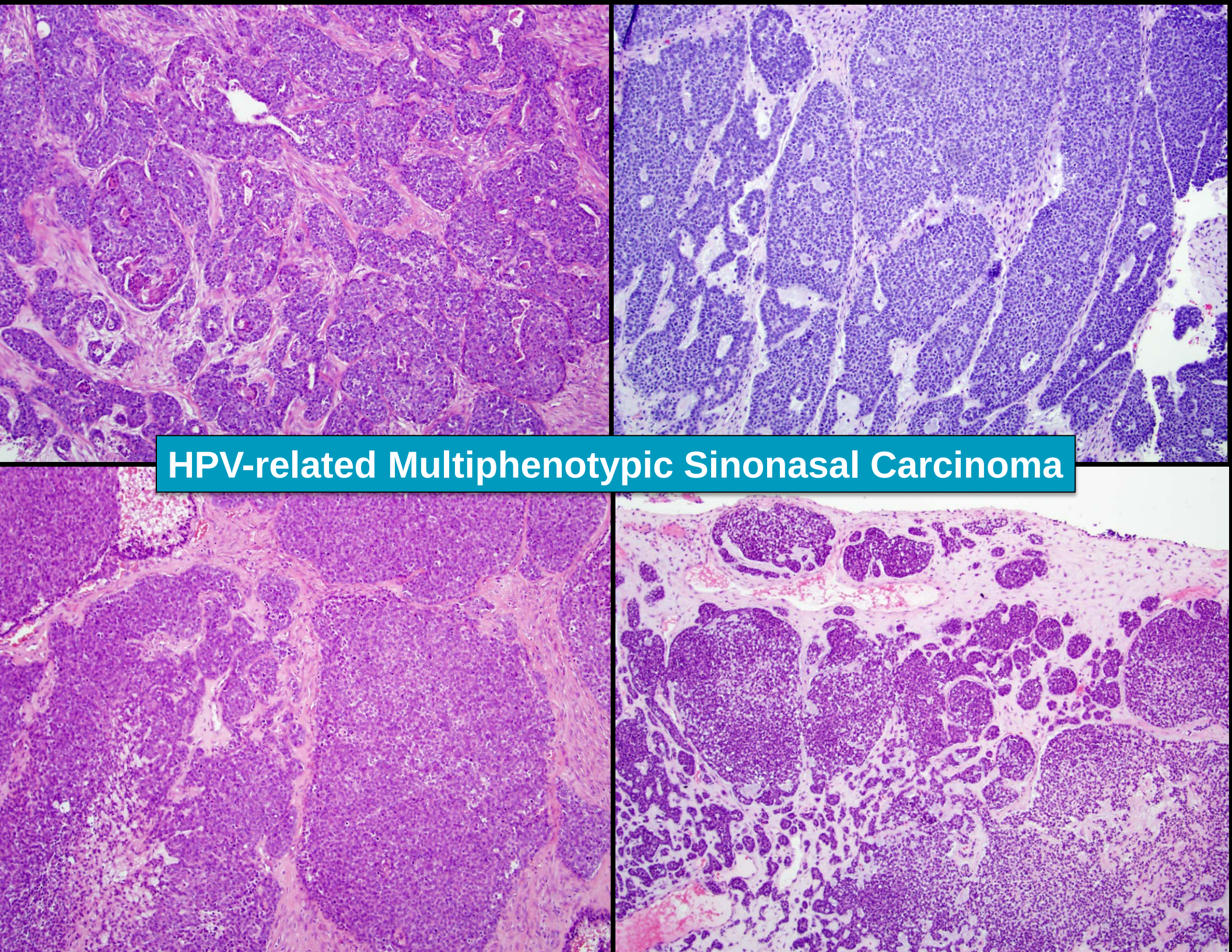
HPV-related Multiphenotypic Sinonasal Carcinoma

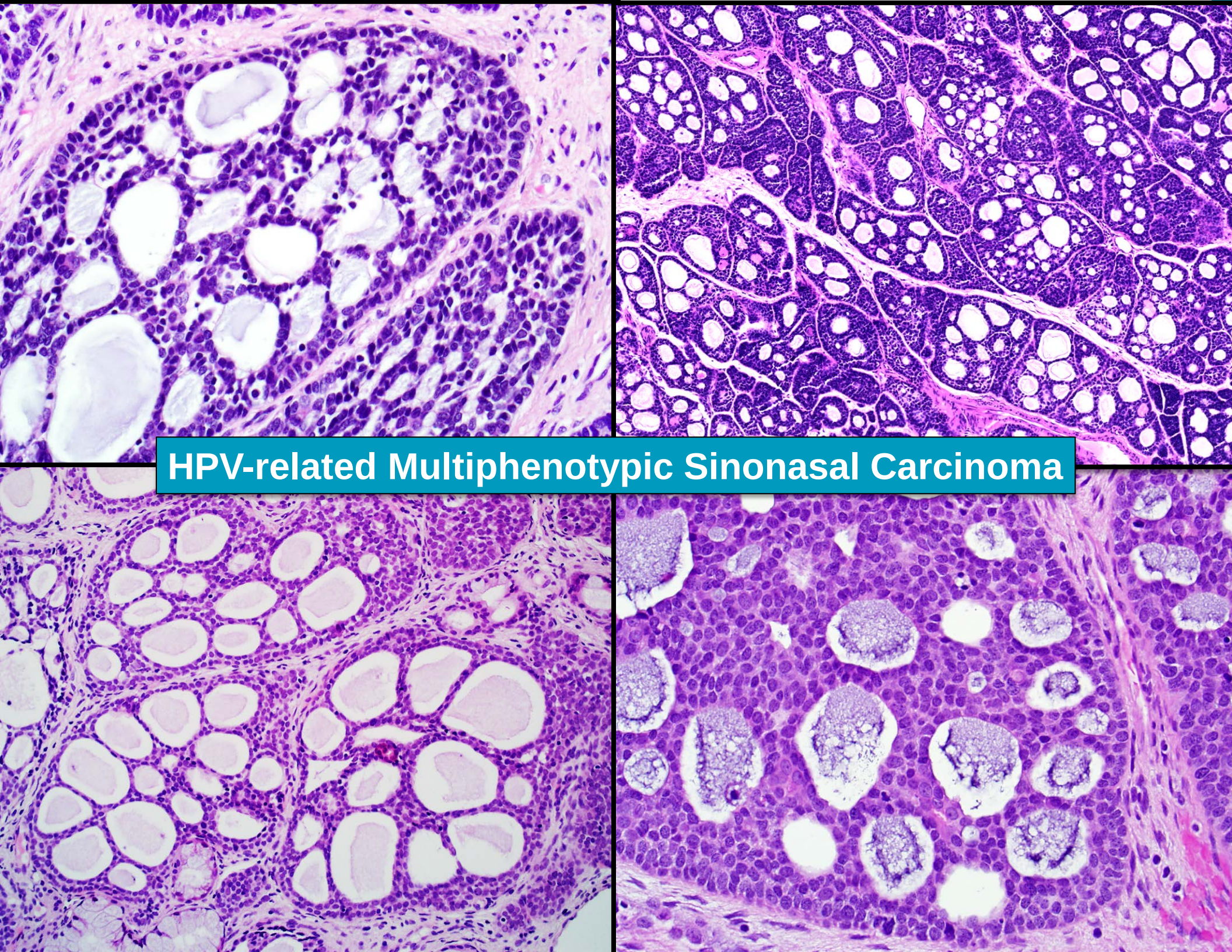
An Expanded Series of 49 Cases of the Tumor Formerly Known as HPV-related Carcinoma With Adenoid Cystic Carcinoma-like Features

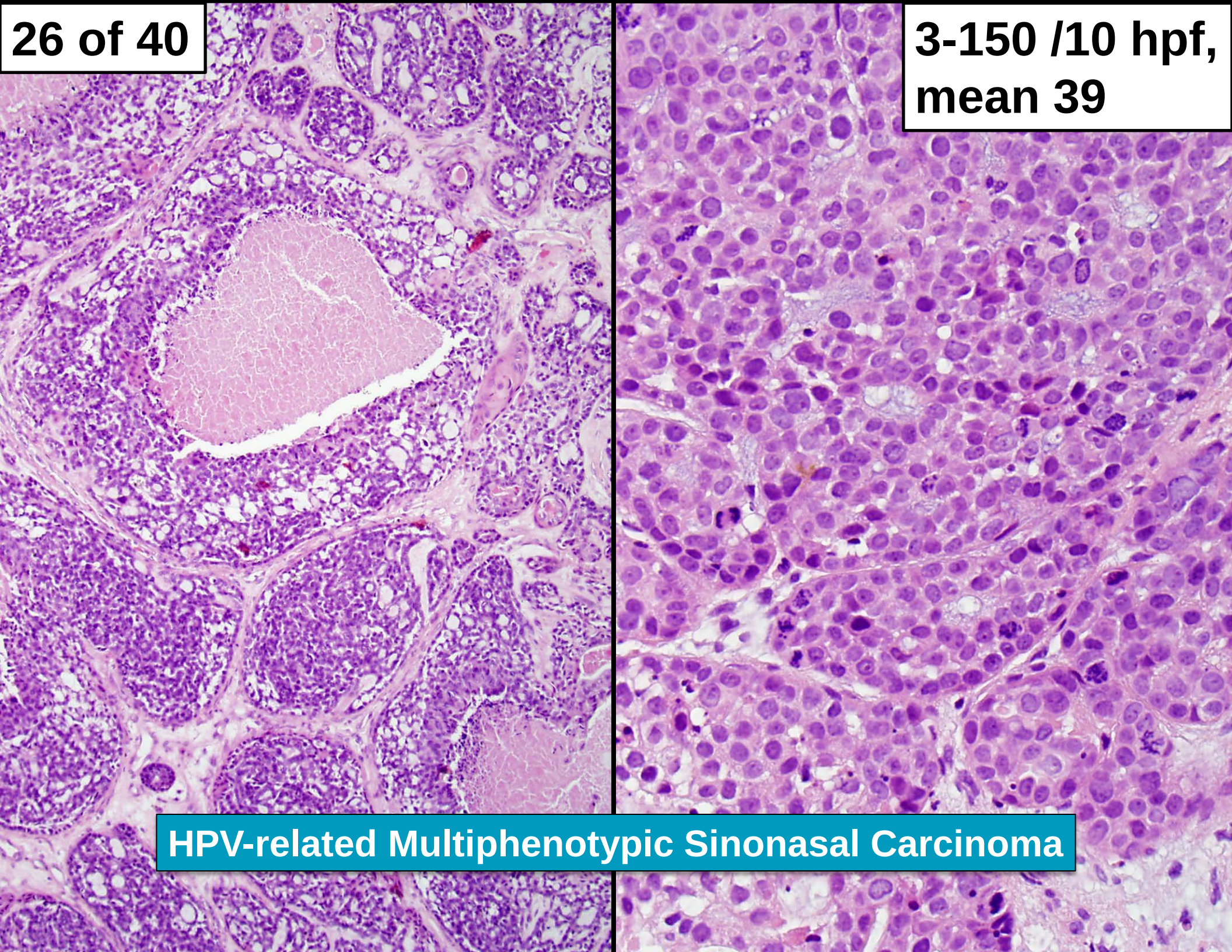
Justin A. Bishop, MD,† Simon Andreasen, MD,‡§ Jen-Fan Hang, MD,‖¶ Martin J. Bullock, MD,# Tiffany Y. Chen, MS,** Alessandro Franchi, MD,†† Joaquin J. Garcia, MD,‡‡ Douglas R. Gnepp, MD,§§ Carmen R. Gomez-Fernandez, MD,‖‖ Stephan Ihrler, MD,¶¶ Ying-Ju Kuo, MD,‖¶ James S. Lewis, Jr, MD,## Kelly R. Magliocca, DDS,*** Stefan Pambuccian, MD,††† Ann Sandison, MD,‡‡‡ Emmanuelle Uro-Coste, MD, PhD,§§§ Edward Stelow, MD,‖‖‖ Katalin Kiss, MD,¶¶¶ and William H. Westra, MD**

Abstract: Human papillomavirus (HPV)–related multiphenotypic sinonasal carcinoma (HMSC), originally known as HPV-related carcinoma with adenoid cystic carcinoma-like features, is a peculiar neoplasm that is restricted to the sinonasal tract, exhibits features of both a surface-derived and salivary gland carcinoma (particularly updated experience of 49 cases. All cases of HMSC were obtained from the authors' files. Immunohistochemistry for p16, c-kit, and myoepithelial cell markers (S100, actin, calponin, p63, and/or p40) was performed along with RNA in situ hybridization for HPV (type 33-specific as well as a high-risk cocktail). Fluorescence in situ

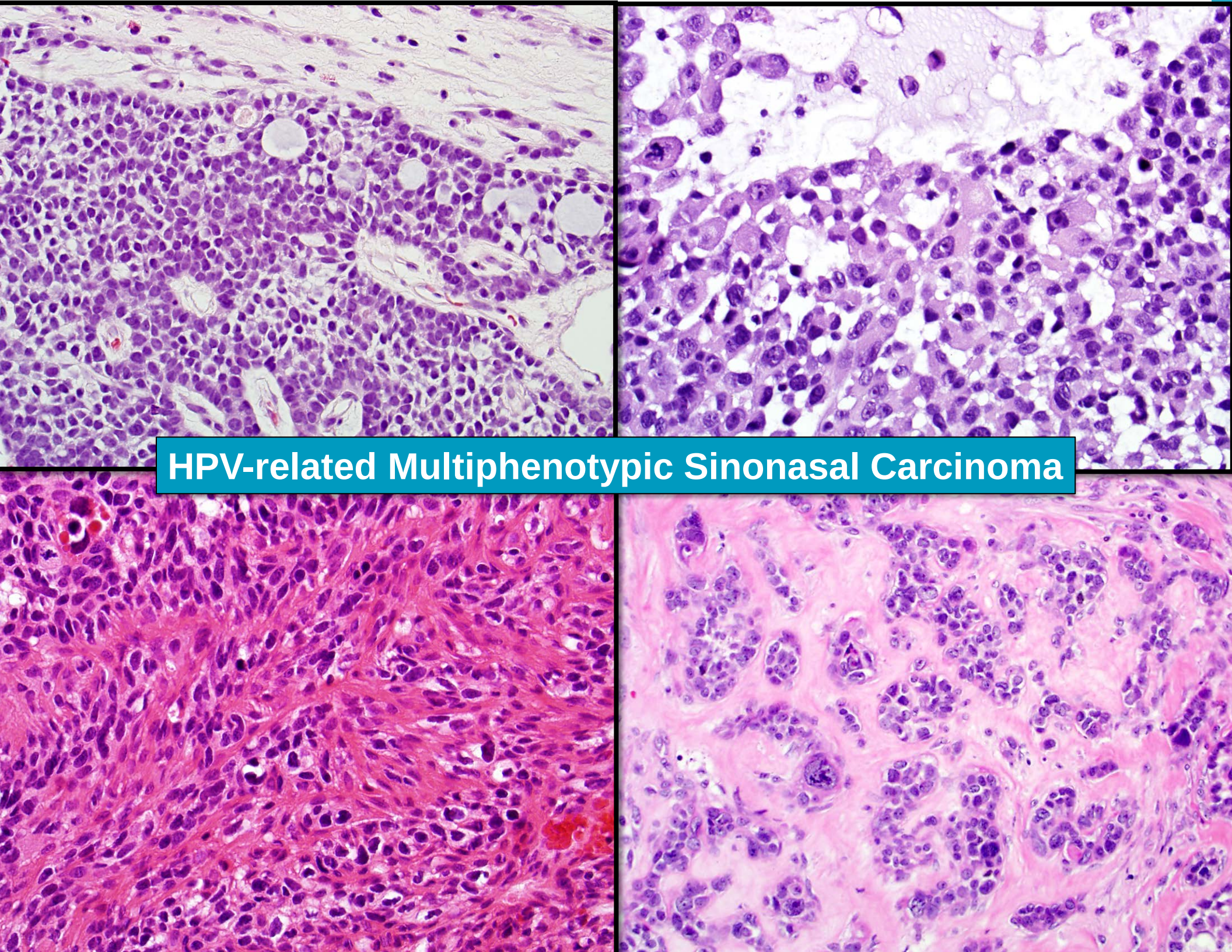
Bishop, et al. Am J Surg Pathol. 2017; 41:1690-1701.

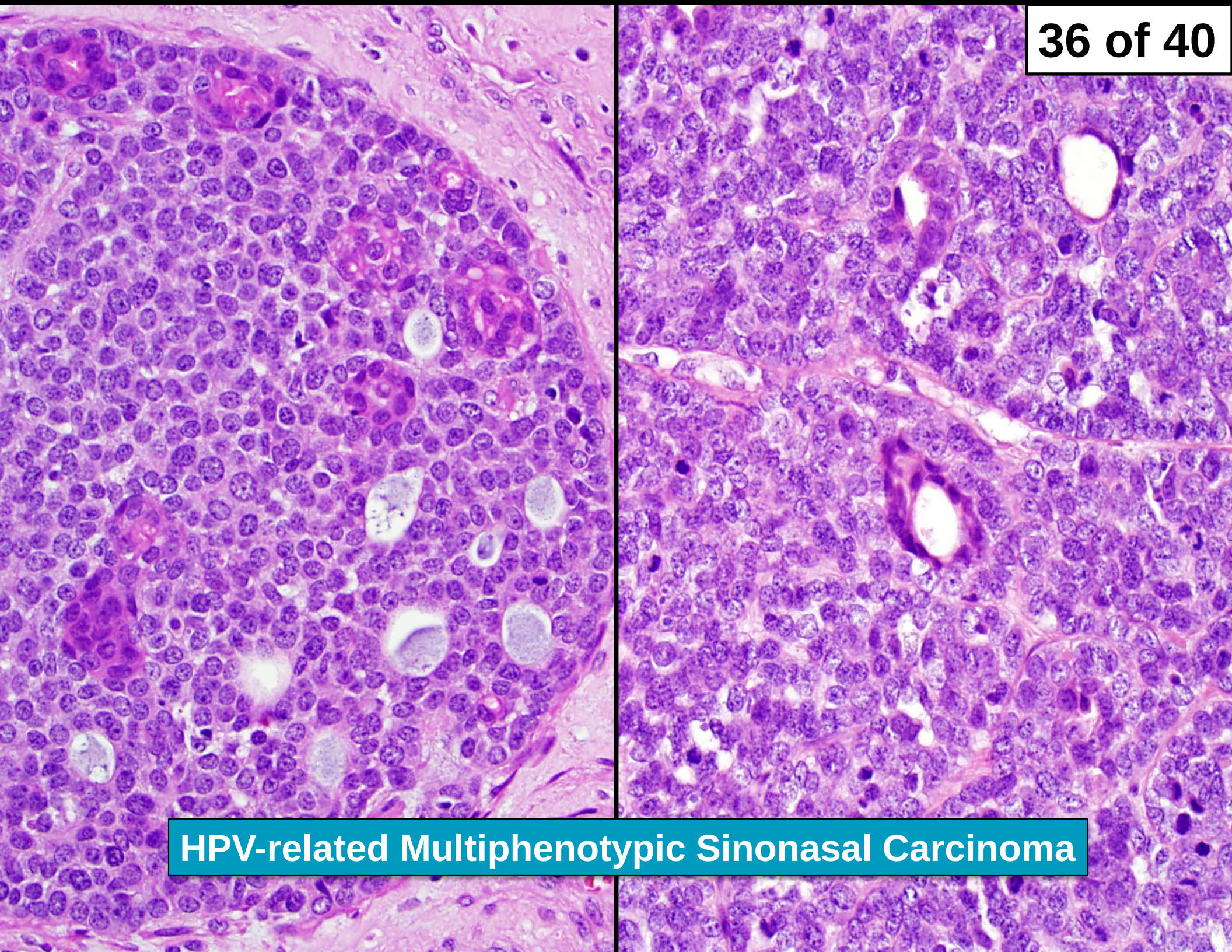

HPV-related Multiphenotypic Sinonasal Carcinoma


HPV-related Multiphenotypic Sinonasal Carcinoma



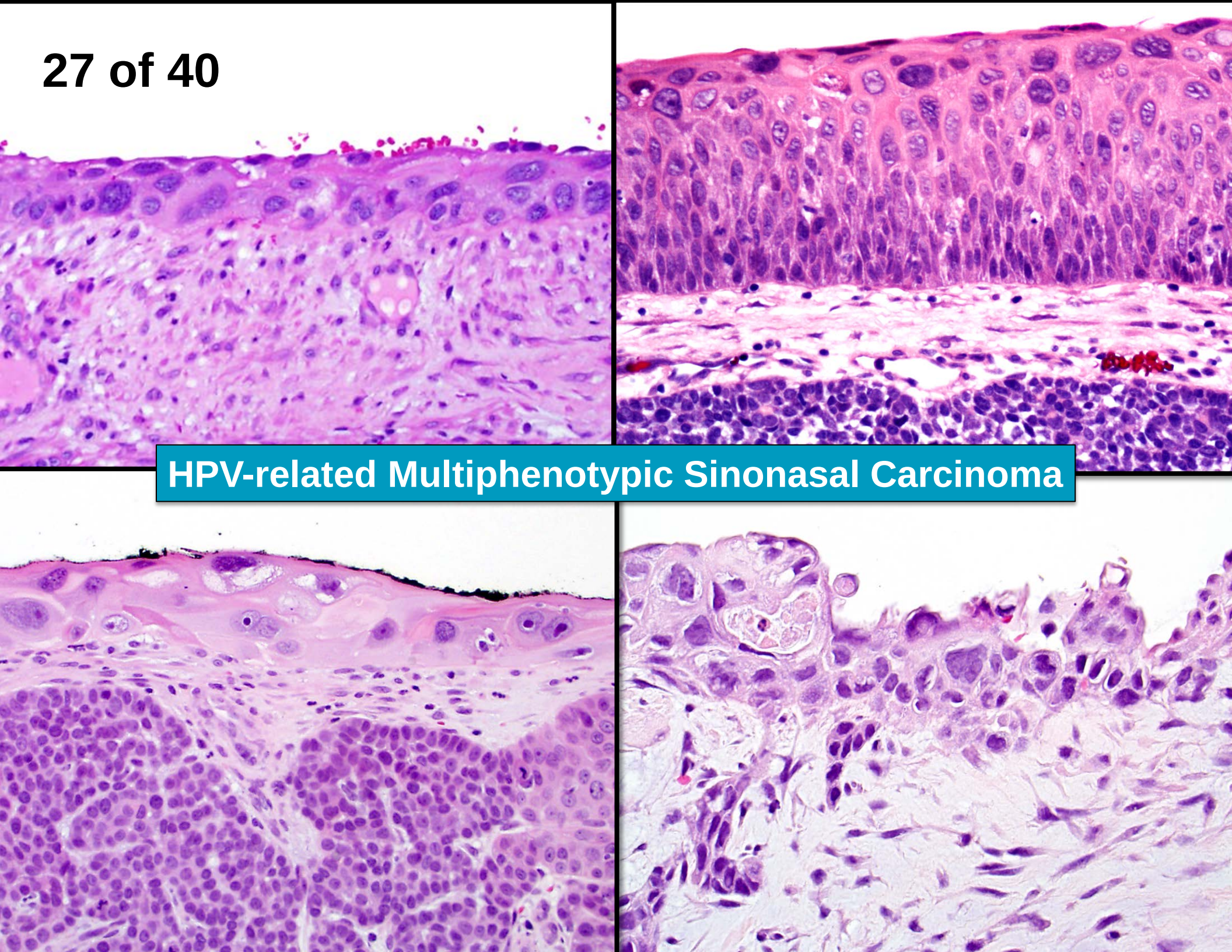
HPV-related Multiphenotypic Sinonasal Carcinoma

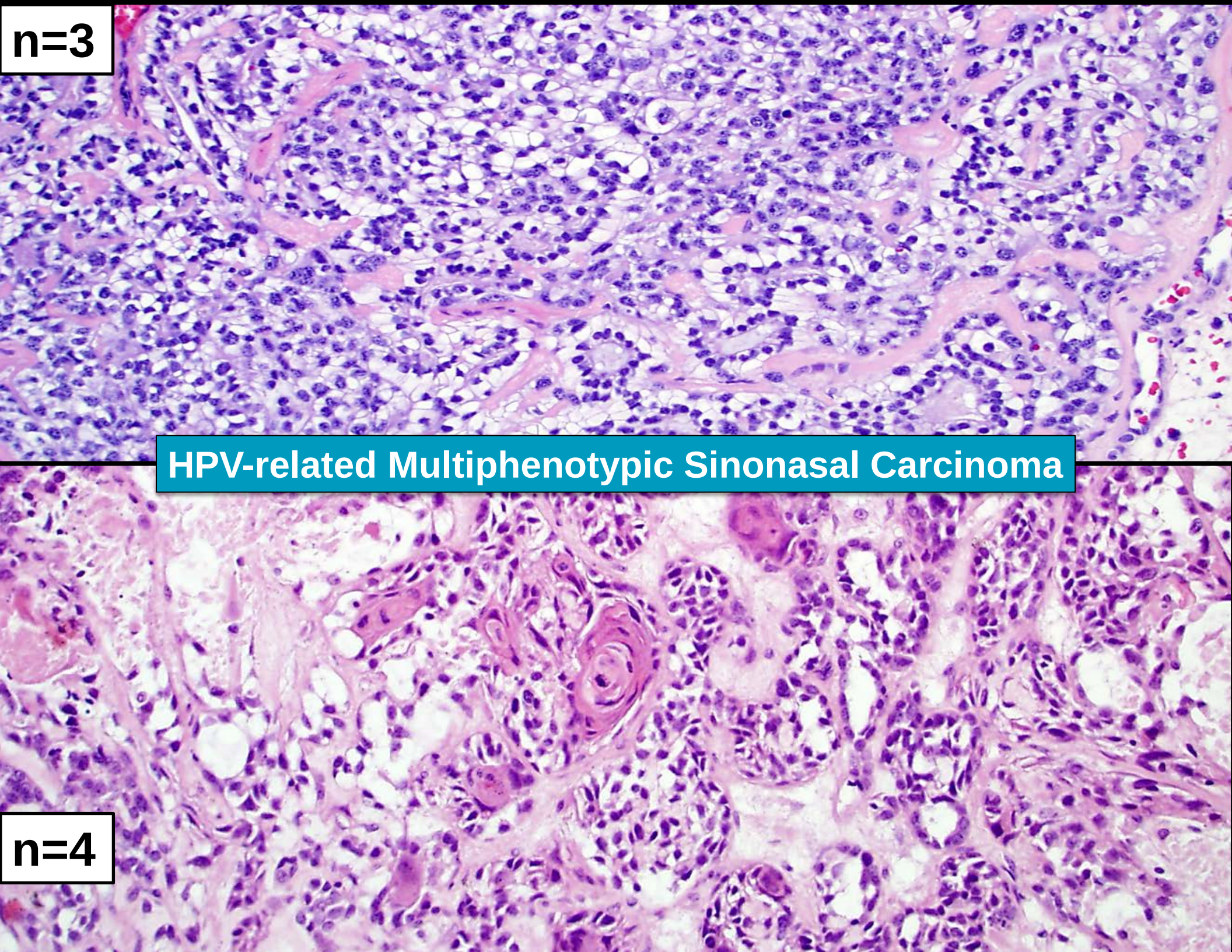

HPV-related Multiphenotypic Sinonasal Carcinoma

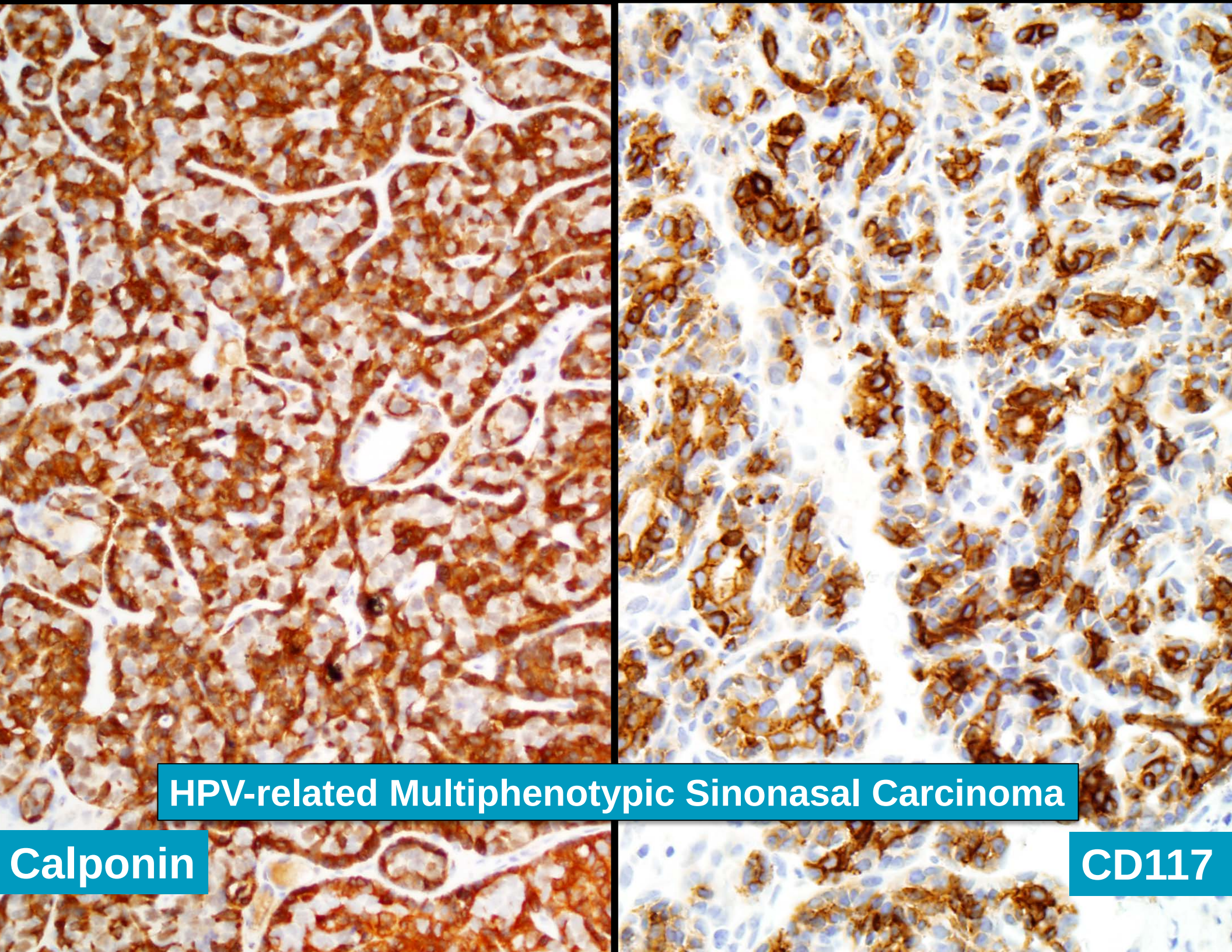


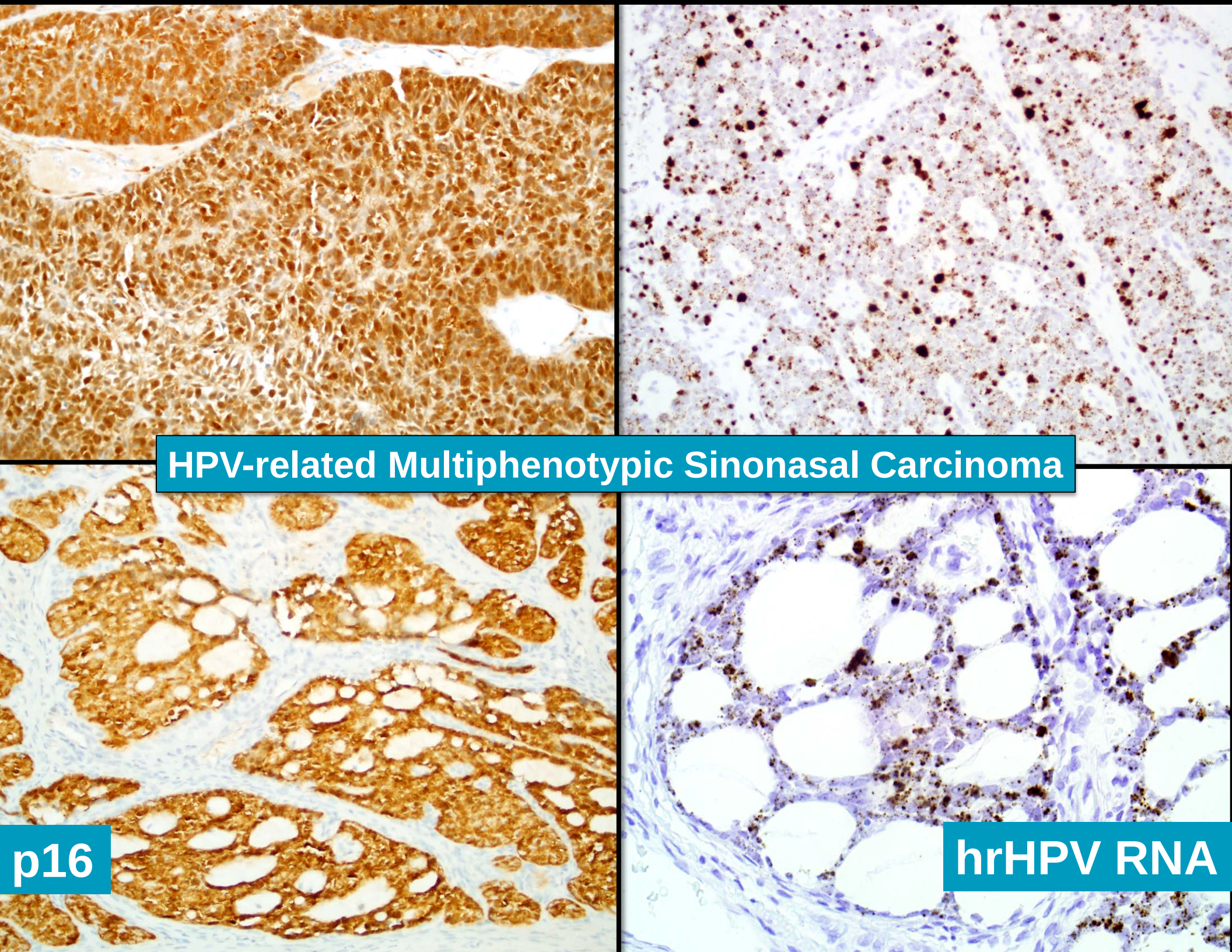
HPV-related Multiphenotypic Sinonasal Carcinoma

HPV-related Multiphenotypic Sinonasal Carcinoma



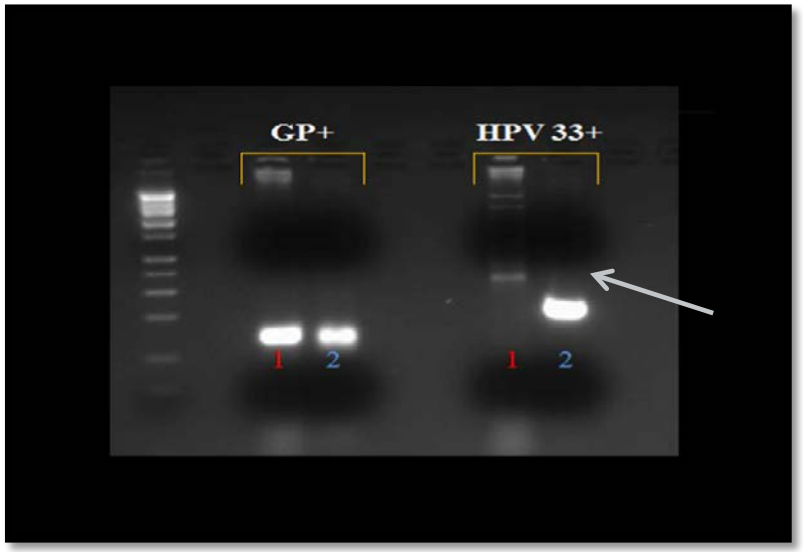

n=3
HPV-related Multiphenotypic Sinonasal Carcinoma
n=4


HPV-related Multiphenotypic Sinonasal Carcinoma
Calponin
CD117


HPV-related Multiphenotypic Sinonasal Carcinoma
p16
hrHPV RNA

HPV-related Multiphenotypic Sinonasal Carcinoma

- **HPV types (ISH and PCR):**
  - **33 type 33**
  - **3 type 35**
  - **1 type 56**
  - **12 type undetermined**
  - **1 type 16**
  - **0 type 18**

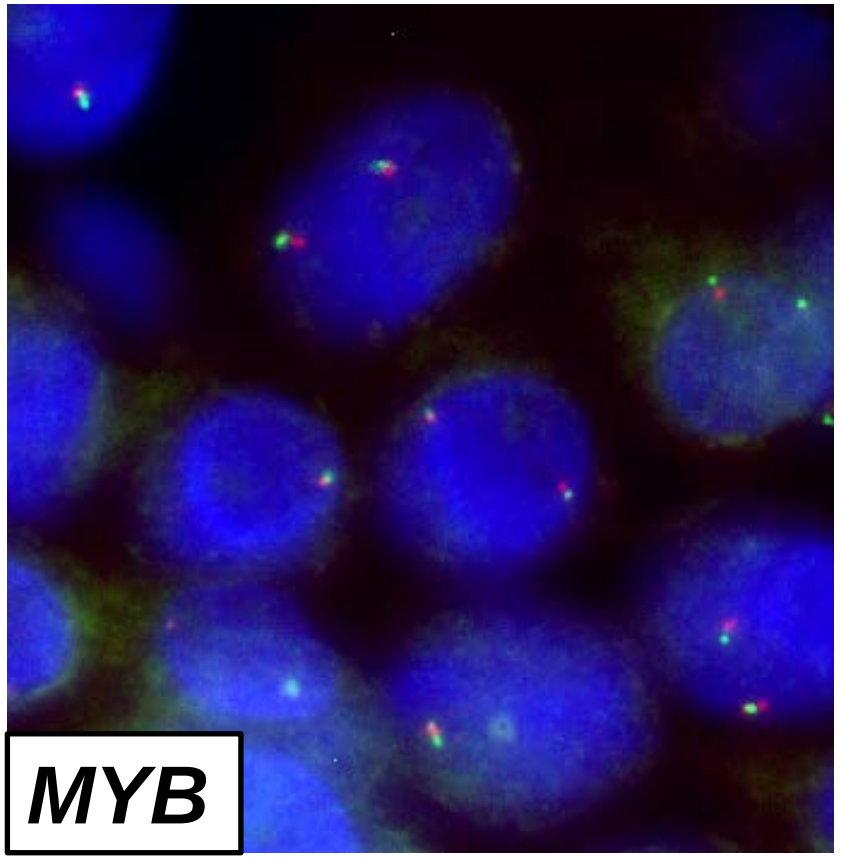


Why not adenoid cystic carcinoma?

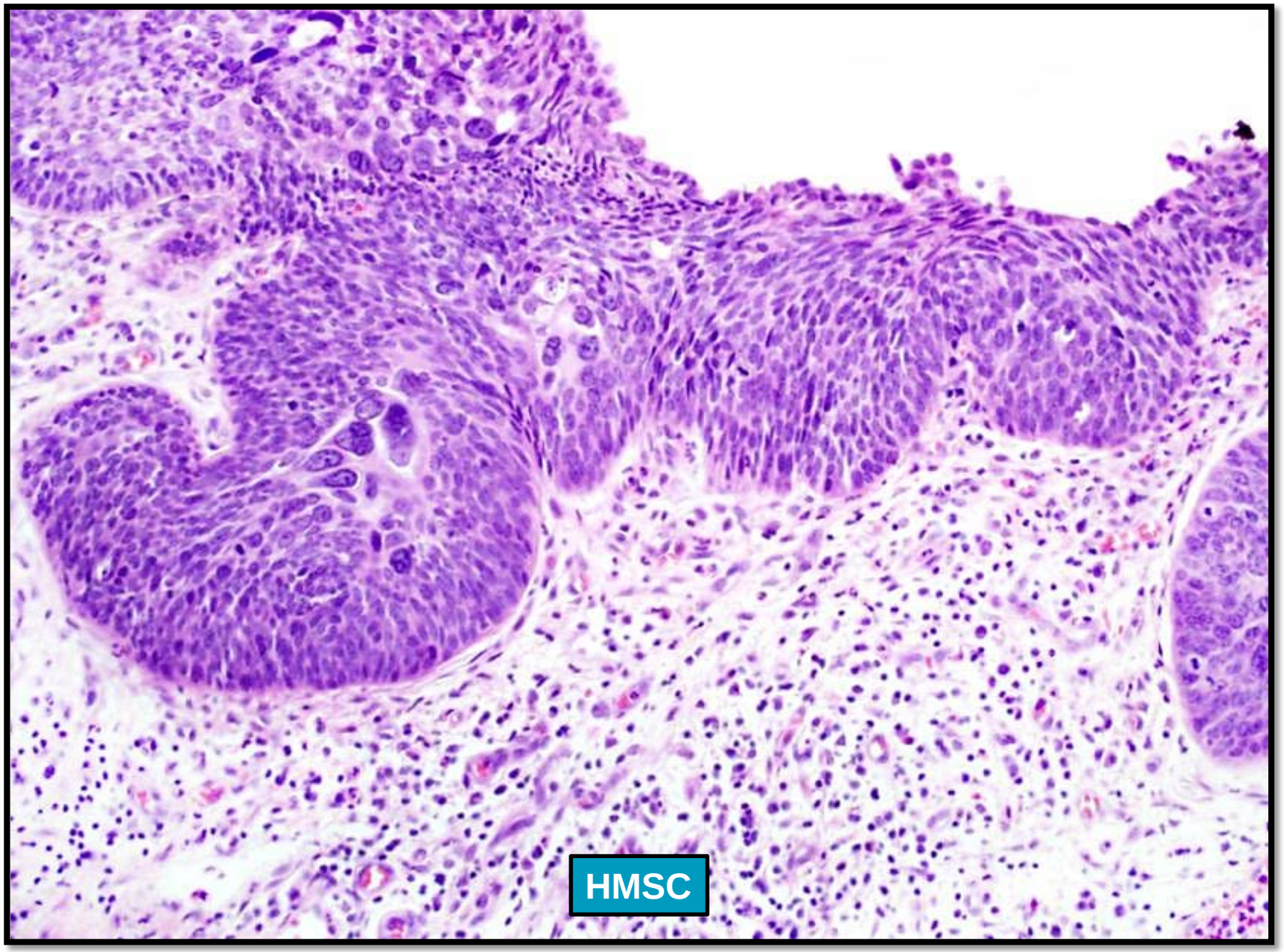
- **Site specificity**
  - **All cases collected have been from sinonasal tract.**
  - **0 of 108 (0%) adenoid cystic carcinomas arising in other ENT sites**

Why not adenoid cystic carcinoma?

No cases have harbored *MYB* or *MYBL1* gene fusions seen in 60-70% of adenoid cystic carcinomas

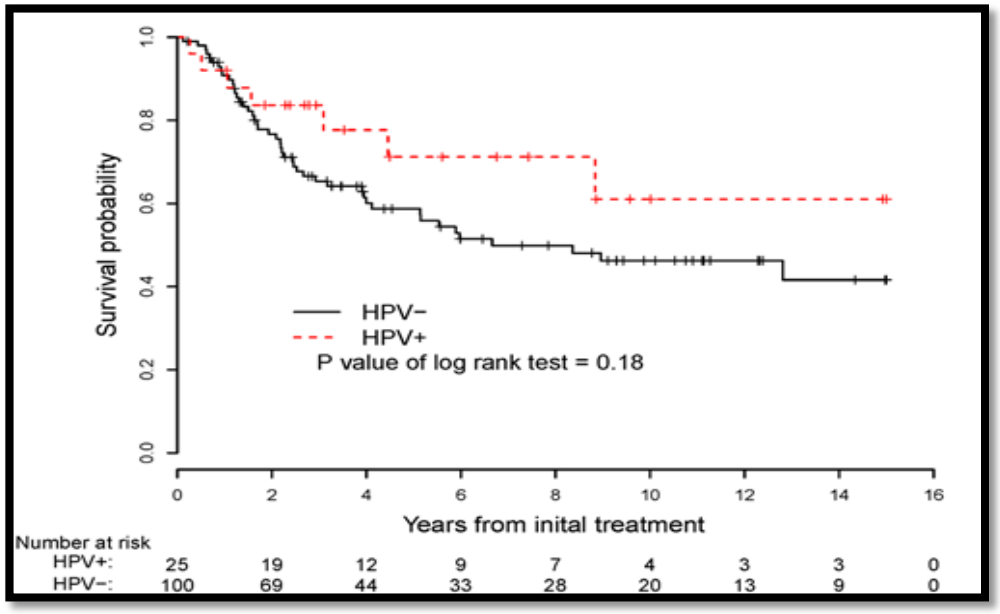


Why not adenoid cystic carcinoma?



Survival in HPV-related sinonasal carcinomas

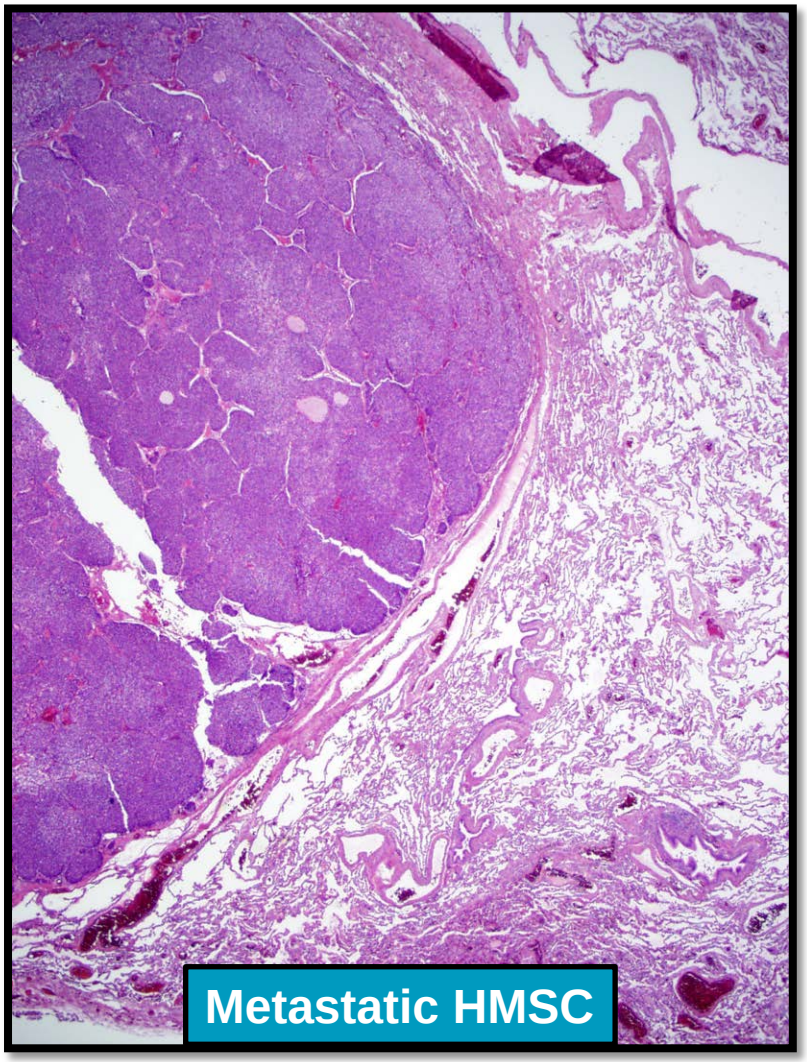
- **Significance not as clear as in oropharynx.**
- ***Trend* towards improved overall disease-free and overall survival.**



Bishop JA, et al. Am. J. Surg. Pathol. 2013. 37(6):836-44.

HPV-related multiphenotypic sinonasal carcinoma

- **39 cases had treatment and follow-up data (mean follow-up, 46.3 months).**
- **Most treated with surgery +/- radiation.**
- **14 recurred locally and 2 metastasized [to lung (n=2) and finger (n=1)].**
- **No regional lymph node metastases, and no tumor-related deaths.**



Summary

- **Sinonasal tract is the second anatomic hot spot for HPV-related head and neck carcinomas**
  - **20-25% harbor transcriptionally active high-risk HPV**
- **Significance of HPV in this site (and other non-oropharyngeal sites) is unclear**
- **CAP: Routine HPV testing not indicated for non-oropharyngeal (including sinonasal) carcinomas at this time.**

Summary

- **Histologic spectrum of HPV-related sinonasal carcinoma includes a peculiar multiphenotypic variant**
  - **High-grade histologic features.**
  - **Biphasic tumor population with myoepithelial cells and ducts, similar to adenoid cystic carcinoma.**
  - **Frequent surface epithelial dysplasia.**
  - **Association with HR-HPV, especially type 33.**
  - **paradoxically behaves in a relatively indolent manner.**
  - **HPV testing is indicated for the multiphenotypic variant because it is part of the tumor definition.**
  - **HPV-specific testing needed, because p16 is a poor HPV surrogate outside of the oropharynx.**

CAP HPV Testing in Head and Neck Cancers Guideline Statements

1. **Pathologists should perform HR-HPV testing on all patients with newly diagnosed oropharyngeal squamous cell carcinoma (OPSCC), including all histologic subtypes. This testing may be performed on the primary tumor or on a regional lymph node metastasis when the clinical findings are consistent with an oropharyngeal primary.**
2. **For oropharyngeal tissue specimens (i.e., non-cytology), 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.**
3. **Pathologists should *not* routinely perform HR-HPV testing on patients with non-squamous carcinomas of the oropharynx.**
4. **Pathologists should *not* routinely perform HR-HPV testing on patients with non-oropharyngeal primary tumors of the head and neck.**
5. **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.**
6. **For tissue specimens (i.e., non-cytology) from patients presenting with metastatic SCC of unknown primary in a cervical upper or mid jugular chain lymph node, pathologists should perform p16 IHC.**
7. **Pathologists should perform HR-HPV testing on head and neck fine needle aspiration (FNA) SCC samples from all patients with known oropharyngeal SCC not previously tested for HR-HPV, with suspected oropharyngeal SCC, 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.**
8. **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**
9. **Pathologists should not routinely perform low-risk HPV testing on patients with head and neck carcinomas.**
10. **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.**
11. **Pathologists should not routinely perform HR-HPV testing on patients with distant metastases if primary tumor HR-HPV status has been established. 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 metastasis or a new primary SCC.**
12. **Pathologists should report primary OPSCCs that test positive for HR-HPV or its surrogate marker p16 as "HPV-positive" and/or "p16-positive."**
13. **Pathologists should not provide a tumor grade or differentiation status for HPV-positive/p16-positive OPSCC.**
14. **Pathologists should not alter HR-HPV testing strategy based on patient smoking history**

Register for Upcoming Webinar

DATE	TOPIC	SPEAKER
Wednesday, June 13 11:00 AM CT	New Guideline for Lung Cancer Biomarker Testing: Essentials and Applications	Philip T Cagle, MD, FCAP Eric H Bernicker, MD

Register for upcoming & archived webinars:
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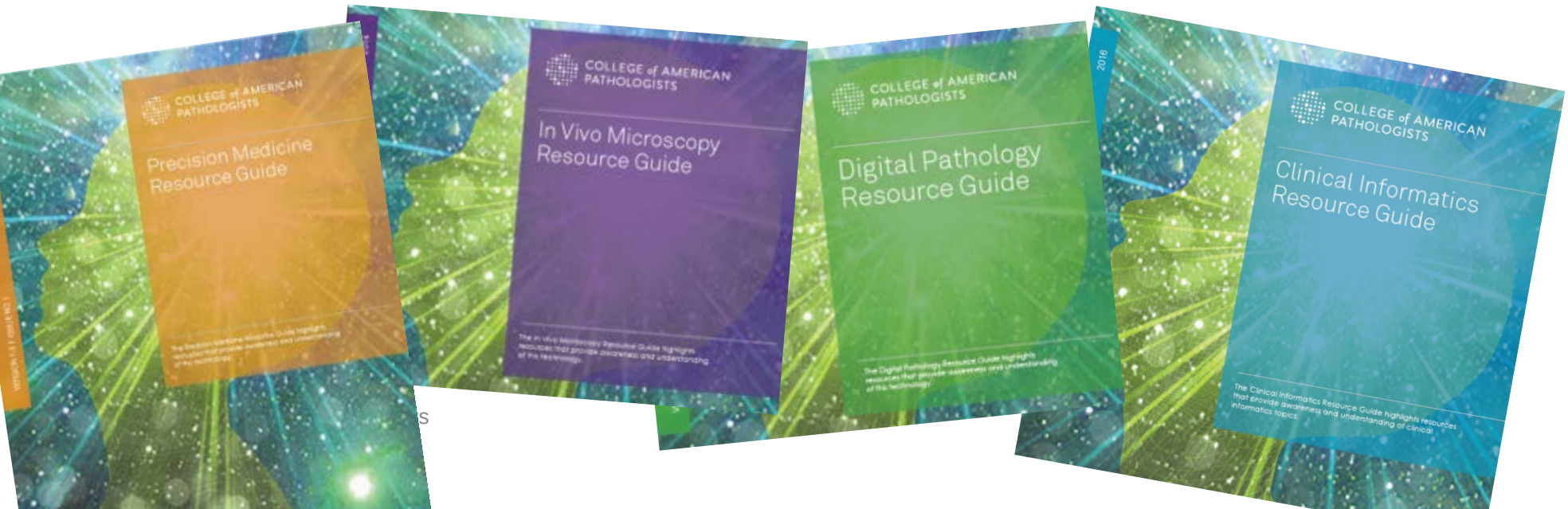
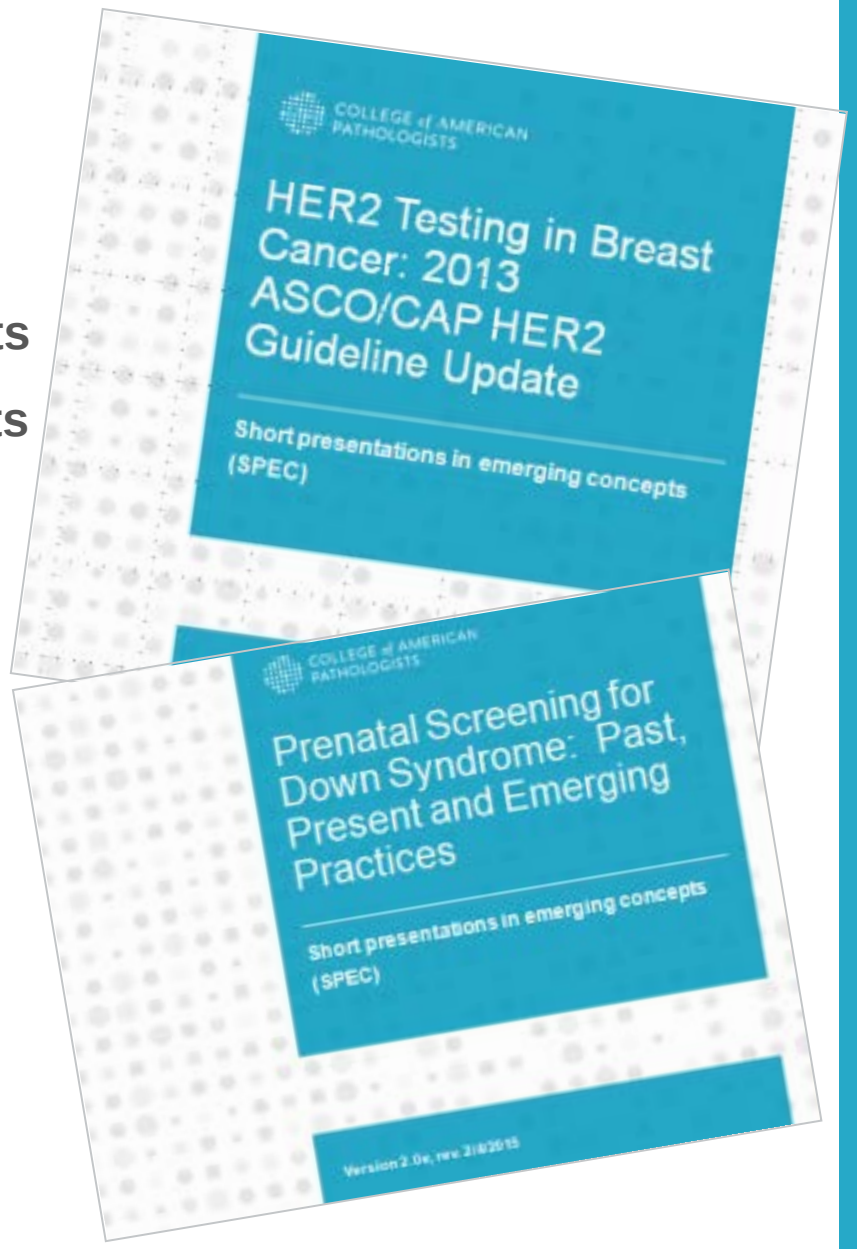
- **The CAP has created the Pathology Resource Guides to assist pathologists in understanding key emerging technologies.**
  - **Printed guides are now available for members ($39) and non-members ($69)**
  - **The digital copy of the Resource Guides are a complimentary member benefit**
  - **Access them www.cap.org > Resources and Publications**



Short Presentations on Emerging Concepts (SPECS)

- **Pathology SPECs are:**
  - **Short PowerPoints, created for pathologists**
  - **Focused on diseases where molecular tests play a key role in patient management**
- **Recent topics include:**
  - **Microbiome**
  - **Biomarkers in Lung Cancer**
  - **MDS**
  - **Other emerging topics**
- **Access them at www.cap.org > Resources and Publications**



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THANK YOU!

Thank you for attending our webinar, "HPV Testing on Head and Neck Carcinomas: A Review of the CAP Guidelines" by Justin Bishop, MD, FCAP

For comments about this webinar or suggestions for upcoming webinars, please contact phcwebinars@cap.org.

NOTE: There is no CME/CE credit available for today's free webinar. The PDF of the presentation will be sent out in a week.

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