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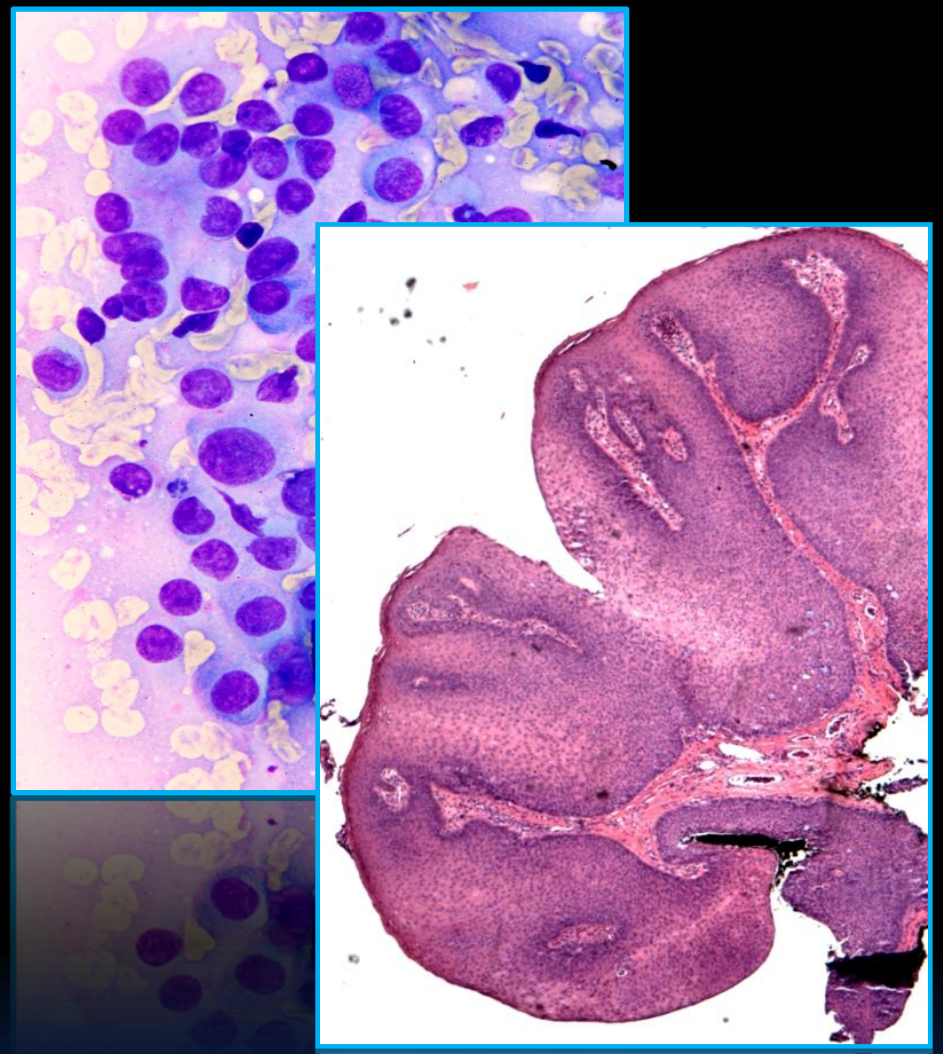


Squamous Dysplasias and Variants of Squamous Cell Carcinoma in the Head and Neck

Head and Neck Squamous Cell Carcinoma

- Over 95% of head and neck cancers
- 600,000 new cases worldwide per year
- 40-50% 5-year survival
  - Prognosis linked strongly to stage at presentation
- Risk factors:
  - Tobacco and alcohol – synergistic effect
  - Betel nut, prior radiation, HPV & EBV, genetic cancer syndromes (Fanconi's anemia, Bloom syndrome, Xeroderma Pigmentosa, Ataxia Telangiectasia)
- General trend over 3 decades of decreasing incidence of smoking-related HNSCC
- Treatment focused on surgery, radiotherapy +/- chemo, and selected targeted therapies (e.g. PD-L1/immunecheckpoint)

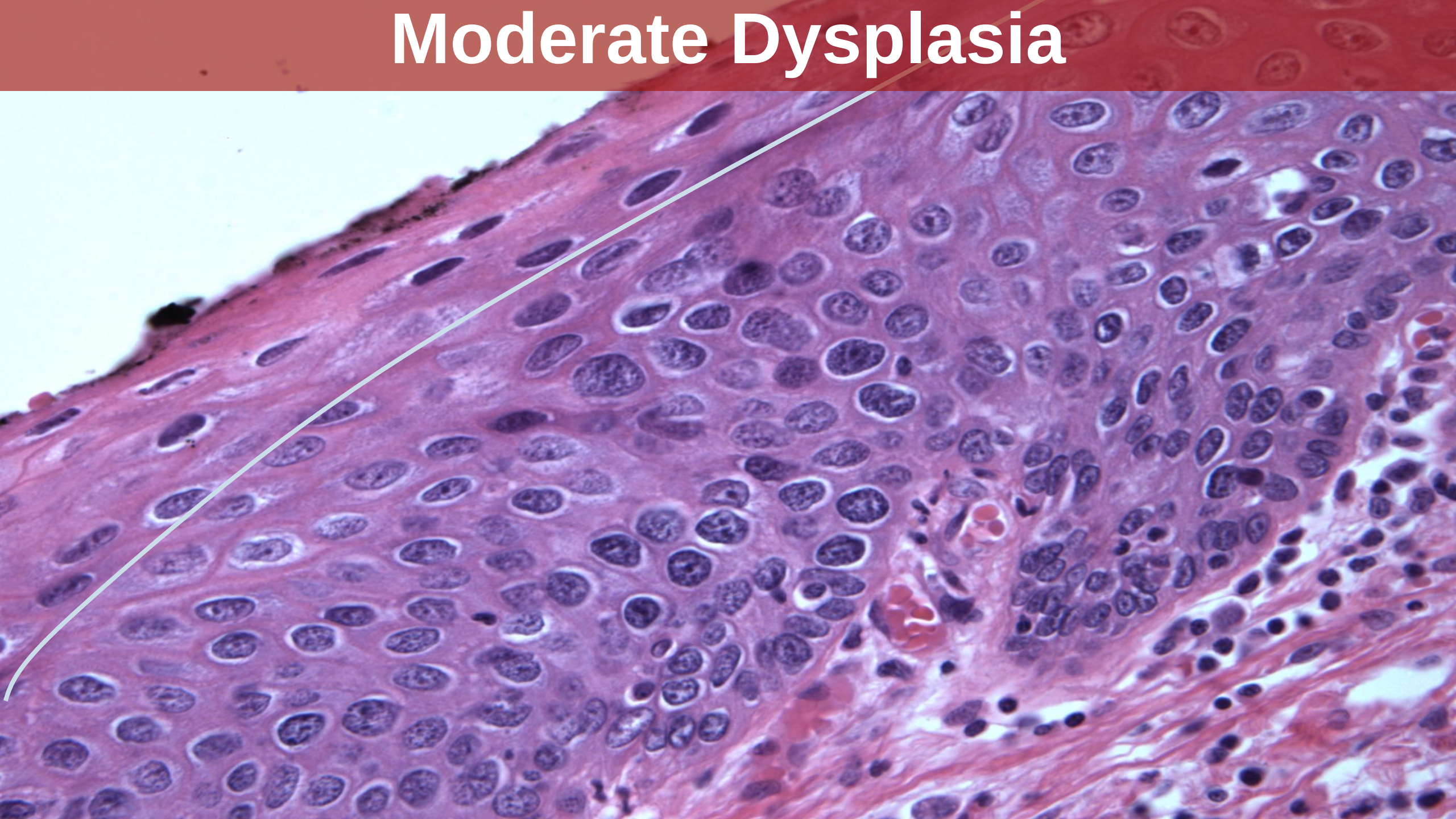
HNSCC and its Precursors

Head and Neck Squamous Cell Carcinoma:Precursor Lesions

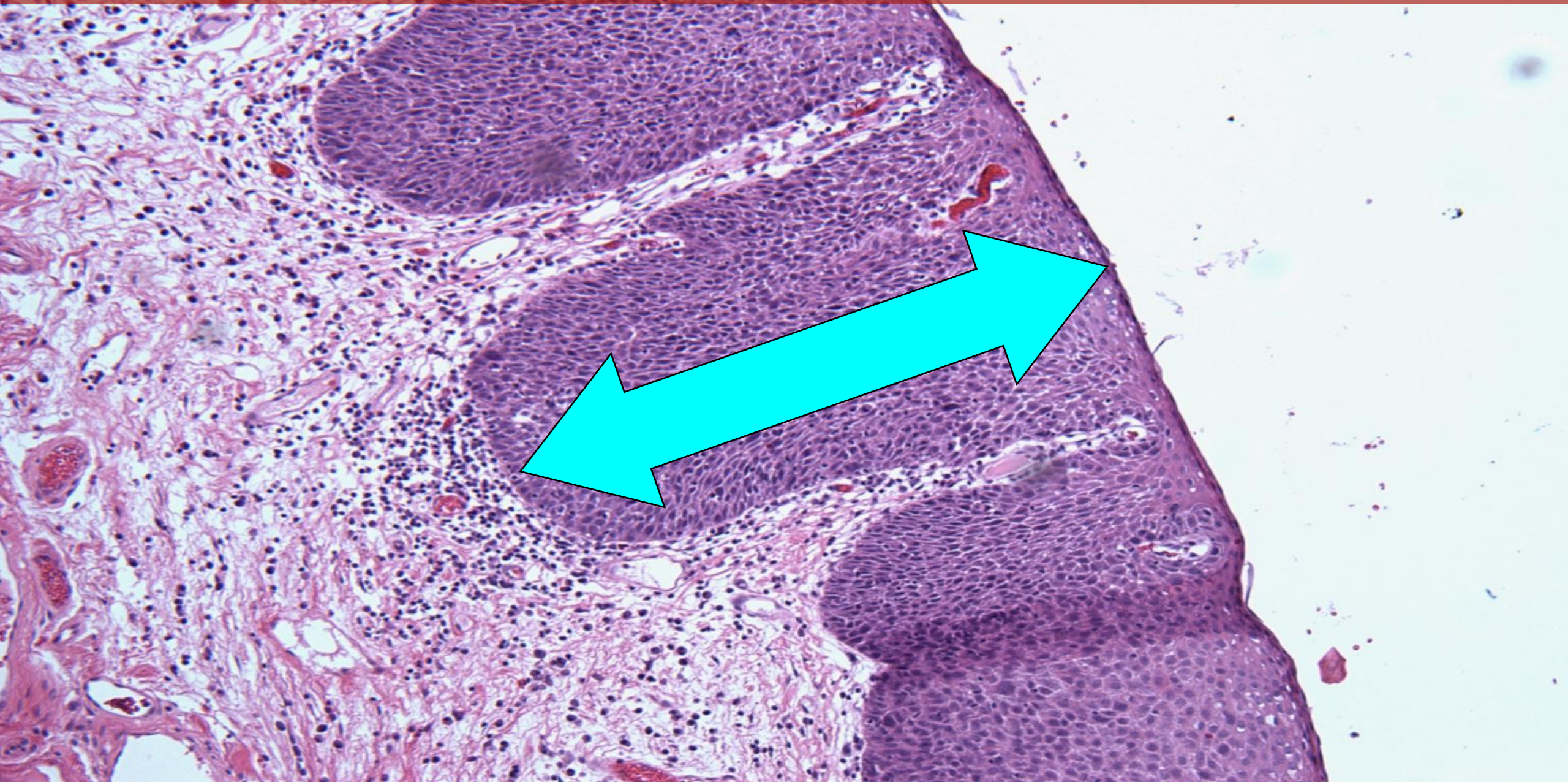
- Non-Keratinizing & Keratinizing Dysplasia:
  - Potentially reversible
  - Increased likelihood of progression to SCC , especially when diffuse
  - Synonyms: Keratosis with atypia, atypia, dysplasia, SIL, SIN
  - M>F
  - Mean age: sixth decade
  - 1-2% annual transformation rate (estimate)


MILD DYSPLASIA

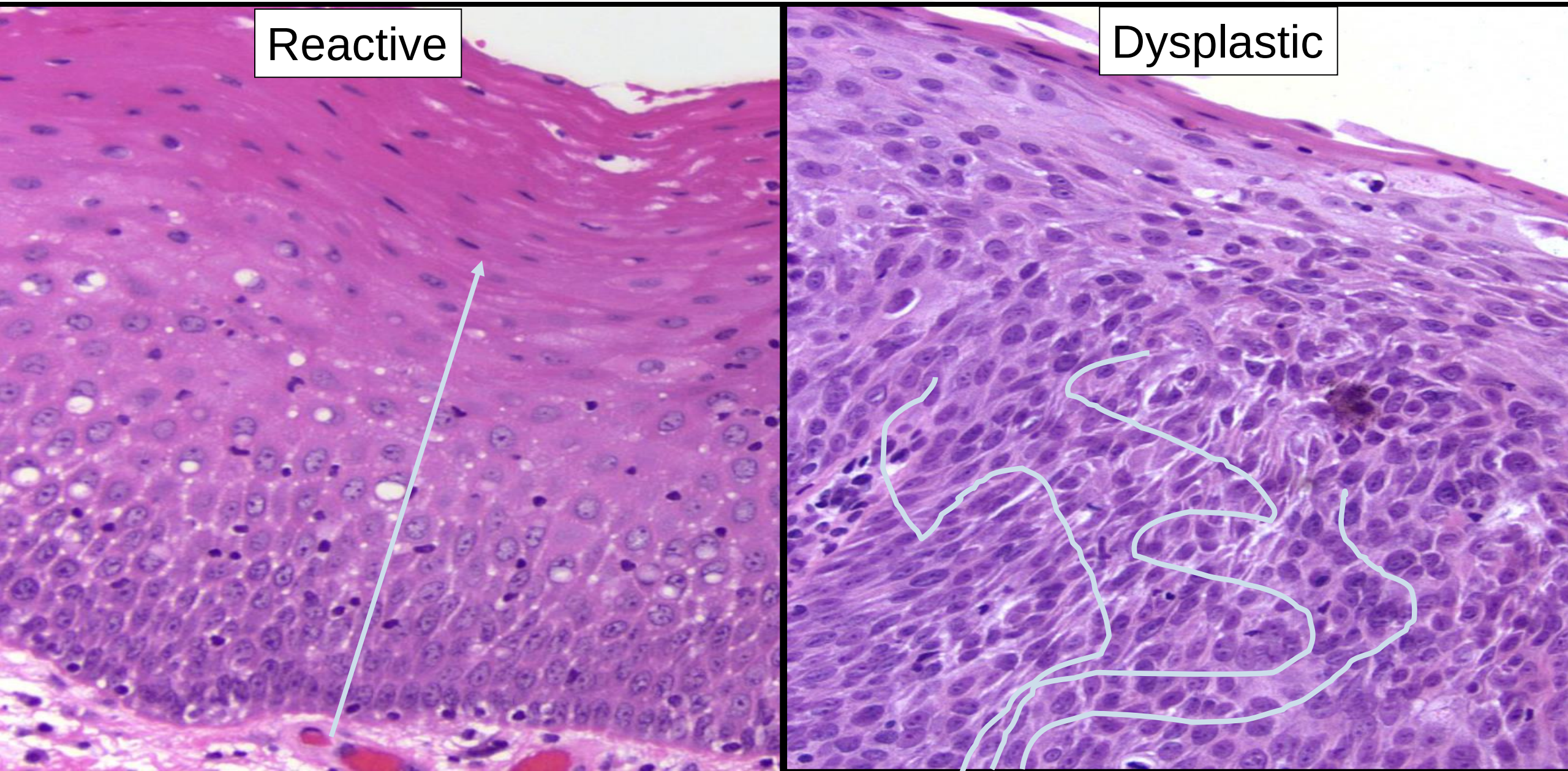
Moderate Dysplasia



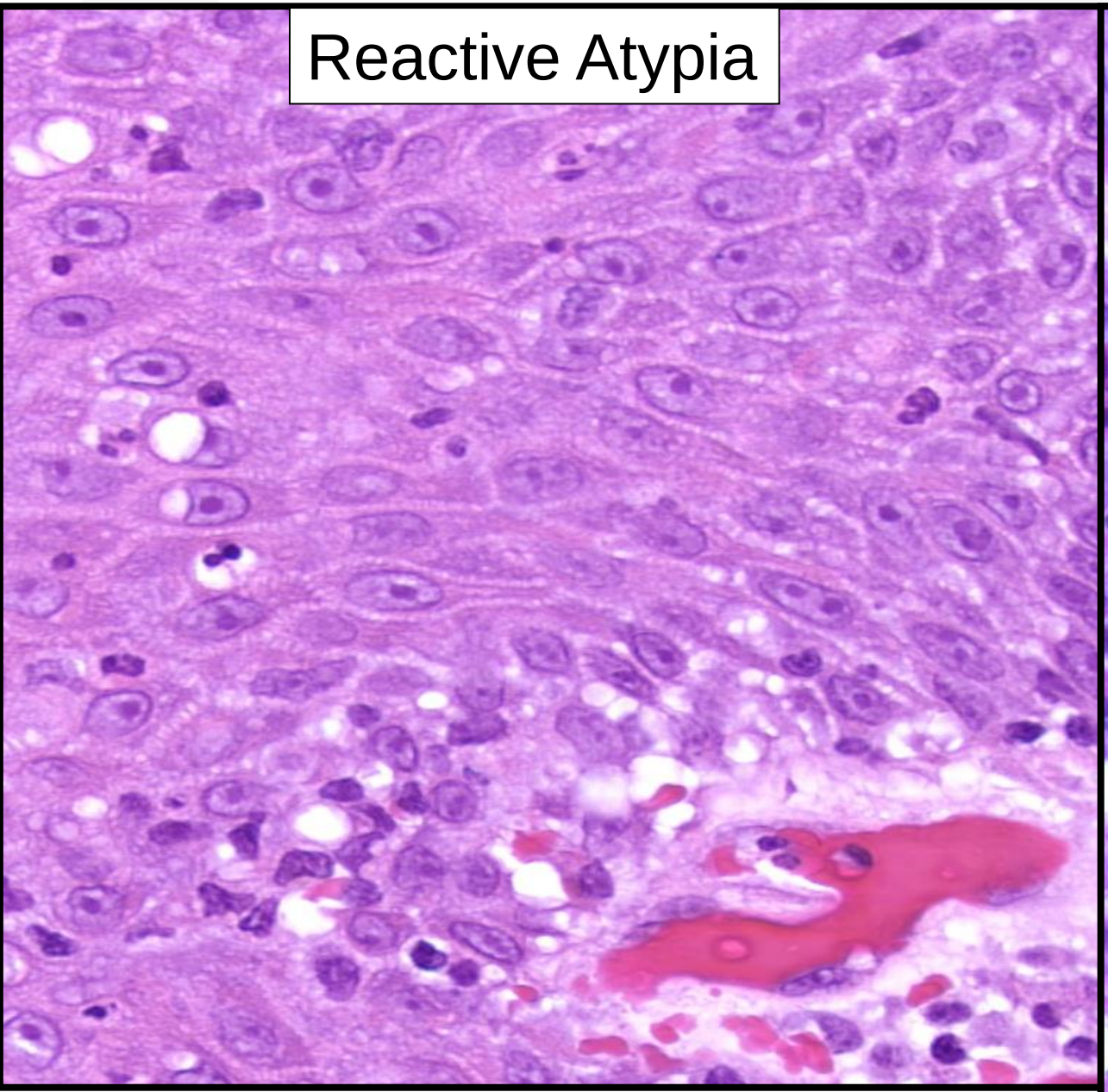
Severe Dysplasia/SCCIS

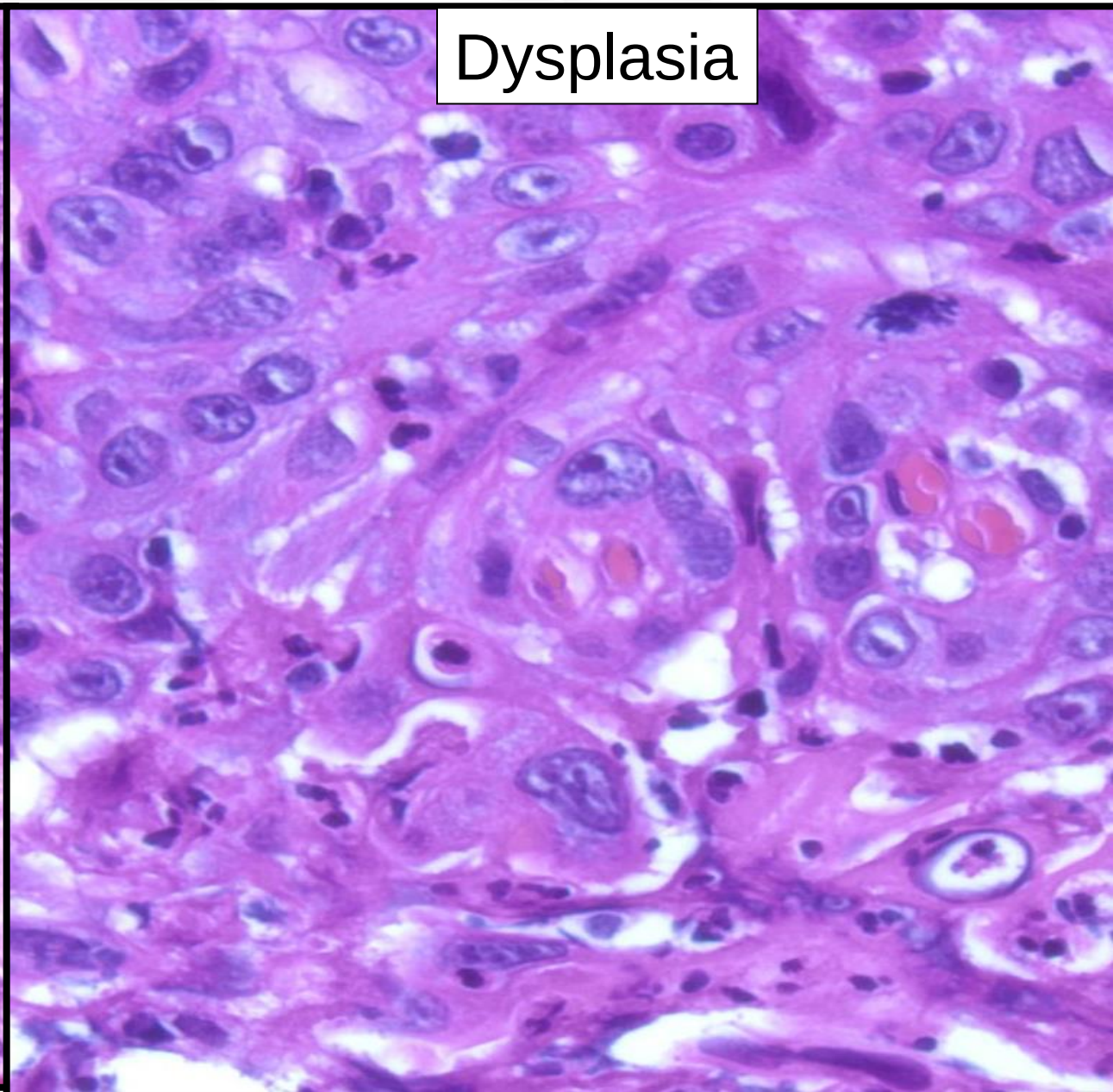


Reactive vs Dysplastic: Poor Organization and Maturation



Problem -Reactive vs Dysplastic: Atypical Cytologic Features





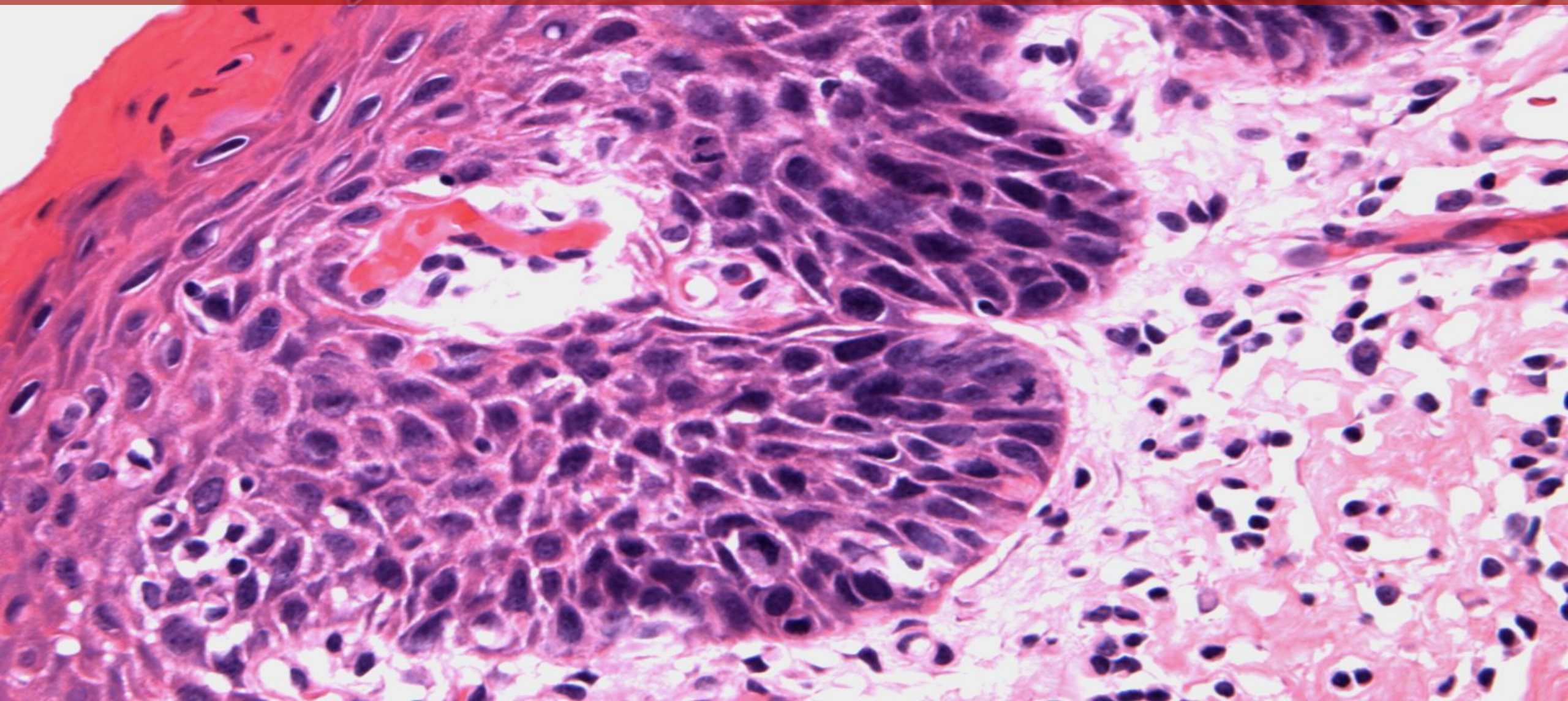
NOTE: **When the biopsy is inflamed, it can be nearly impossible to distinguish between dysplasia and reactive/inflammatory changes.**

Occasionally, p53 and Ki-67 stains can be helpful.

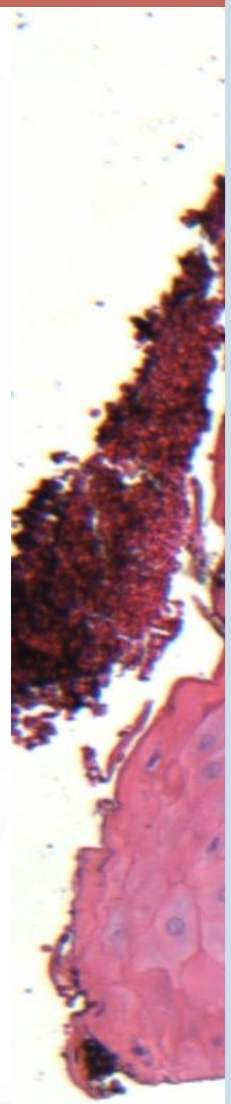
Keratinizing Dysplasia: An important entity in the UADT

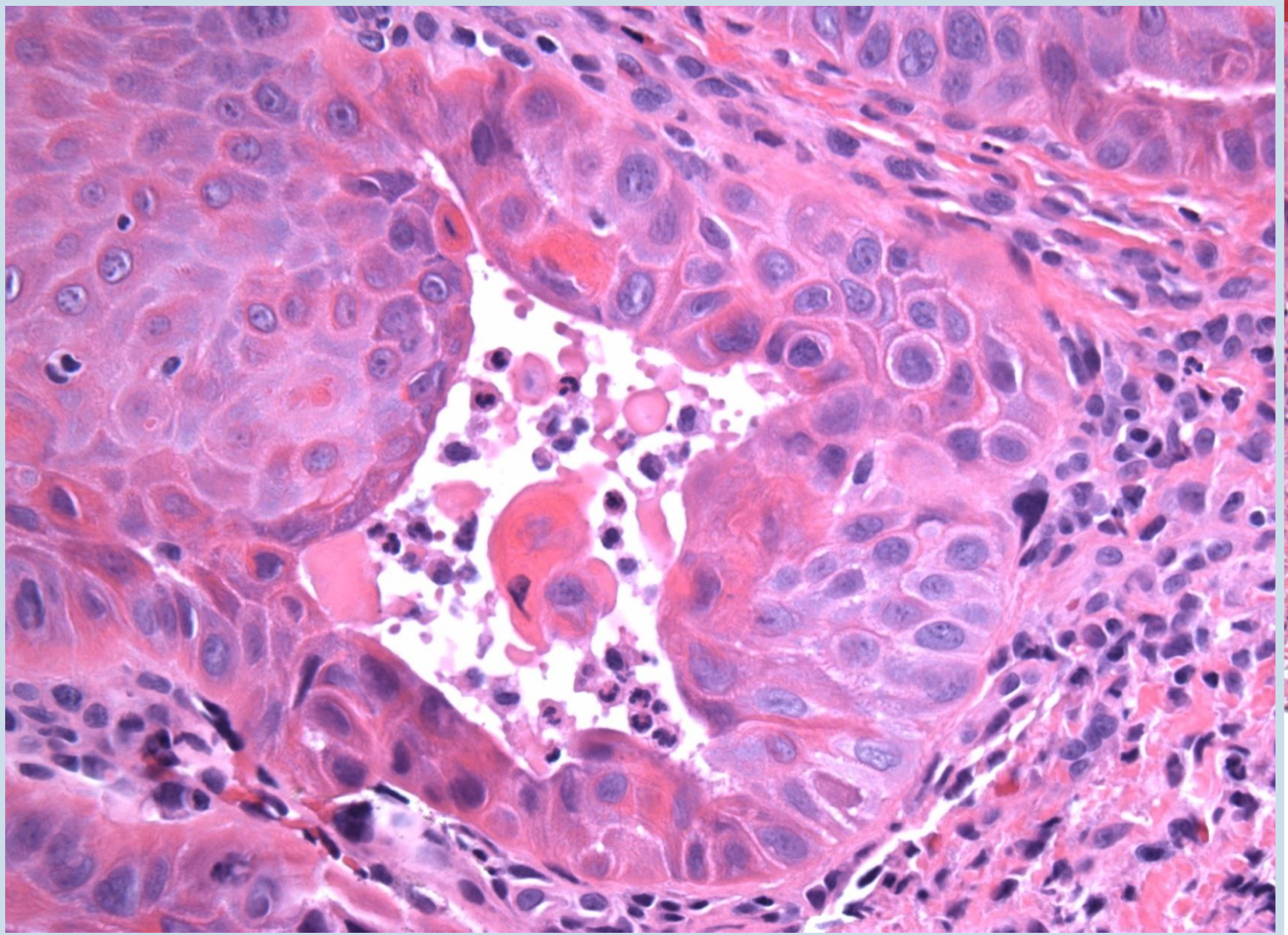
- Many UADT precursor squamous lesions are keratinizing dysplasias (aka basal layer dysplasia)
- Criteria less well defined
- CAUTION: Atypia often limited to basal layer
- Classic CIS is not a feature
- High rate of progression to invasive SCC

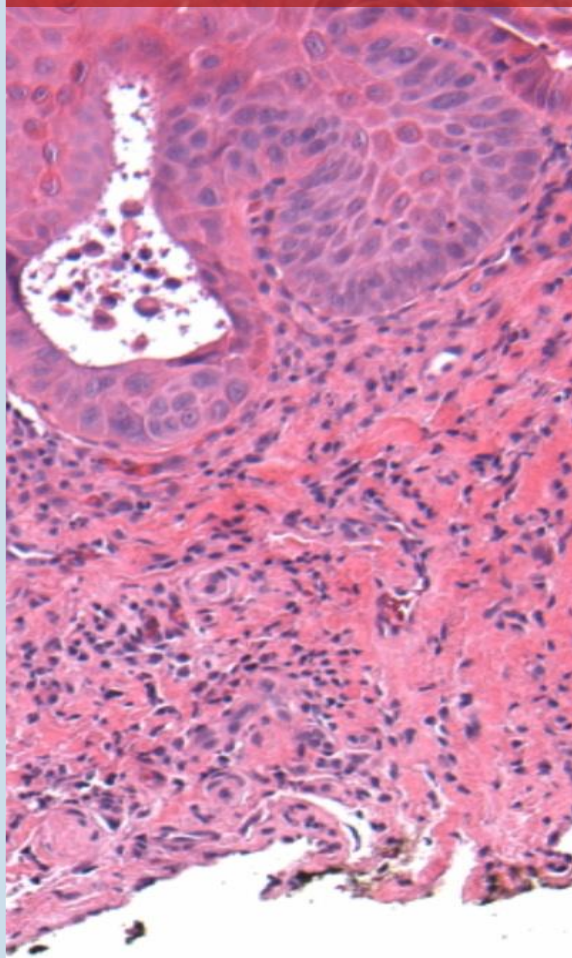
Keratinizing Dysplasia with Moderate to Severe Atypia



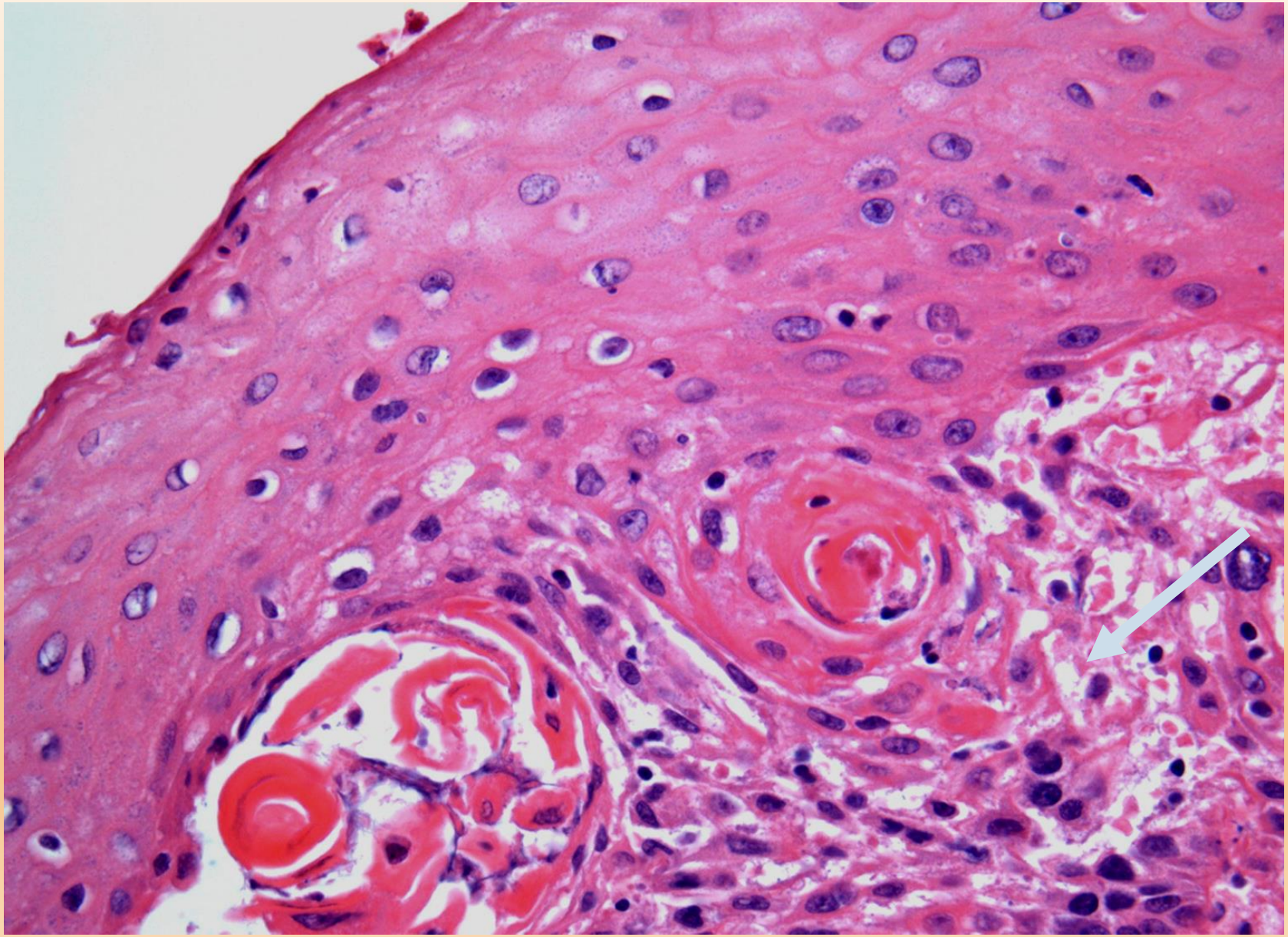
Keratinizing Dysplasia: Danger of Superficial Biopsies







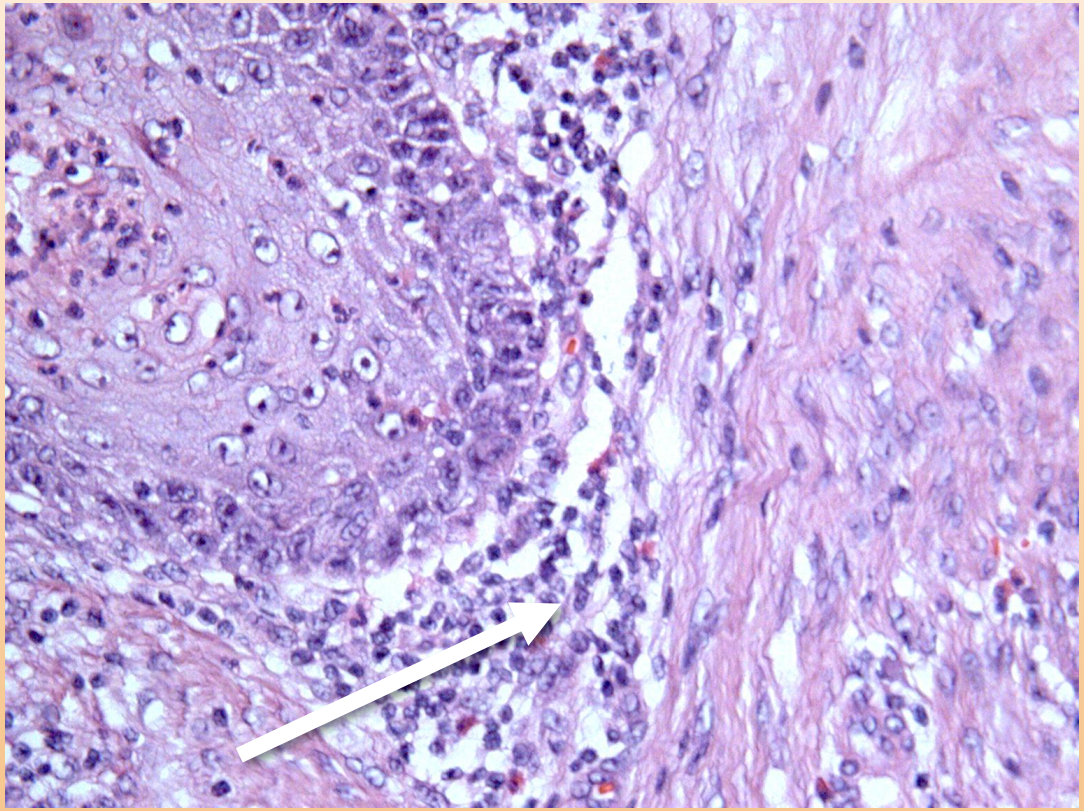
Invasive SCC Arising from Epithelial Base: “Drop down” carcinoma with deep keratinization



Dysplasia vs Invasive Squamous Cell Carcinoma

Requires:

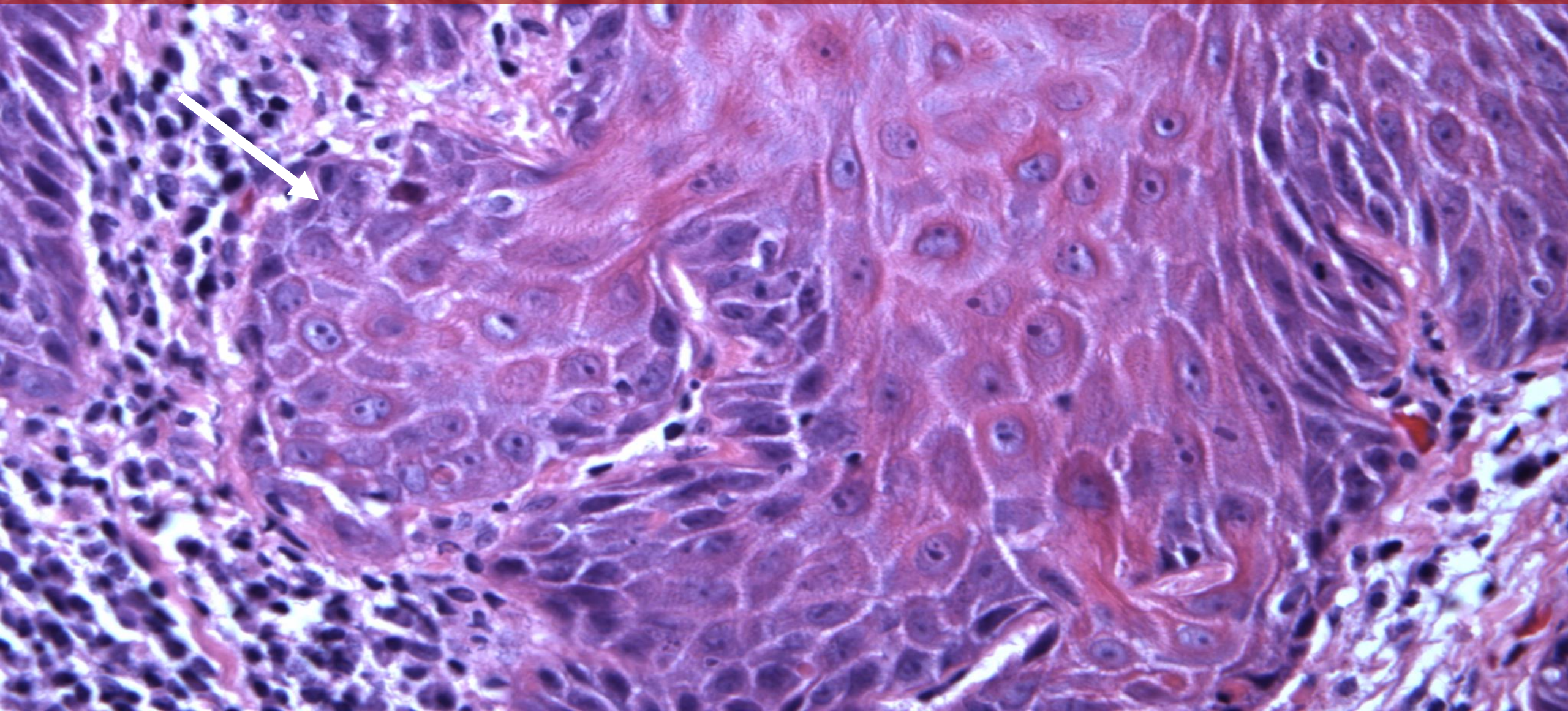
- **Properly oriented biopsy**
- **Adequate subepithelial stromal tissue with one or more of the following:**
  - **Loss of characteristic basal cell layer between the atypical squames and stroma**
  - **Desmoplastic stromal response**
  - **Complex pattern of small nests and/or single cells**
  - **Deep keratinization**



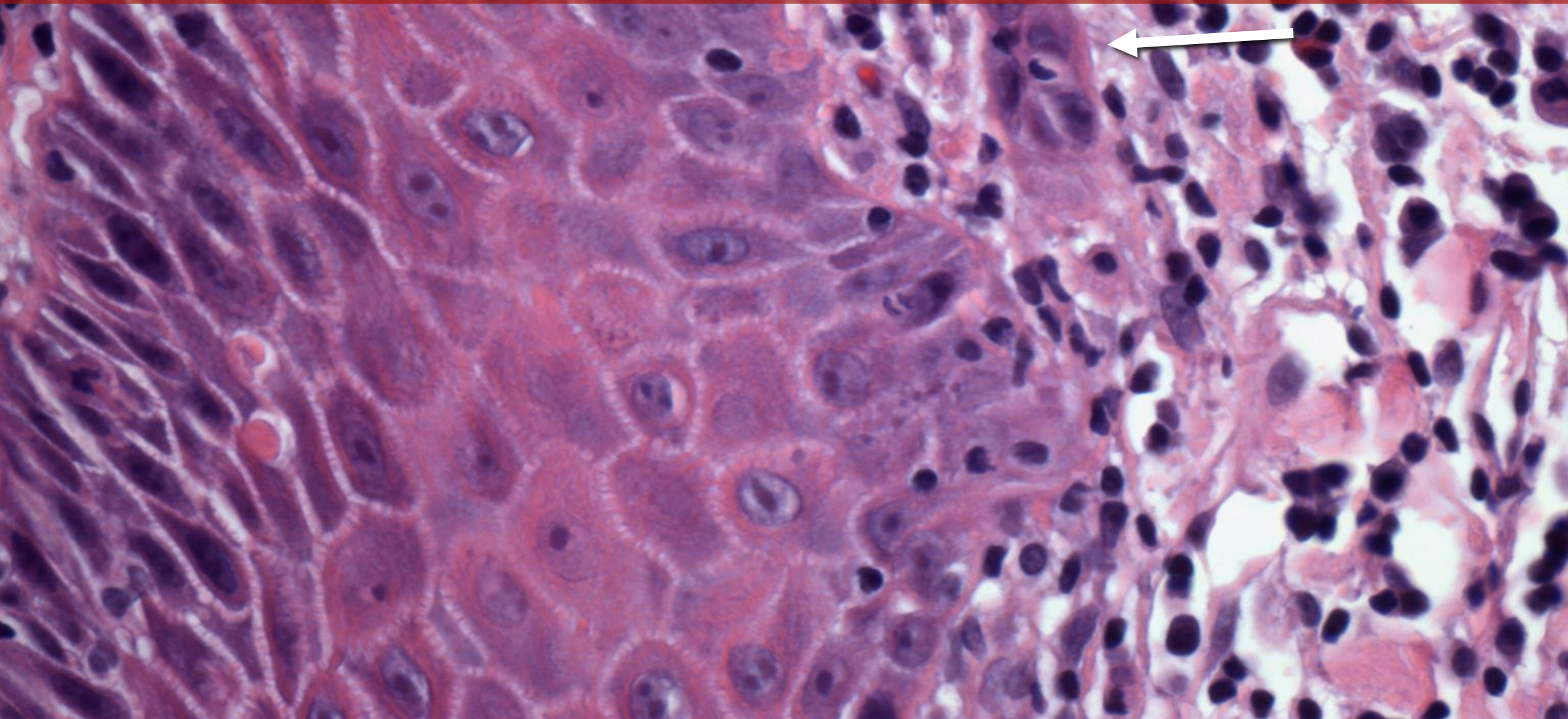
Microinvasive Squamous Cell Carcinoma

- “Microinvasive” and “superficially invasive” are synonymous terms
- Less than 2 mm invasion is often the cutoff
- Can be difficult to assess in an inflammatory background

Suspicious for Microinvasive SCC: Budding Pattern



Microinvasive SCC:
Detached Single Cells or Small Clusters



Key Components of a Squamous Cell Carcinoma Pathology Report

- 3 Histologic Categories of SCC:
  - In situ
  - Microinvasive/superficially invasive
  - Deeply invasive
- Keratinizing vs non-keratinizing
- 3 Histologic grades
- Specific variant of SCC

- Reports should also mention:
  - Specific positive margin(s)
  - Distance to closest margin(s)
    - Generally, any closer than 5 mm
  - DOI
  - Presence of LVI and PNI
  - Invasion of cartilage/bone and adjacent structures

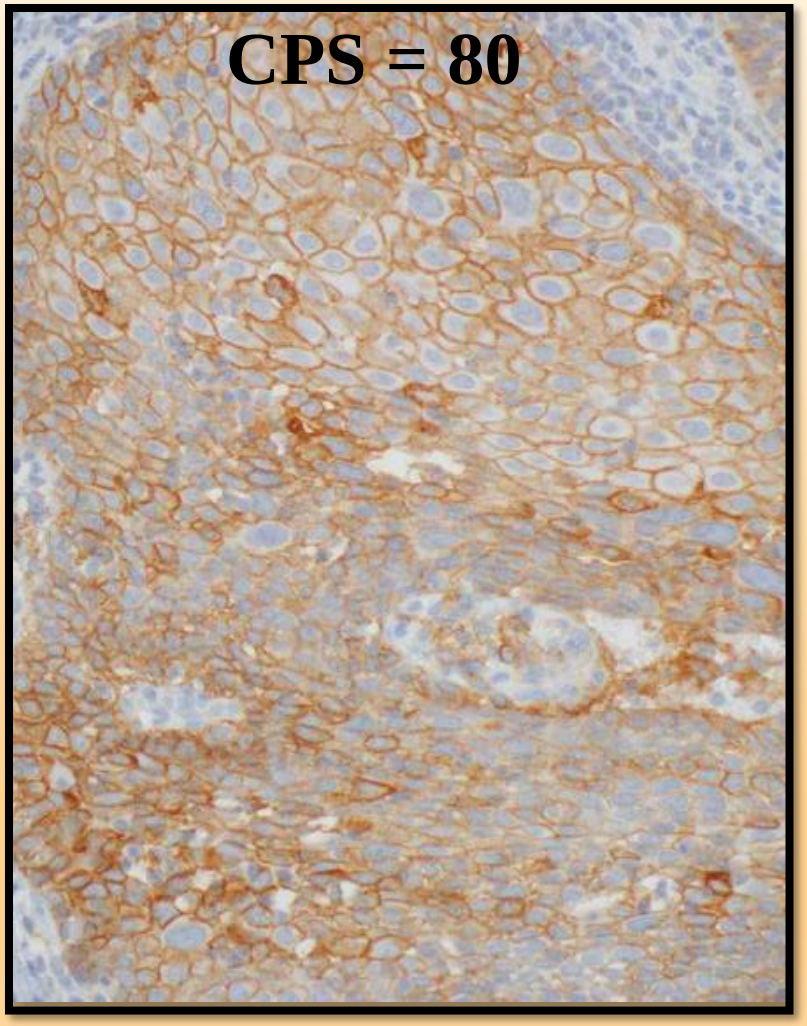
PD-L1 Testing in HN SCC

- **Reflex testing is routine practice**
- **Used for patients with aggressive HNSCC or cases that are refractory to conventional treatment or as adjuvant in clinical trials**
- **Reflexive testing to determine the CPS:**

PD-L1 EXPRESSION BY IMMUNOHISTOCHEMISTRY:

Combined Positive Score (CPS) = xx

Comment: A PD-L1 immunohistochemical stain was performed, and at least 100 tumor cells are present. The CPS is defined as the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100. The specimen is considered to have PD-L1 expression if CPS greater than or equal to 1.



Selected Variants of HNSCC

Squamous Cell Carcinoma

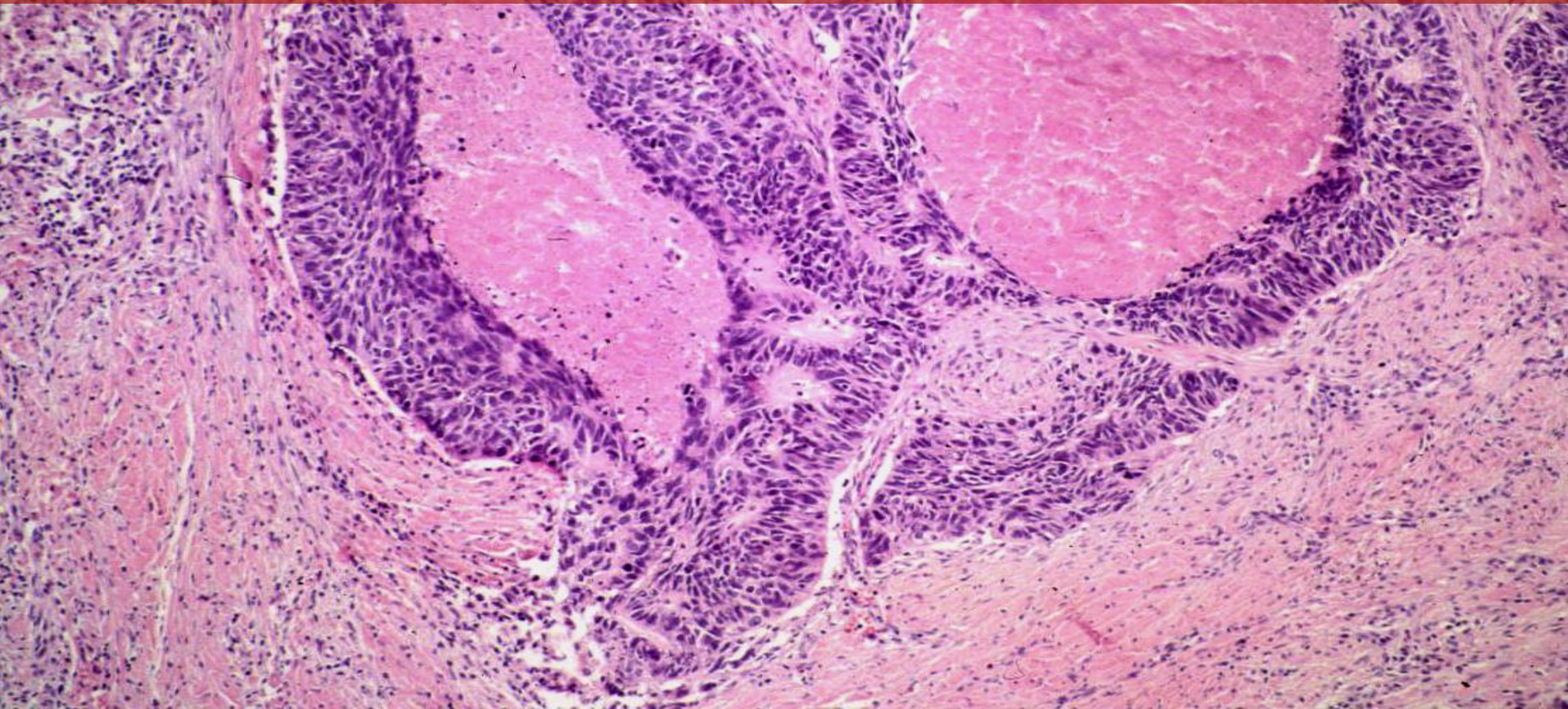
Multiple Subtypes/Variants:

- Conventional:
  - Keratinizing vs non-keratinizing
- Verrucous
- Basaloid
- Spindle cell (sarcomatoid)
- Papillary
- Adenosquamous
- Acantholytic
- HPV-associated oropharyngeal
- Lymphoepitheliomatous
- NUT

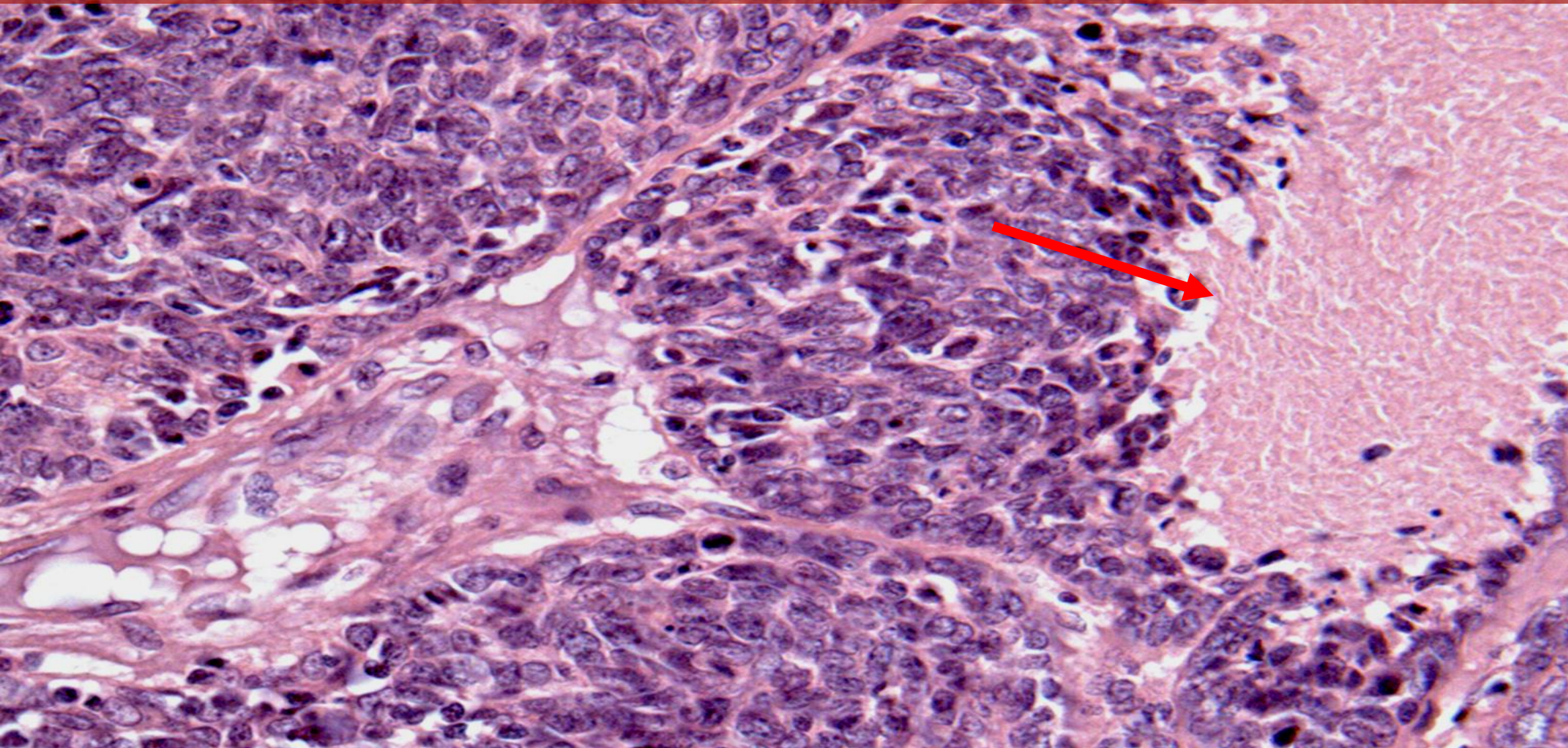
Basaloid Squamous Cell Carcinoma

- High-grade variant of SCC
- Often aggressive/poor prognosis
- <3 year average survival
- Elderly males
- BOT, hypopharynx, supraglottic larynx
- Alcohol, tobacco
- Negative for HPV

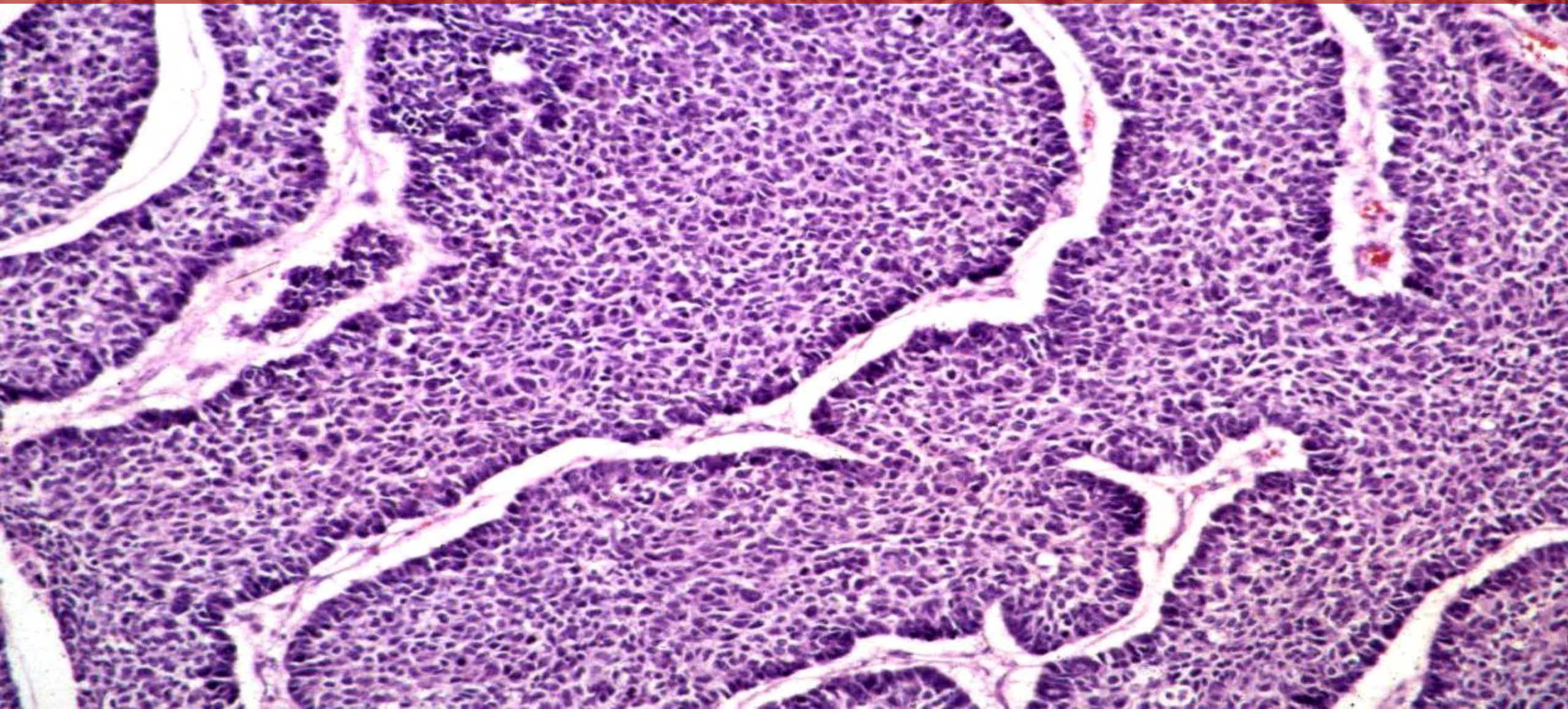
Basaloid Squamous Cell Carcinoma: Comedonecrosis; LOH at chromosomes 9 & 11



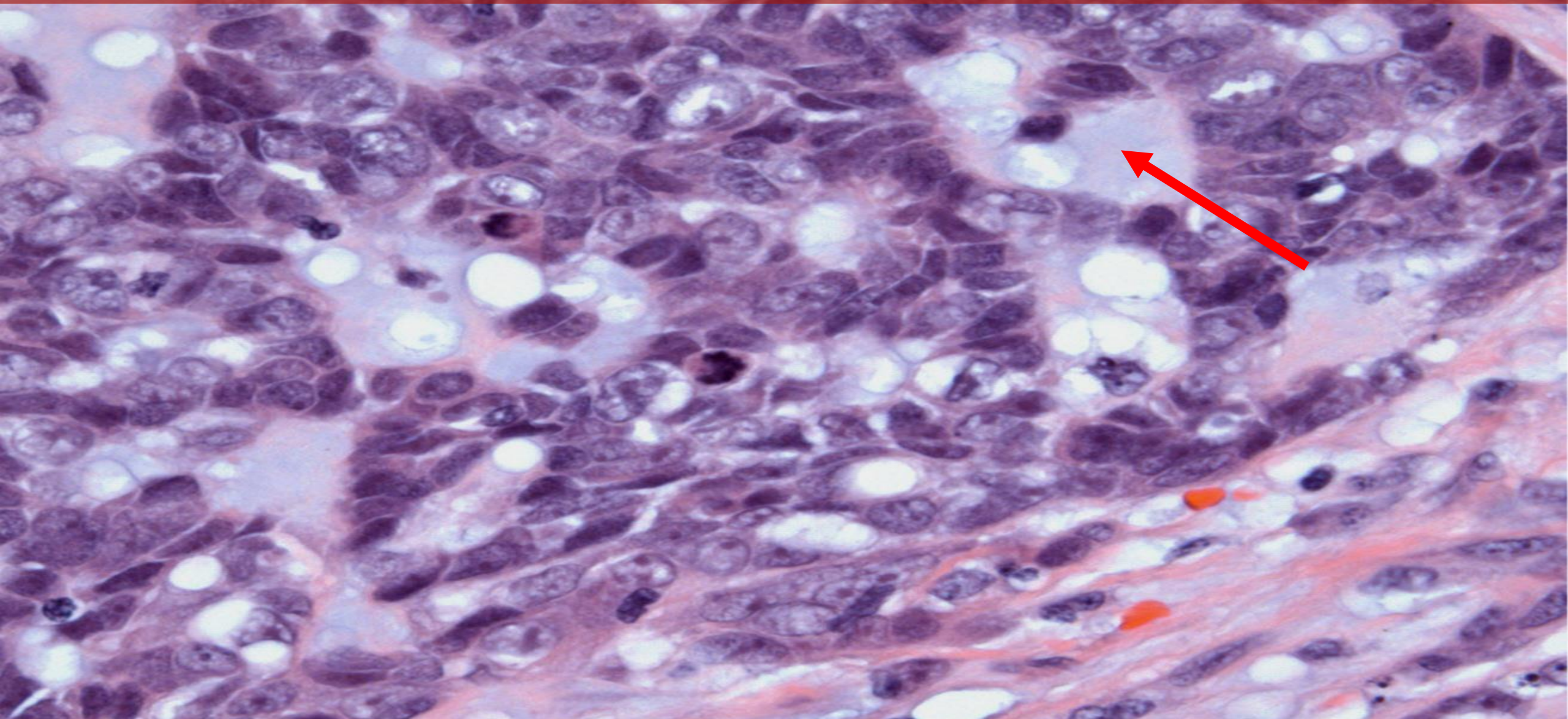
Basaloid Squamous Cell Carcinoma



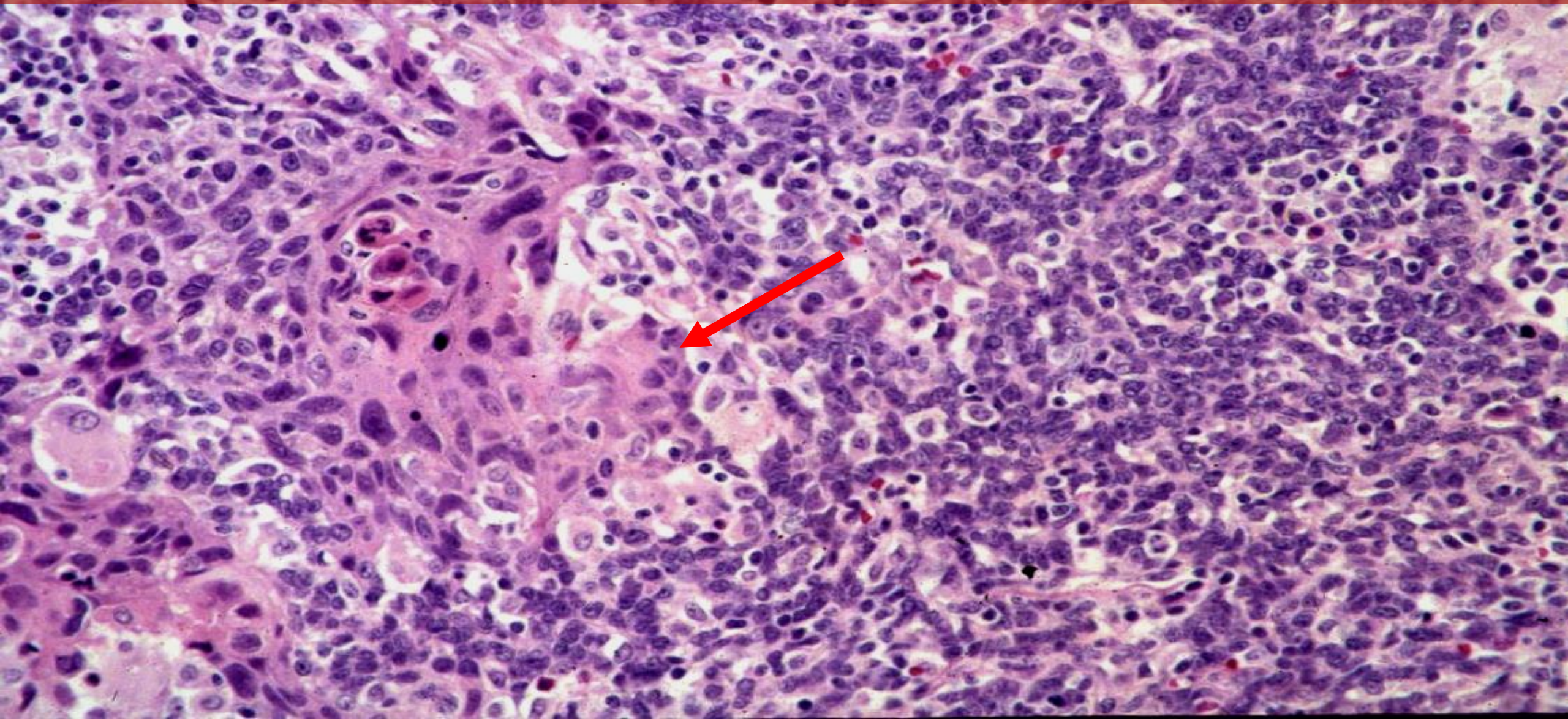
Basaloid Squamous Cell Carcinoma: Peripheral Palisading



Basaloid Squamous Cell Carcinoma: Mucohyaline Material Can Resemble Adenoid Cystic Carcinoma



Basaloid Squamous Cell Carcinoma: Focal Keratinizing SCC



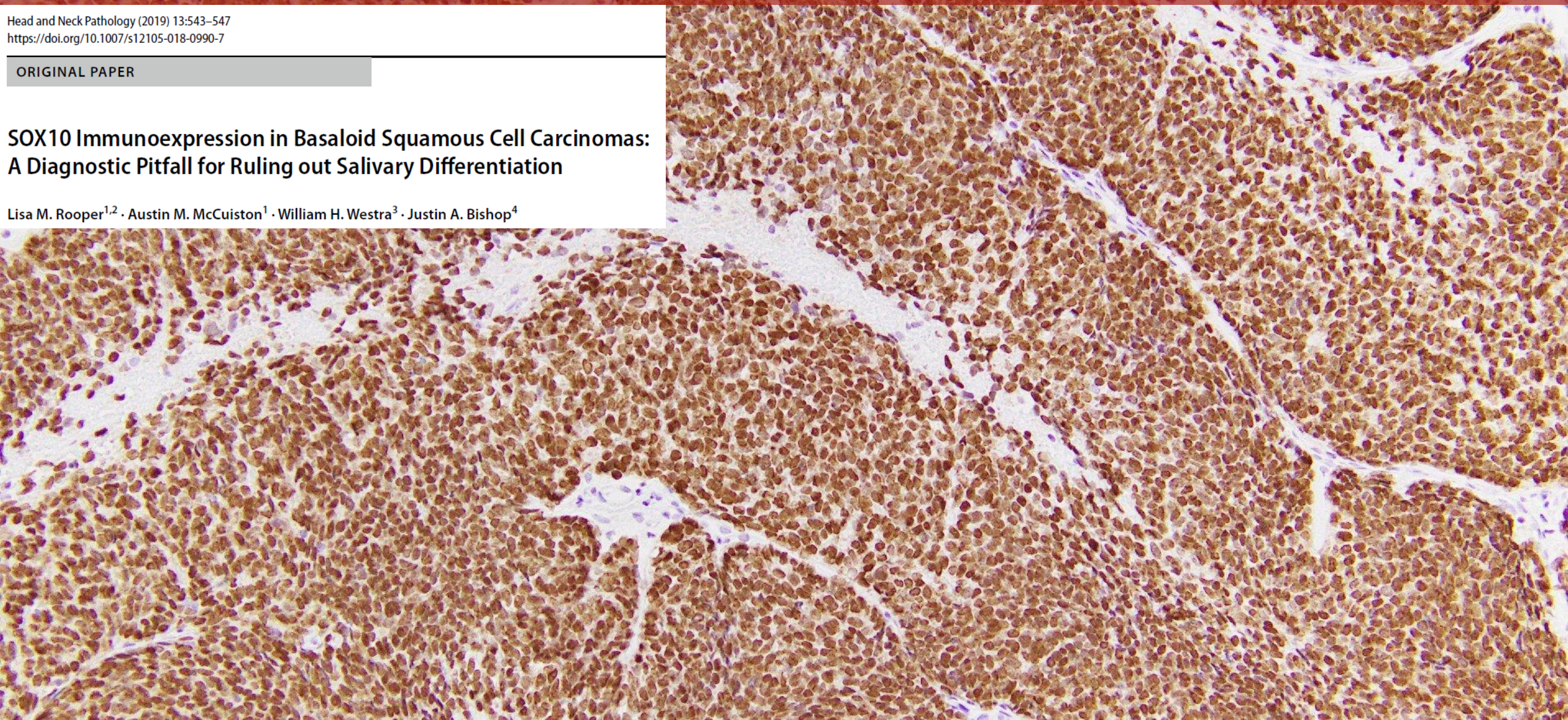
Basaloid Squamous Cell Carcinoma: Often Positive for SOX-10

Head and Neck Pathology (2019) 13:543–547
https://doi.org/10.1007/s12105-018-0990-7

ORIGINAL PAPER

SOX10 Immunoexpression in Basaloid Squamous Cell Carcinomas: A Diagnostic Pitfall for Ruling out Salivary Differentiation

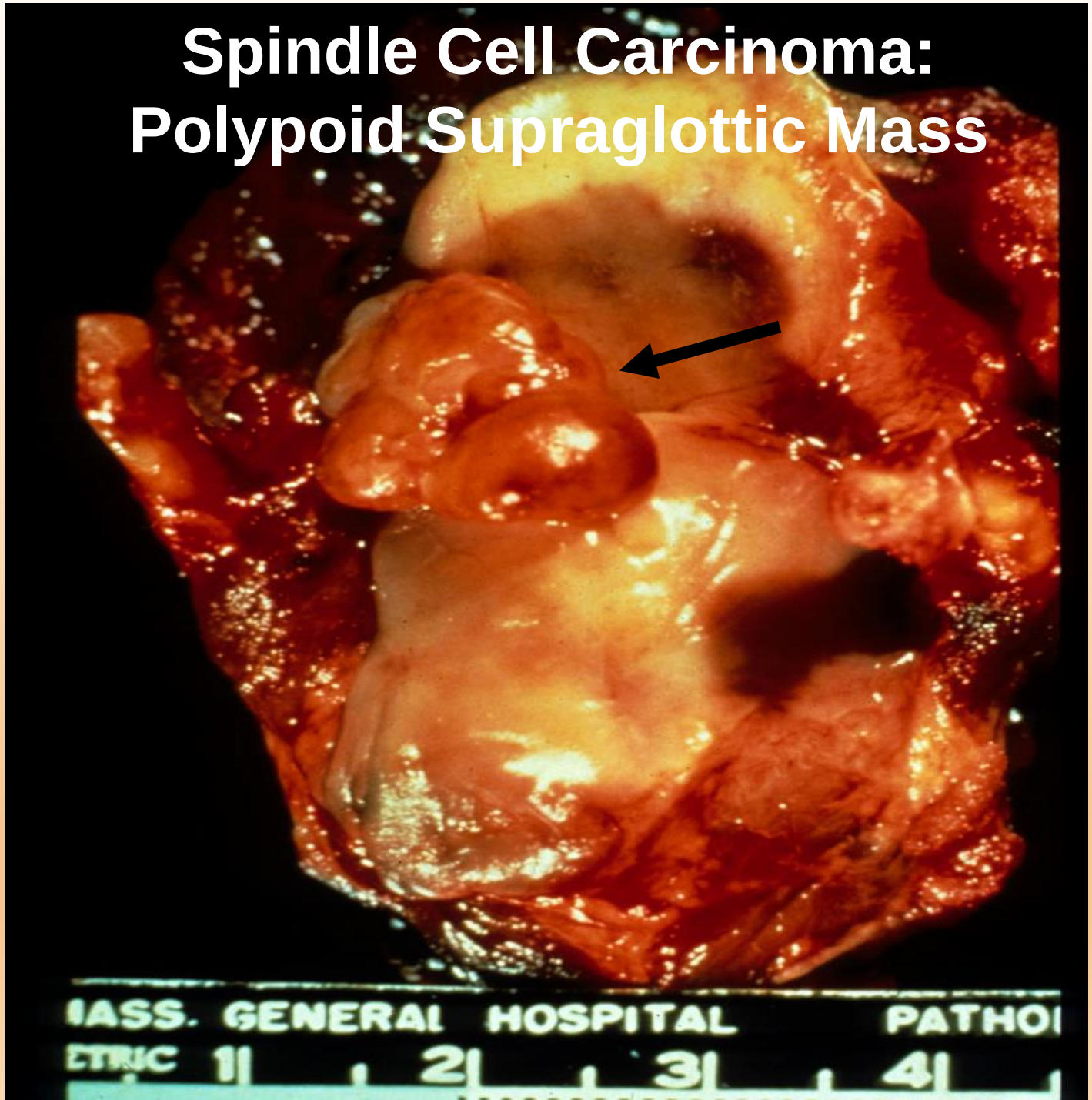
Lisa M. Rooper[1,2] · Austin M. McCuiston[1] · William H. Westra[3] · Justin A. Bishop[4]



Spindle Cell Carcinoma

- Aka Sarcomatoid carcinoma
- 85% in men (6th to 8th decade)
- Supraglottic larynx, oral cavity, skin, tonsil
- ± Prior irradiation
- More aggressive than conv. SCC
  - Less responsive to RT
- Often presents as a polypoid or fungating mass

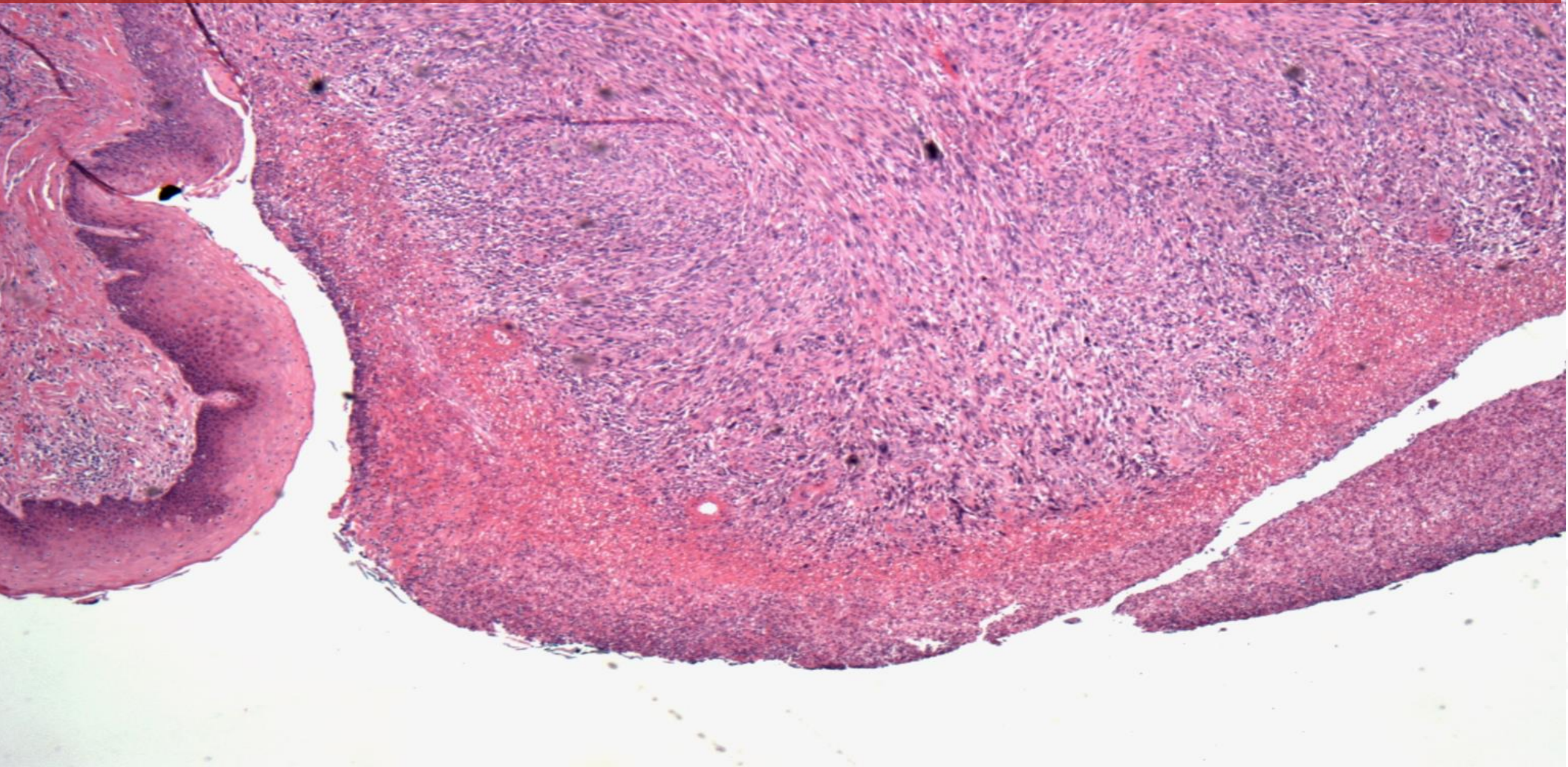
Spindle Cell Carcinoma: Polypoid Supraglottic Mass



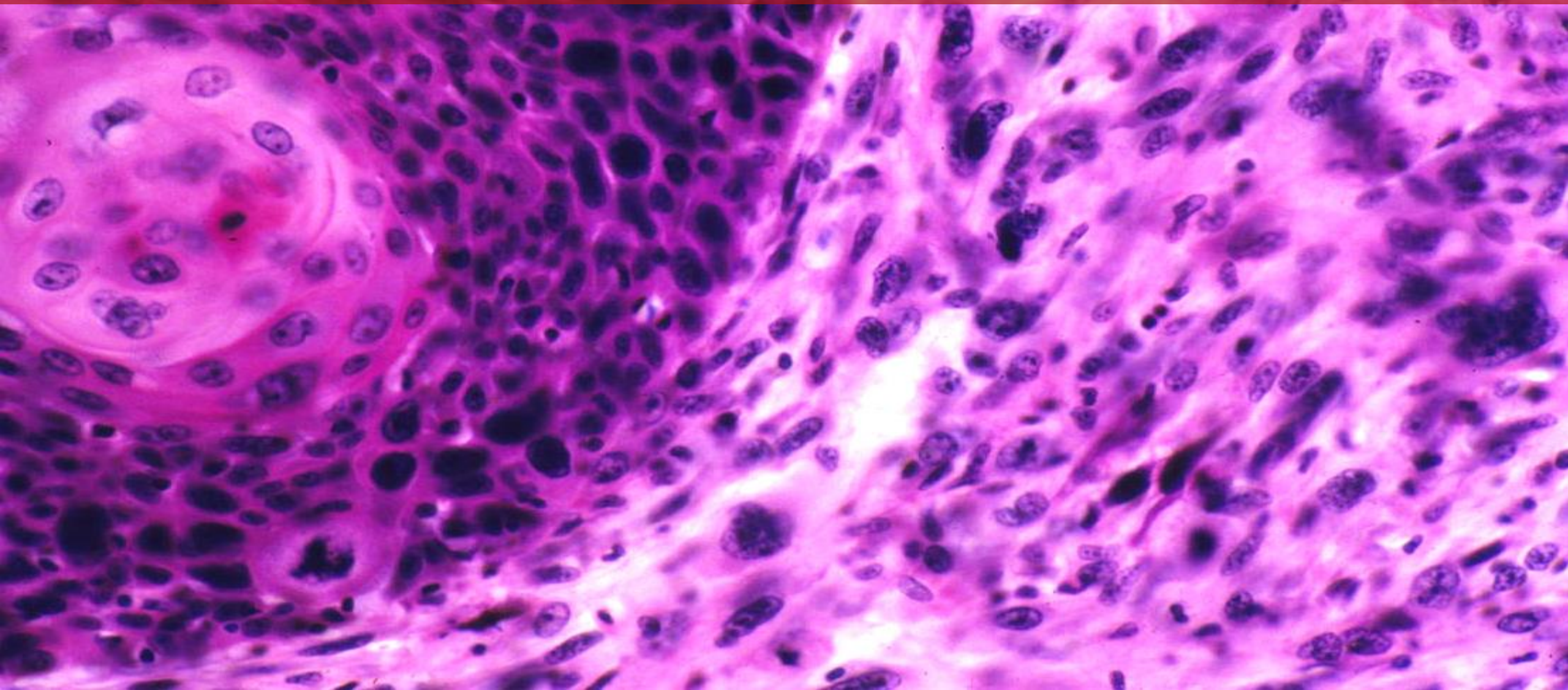
Spindle Cell Carcinoma

- Synchronous HG dysplasia/Conventional SCC
- Histogenesis of the spindled cells is controversial – favored to be epithelial
- May be keratin negative in up to 40% of cases
- Keratin panel, p40/p63, p53, vimentin
- Myogenic markers may be positive

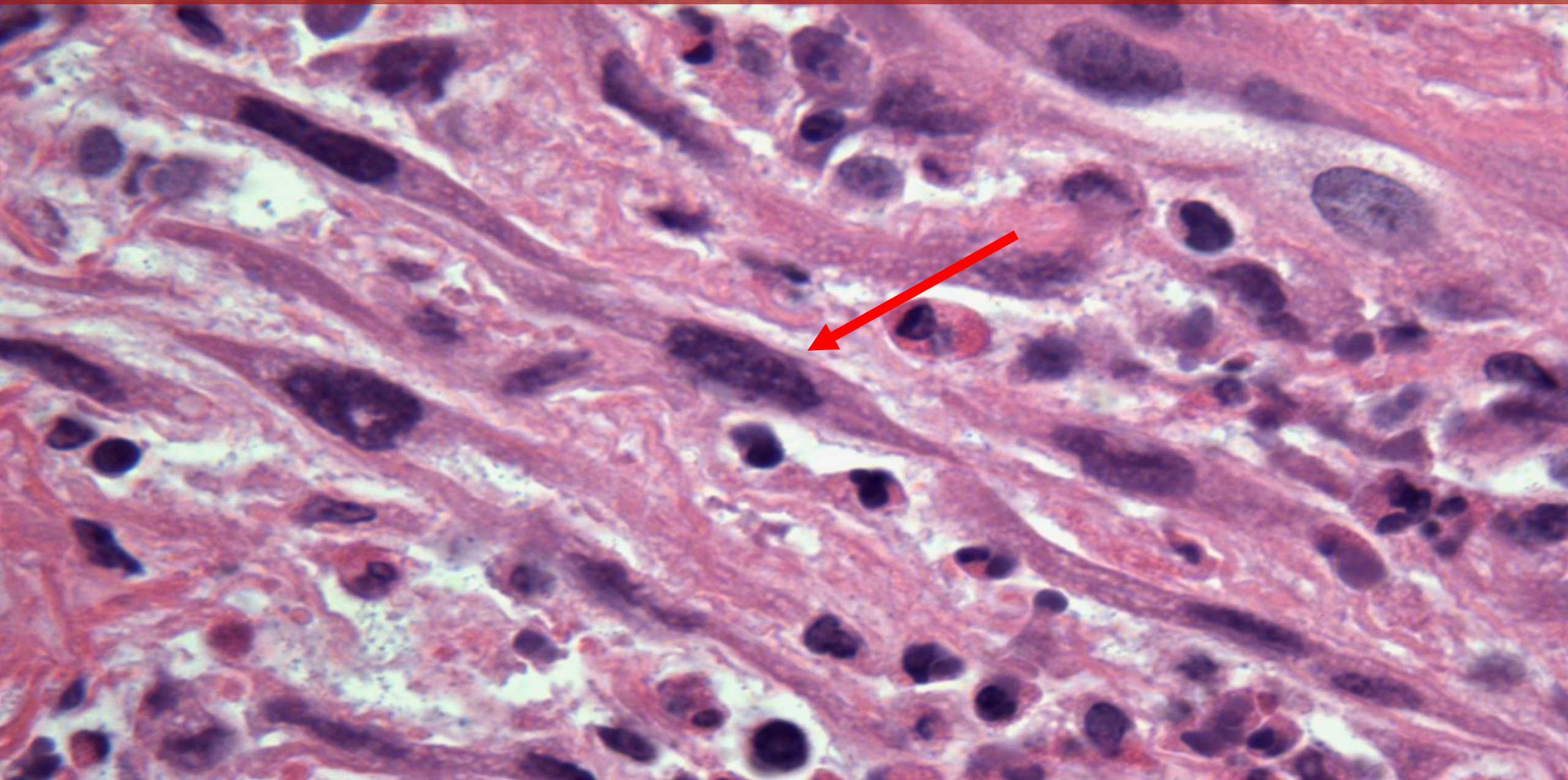
Spindle Cell Carcinoma: Ulcerated Exophytic Mass



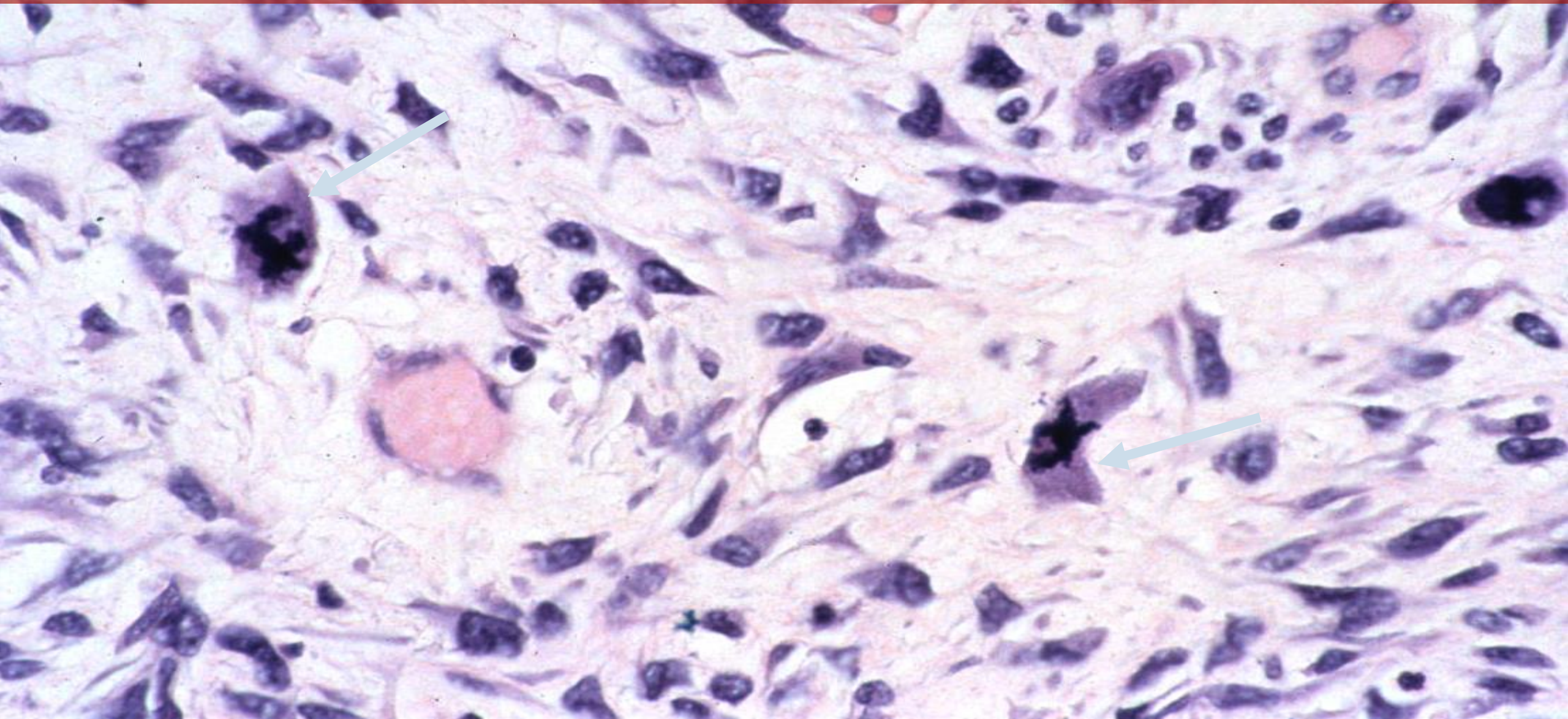
Spindle Cell Carcinoma:
LOH at chromosomes 4, 9, and 17p



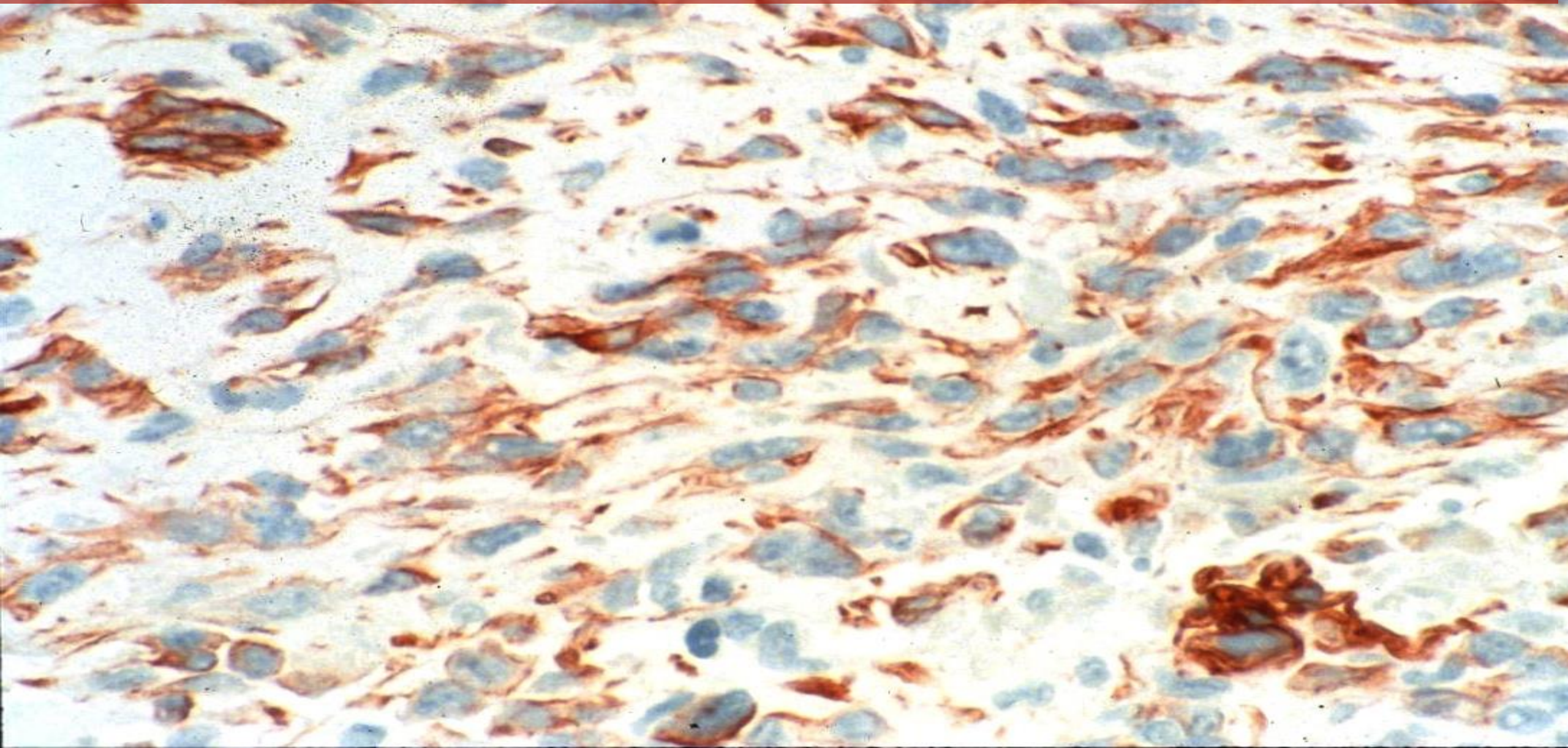
Malignant Spindle Cell Proliferation



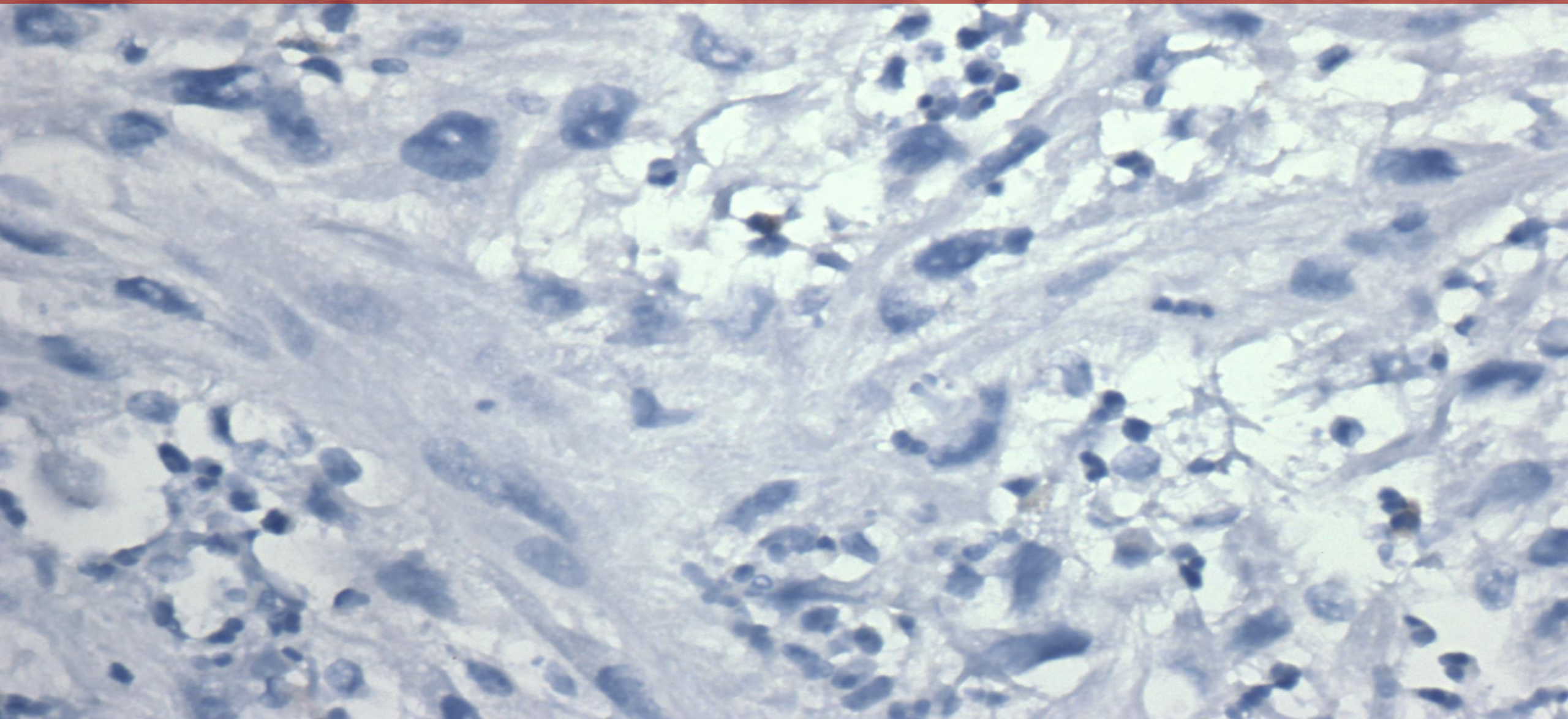
Spindle Cell Carcinoma: Marked Pleomorphism and Atypical Mitoses



Spindle Cell Carcinoma: Keratin Positive



Spindle Cell Carcinoma:
THE PROBLEM: Keratin Negative



Spindle Cell Carcinoma: Differential Diagnosis

Reactive spindle cell lesions

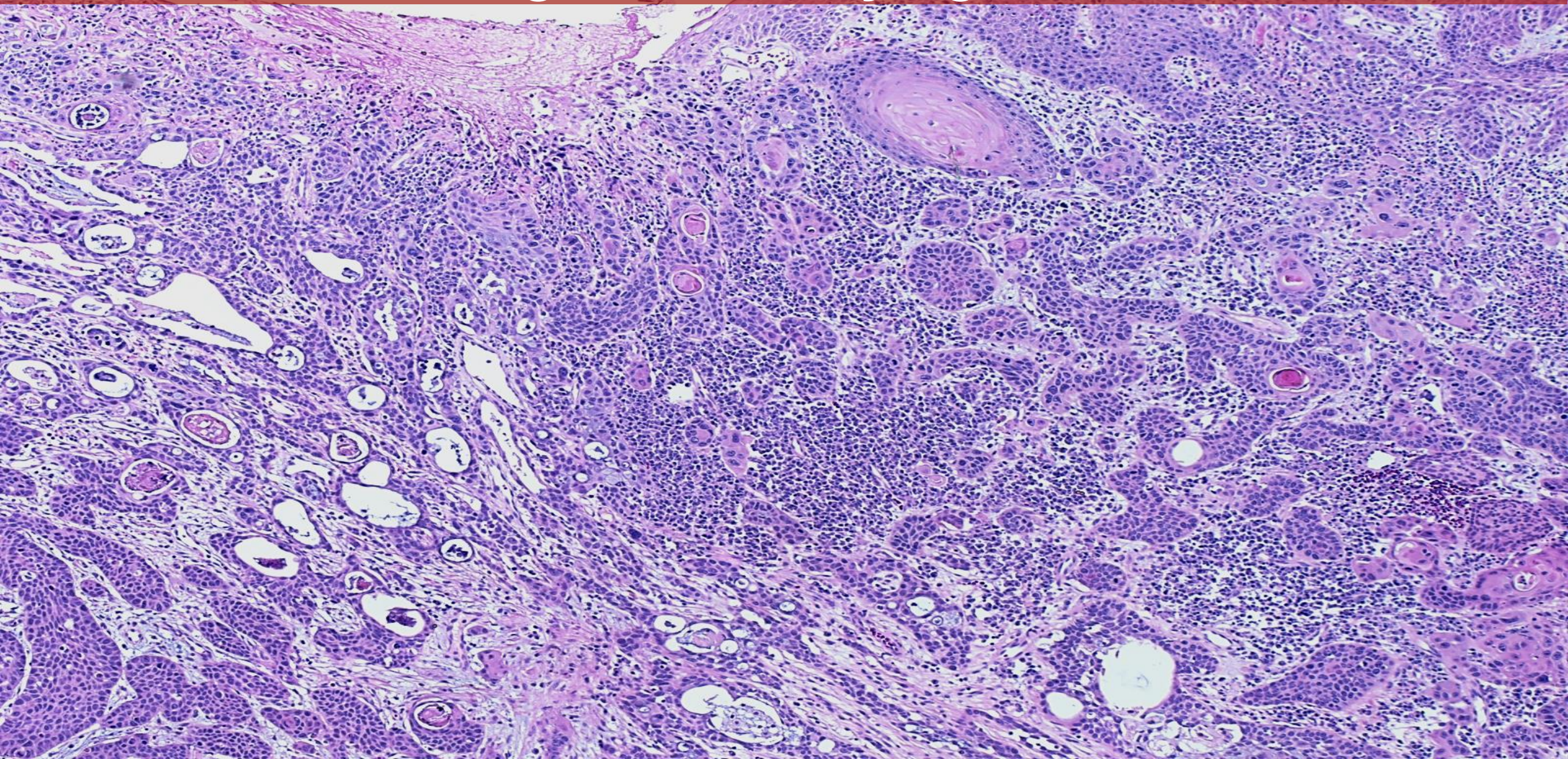
Spindle cell malignant melanoma

Sarcoma

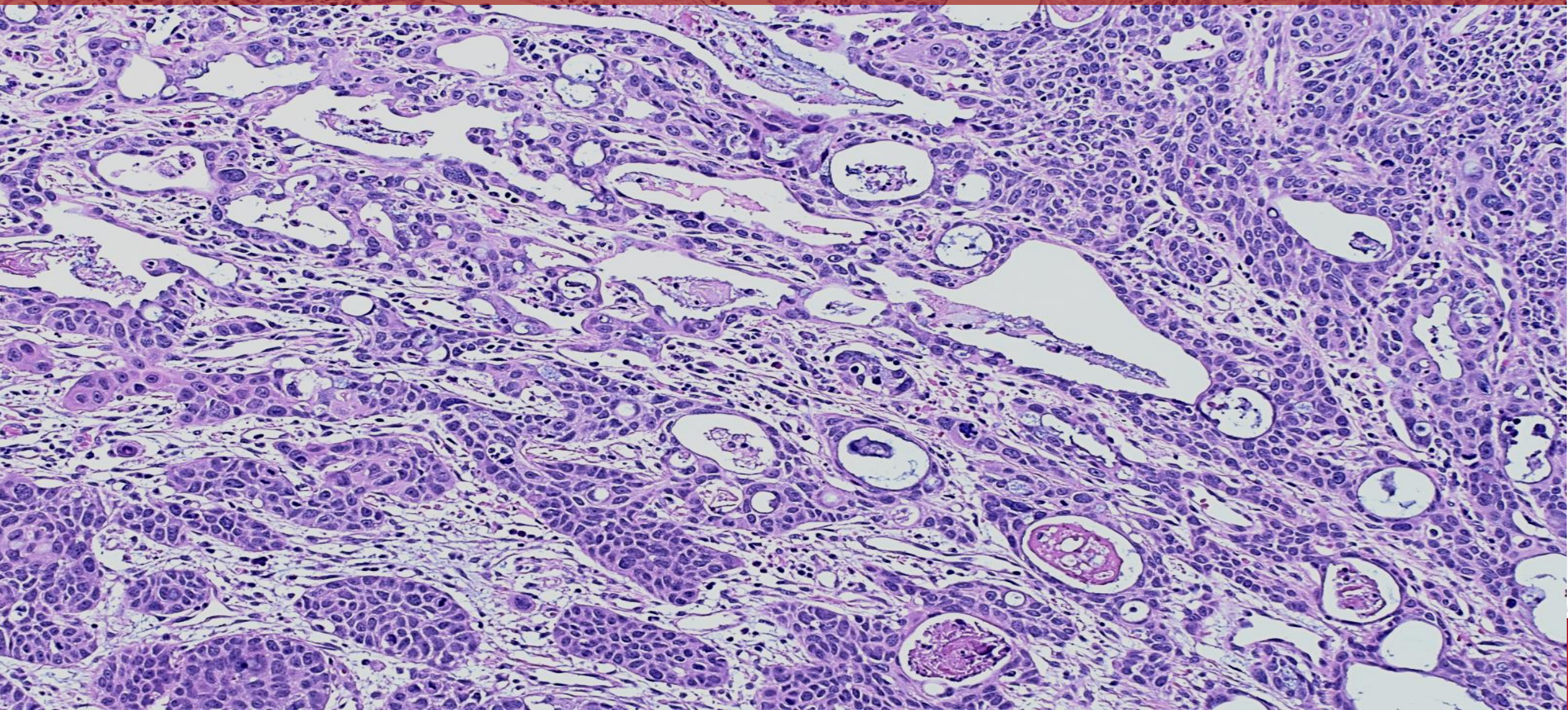
Adenosquamous Carcinoma

- Derived from overlying mucosa
- Both squamous and glandular components
  - Often separated/ adenocarcinoma deeper
- More aggressive than conventional SCC
  - 5-year survival 10-25%
- M>F; elderly
- DDX includes mucoepidermoid carcinoma

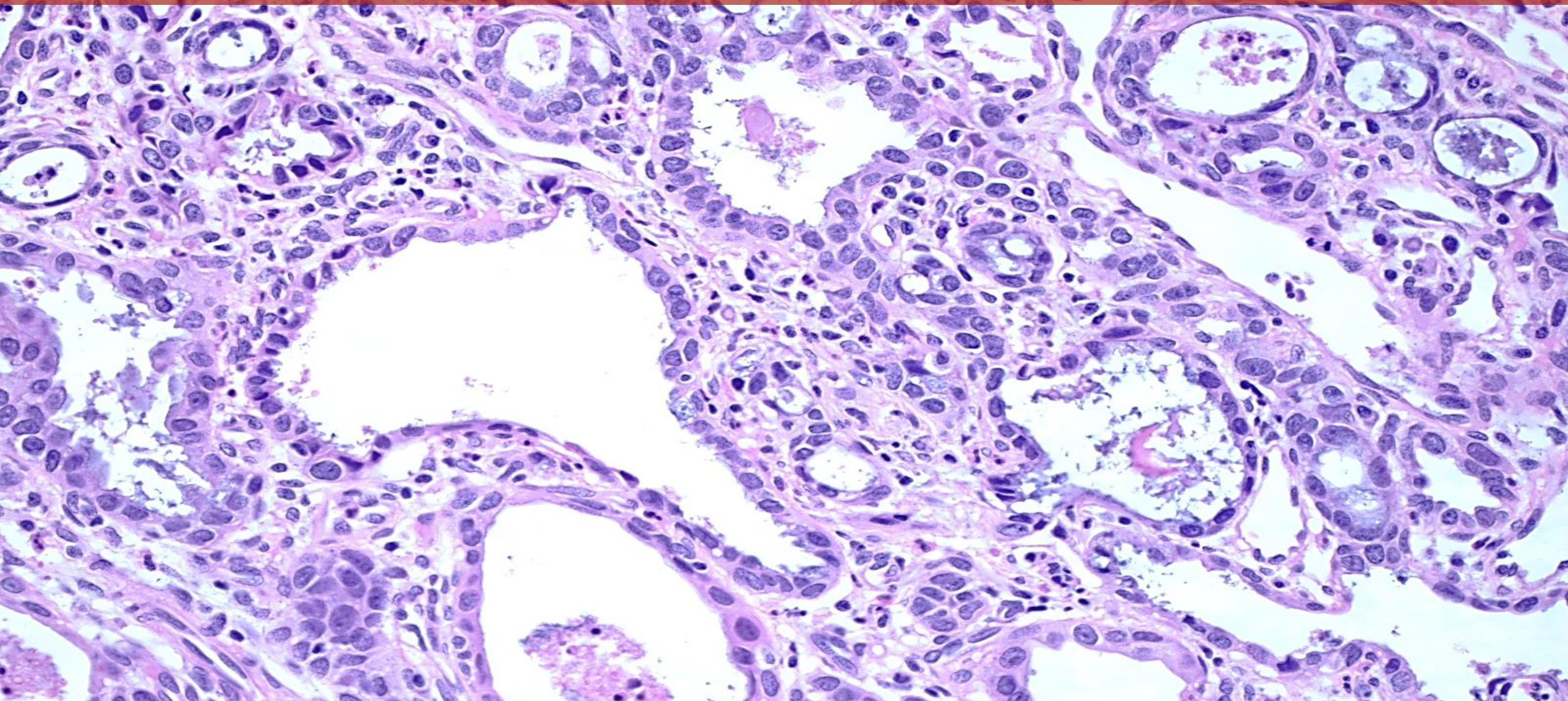
Adenosquamous Carcinoma: Arising from Overlying Mucosa



Adenosquamous Carcinoma: Both Squamous and Glandular Components



Adenosquamous Carcinoma: Deeper Glandular Component

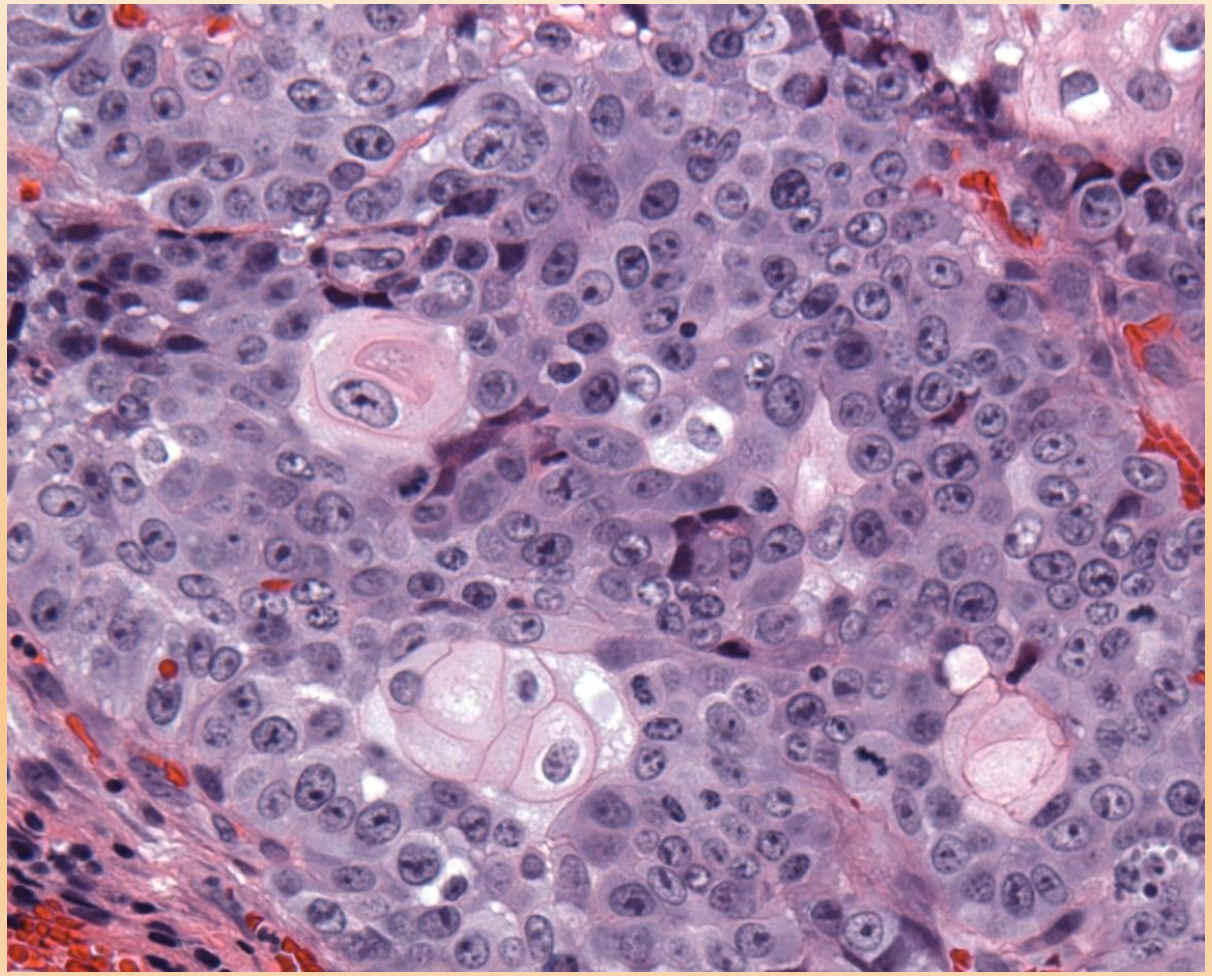


NUT Carcinoma

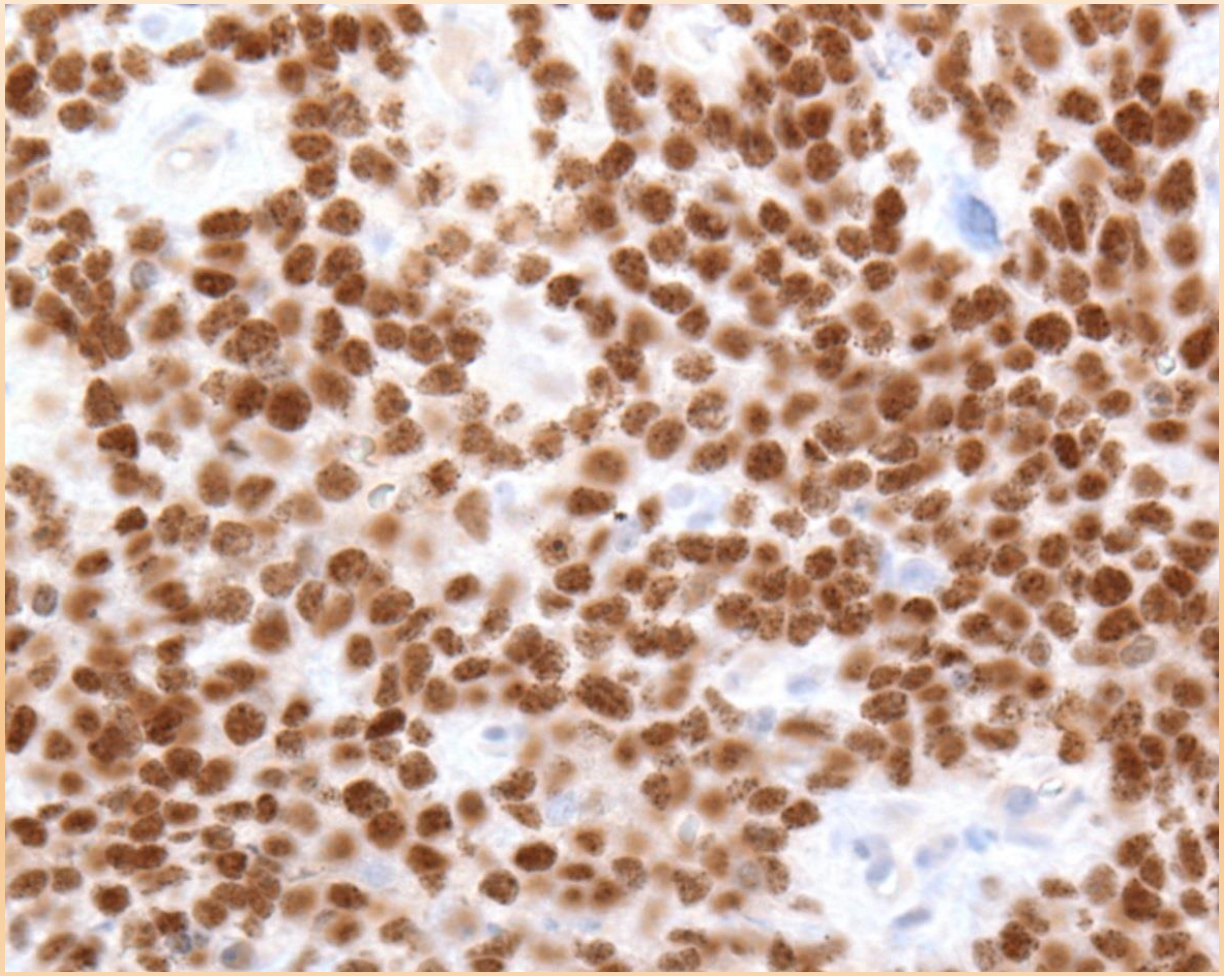
- Considered by many a lethal variant of SCC
- Rearrangement involving NUT gene and BRD gene t(15;19) or t(9;15)
- Head and neck & mediastinum
- M=F
- <50 years old
- Positive for keratin 5/6, P63, p40, NUT

NUT Midline Carcinoma: Antibody is Most Useful

PD & Abrupt Keratinizing SCC



NUT+



HPV-Associated HNSCC

HPV "Epidemic" in HNSC

HPV-Associated Head and Neck Cancer: A Virus-Related Cancer Epidemic

Trends in Head and Neck Cancer Incidence in Relation to Smoking Prevalence

An Emerging Epidemic of Human Papillomavirus-Associated Cancers?

- Reflex testing for HR-HPV is indicated for certain HN cancers:
  - Diagnosis
  - Prognosis
  - Guide Management
- Guidelines are needed to establish:
  - When should reflex testing be performed?
  - Which testing method(s) should be used?
  - How should HPV testing be applied to Cytology?

Clinical presentation of HPV-associated HNSCC is different than smoking-related cancer

This pertains especially to the oropharynx

More likely to be younger, male, married, and college educated

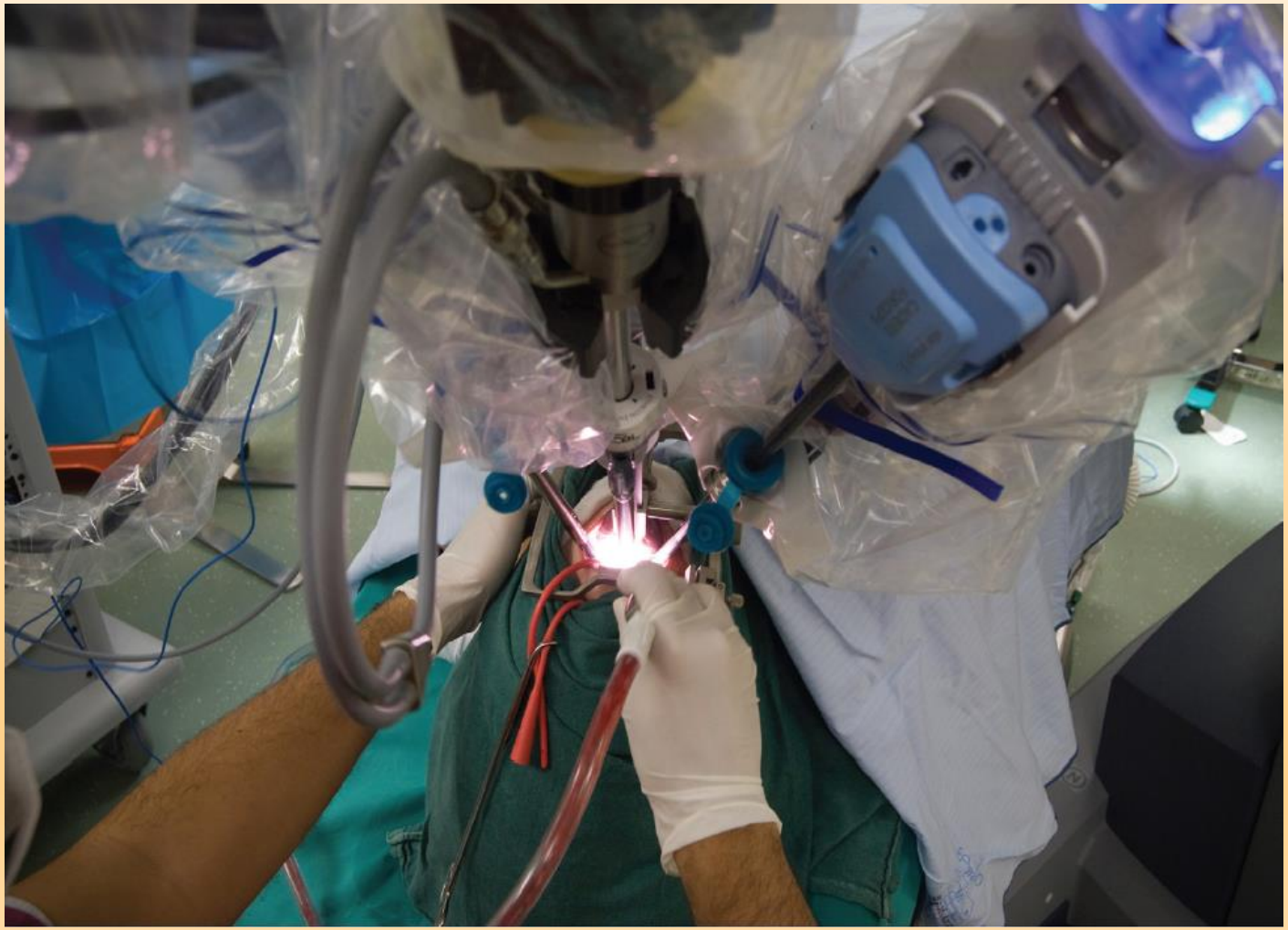
- **>3:1-8:1 M:F**
- **Typically lack a significant history of tobacco or alcohol abuse.**
- **Sexual risk factors for oral or genital HPV exposure.**
- **Low T and high N stage tumors.**

Survival in HPV(+) OPSCC

- Retrospective analyses of clinical trials suggest that there is a survival benefit in HPV(+) OPSCC.
- 53% better overall and 74% better disease-specific survival for HPV(+) OPSCC
- There is still a subset of patients with aggressive disease
- Smokers with HPV+ OPSCC have intermediate to poor prognosis

Transoral Robotic Surgery (TORS)

Has allowed for increased use of primary surgery for T1 HR-HPV+ OPSCC

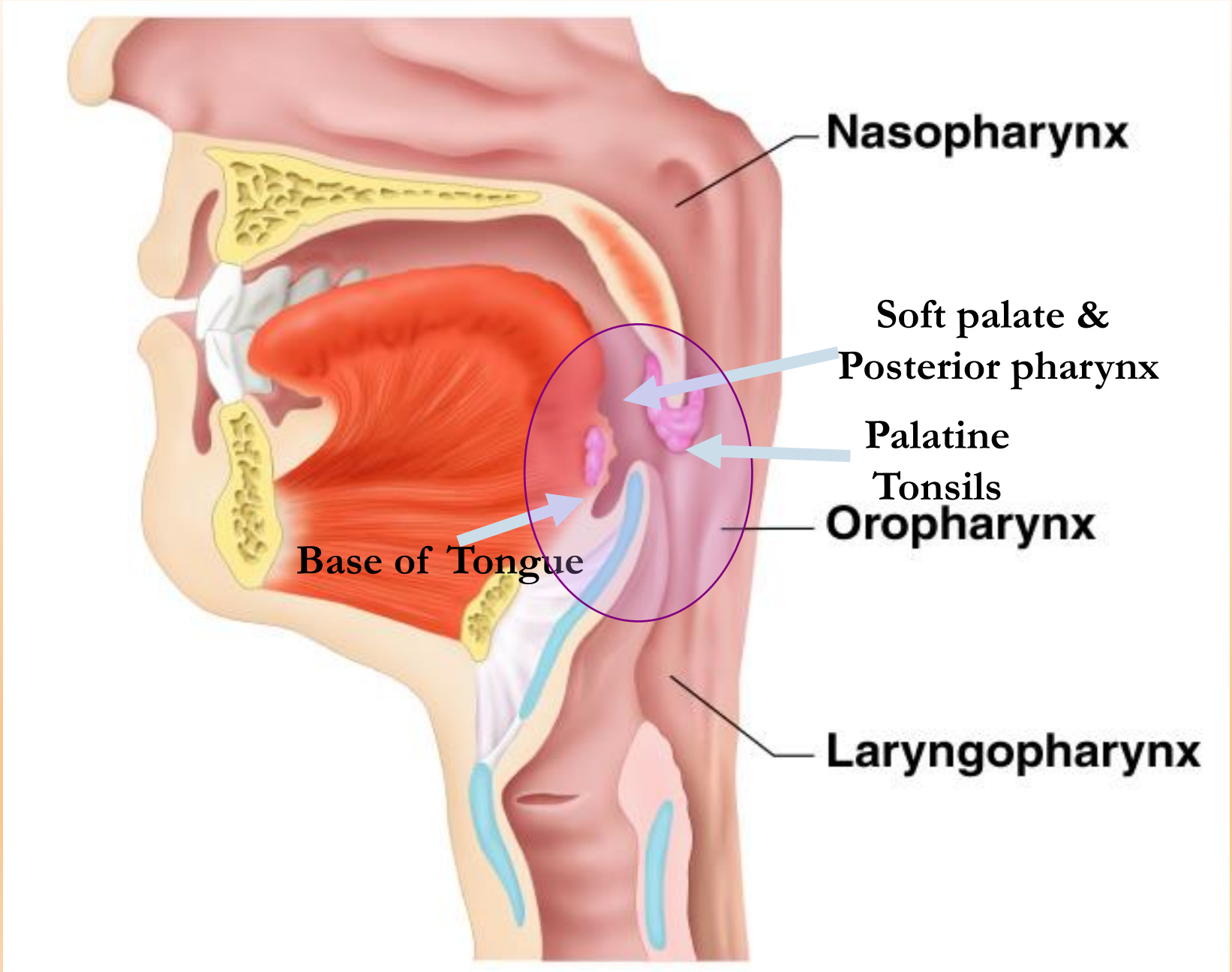


J Clin Oncol 33:3285-3292.

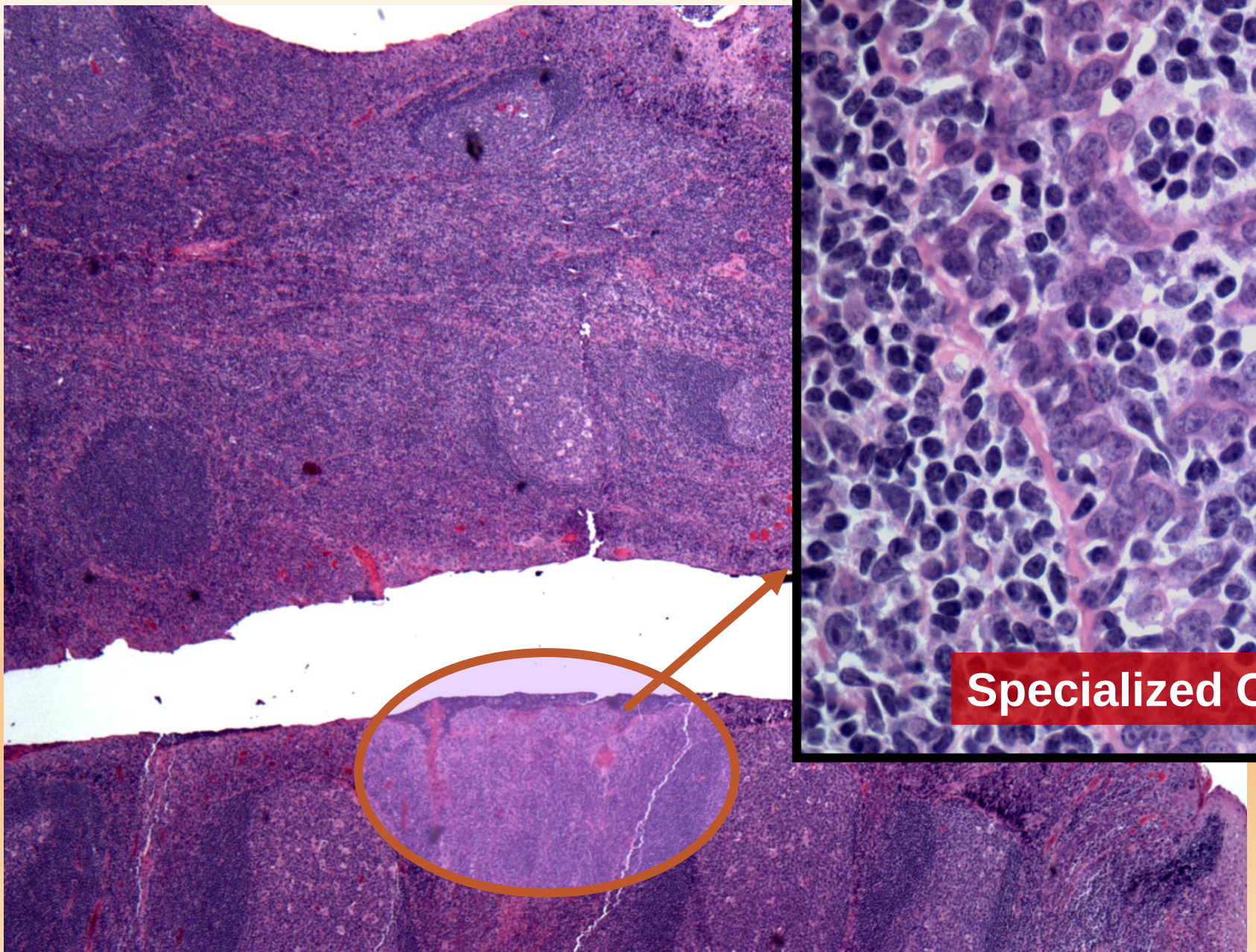
Role of HR-HPV in Head and Neck Cancer at Various Sites

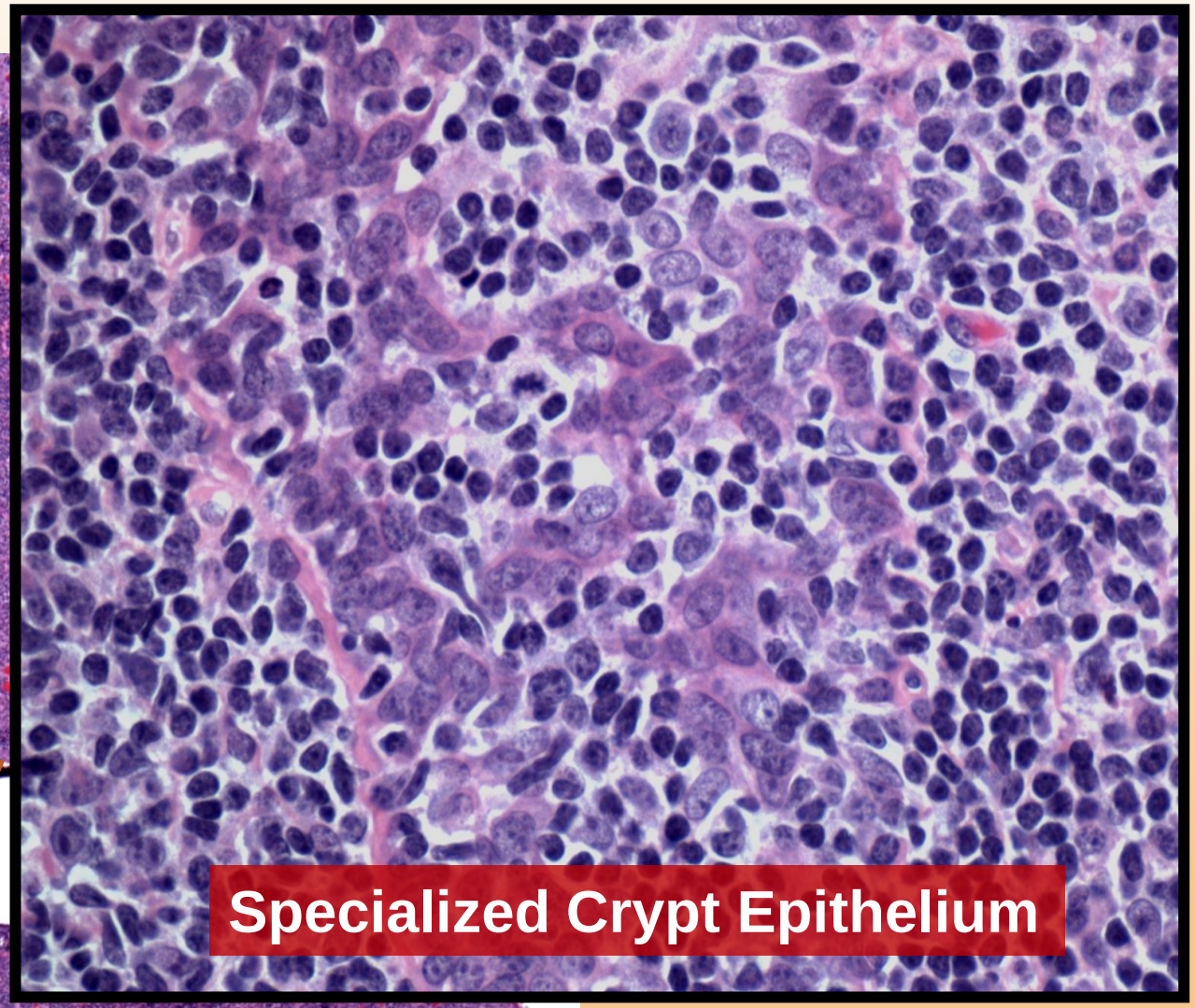
- **Association between HR-HPV and cancer at various HN sites:**
  - **Oropharynx: 80-90%**
  - **Sinonasal Cavity: 20-25%**
  - **Oral Cavity: 3-6%**
  - **Larynx: <5%**
  - **Other HN sites: e.g. Periocular, Nasopharynx**

OROPHARYNGEAL CARCINOMA AND HPV



OROPHARYNGEAL CARCINOMA

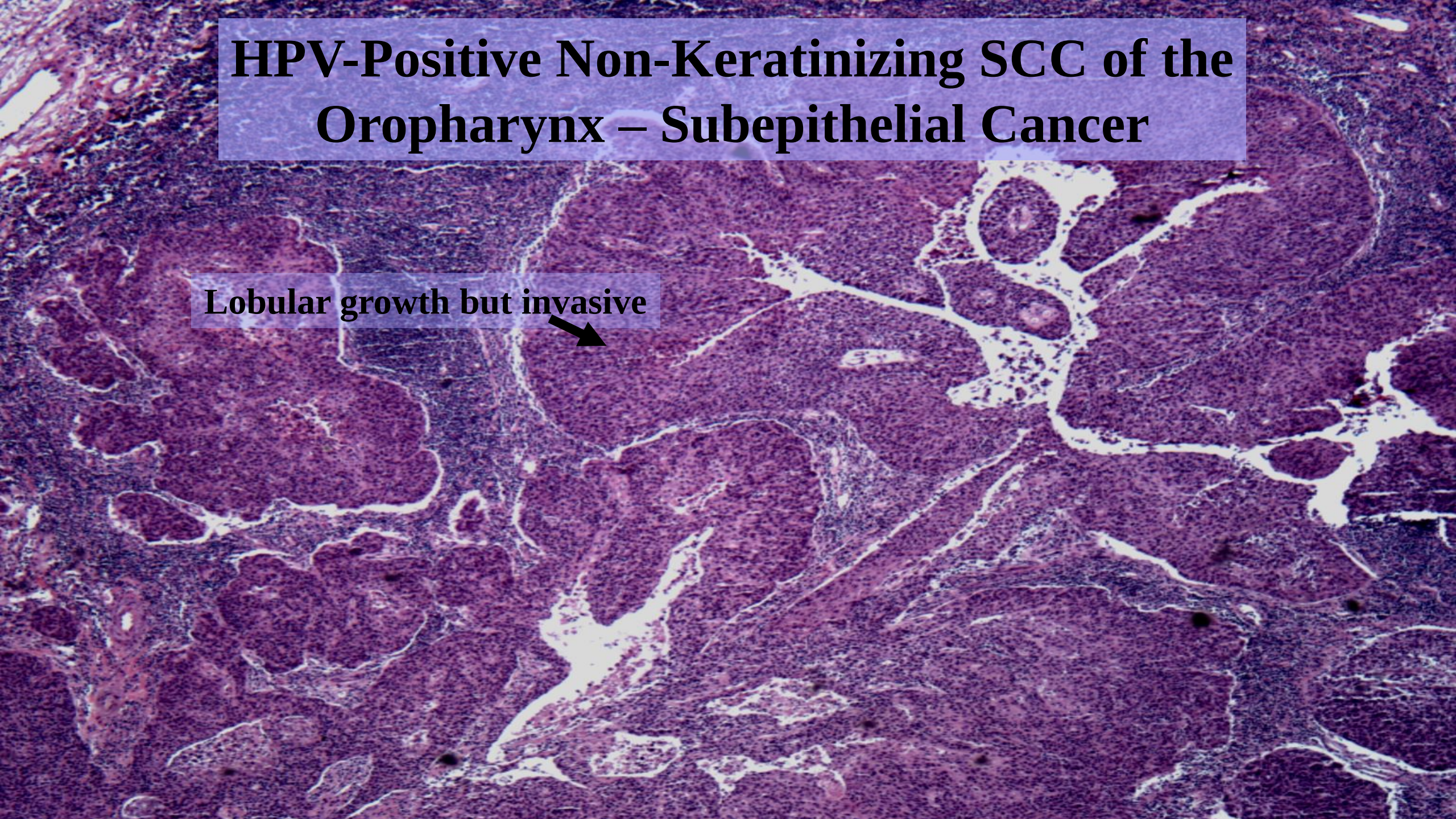




HPV in Oropharyngeal SCC

- Non-keratinizing or partially keratinizing
- Basaloid appearance
- 90-95% are due to HPV type 16
- Small subset due to HPV 18 and other HR-HPV types (31, 33, 53 etc)
  - Must include “cocktail” in any HPV-specific test

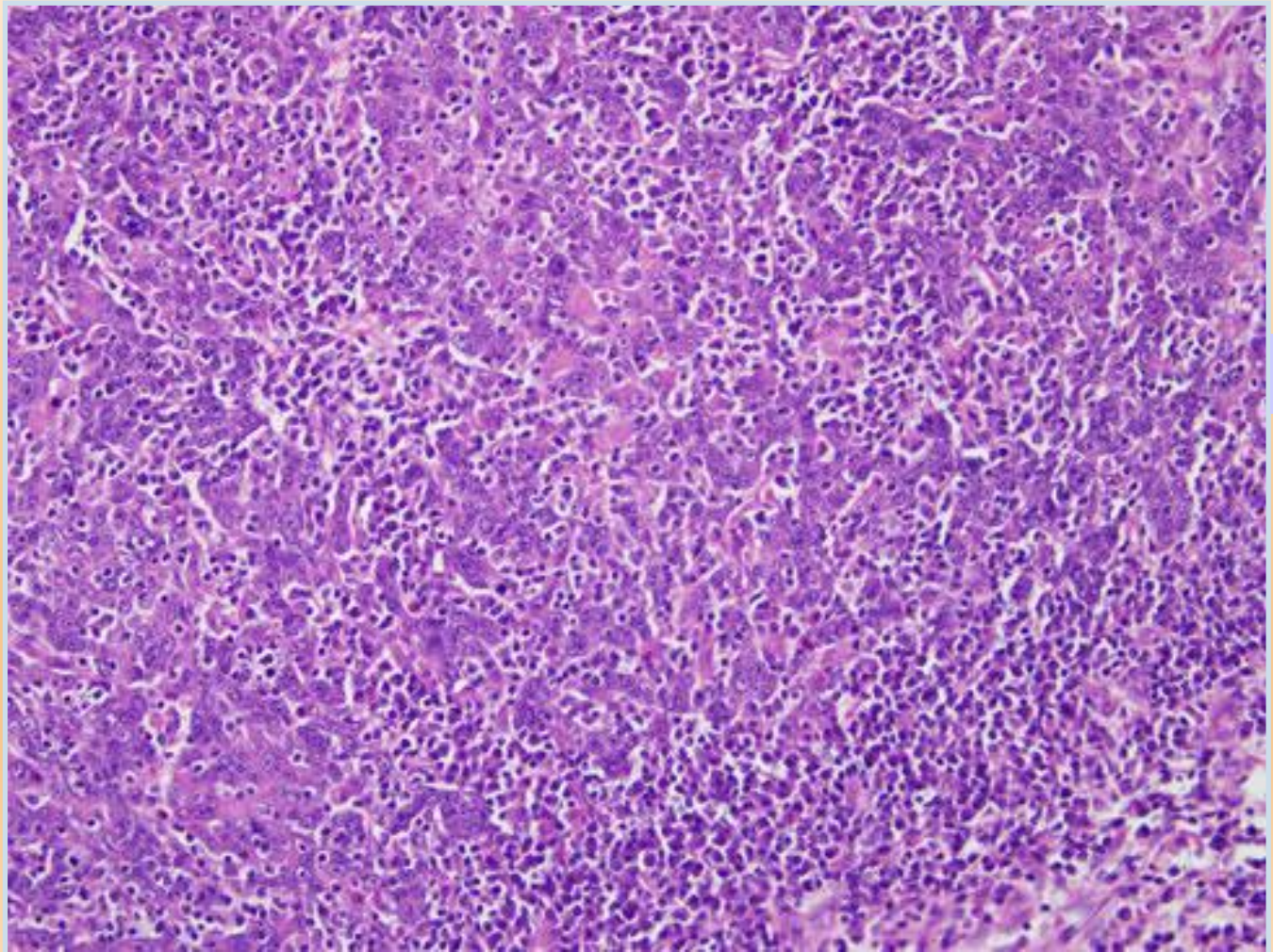
HPV-Positive Non-Keratinizing SCC of the Oropharynx – Subepithelial Cancer



Other Histologic Patterns of HPV+ OPSCC:

All patterns seem to share good prognosis

Lymphoepithelial-Like

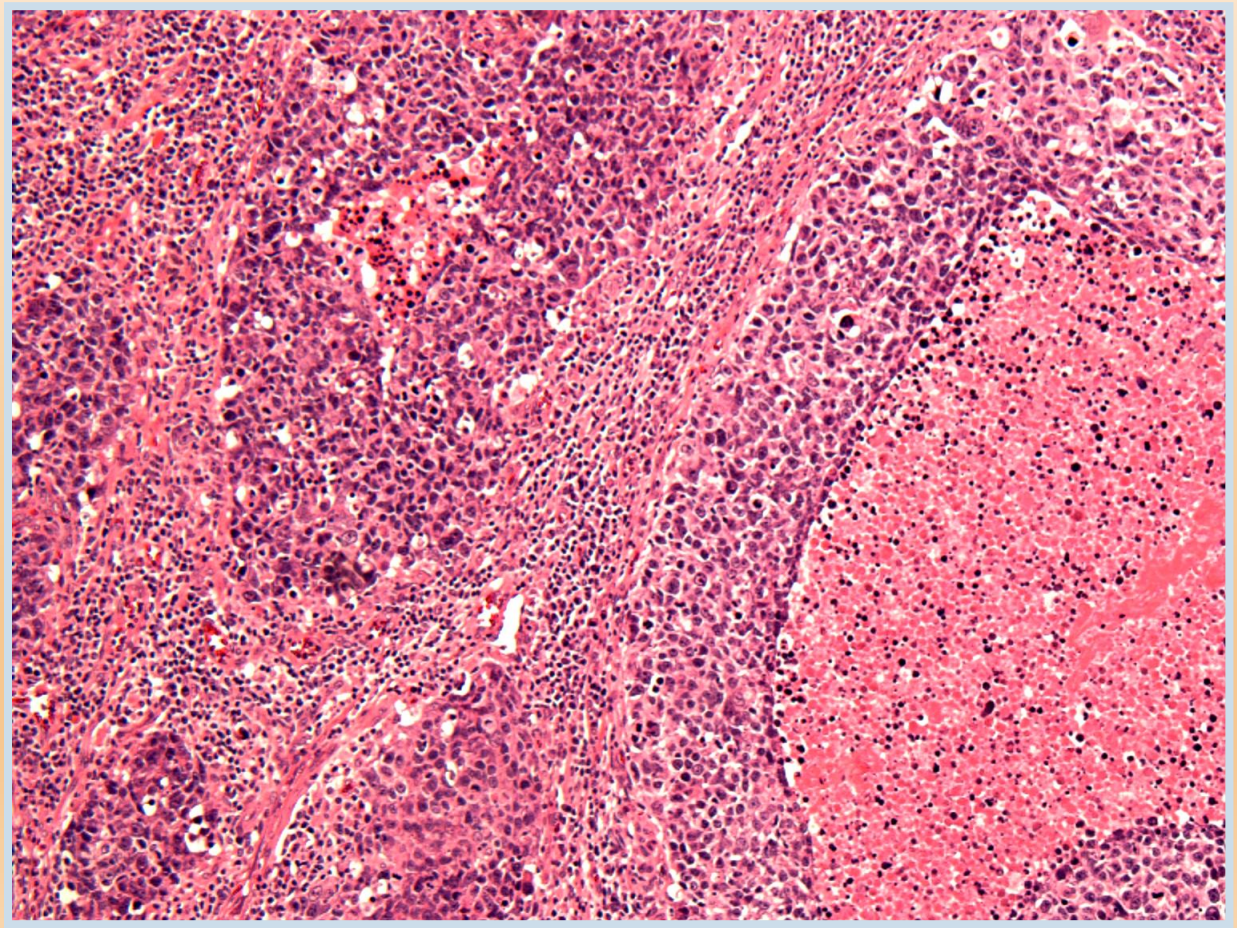


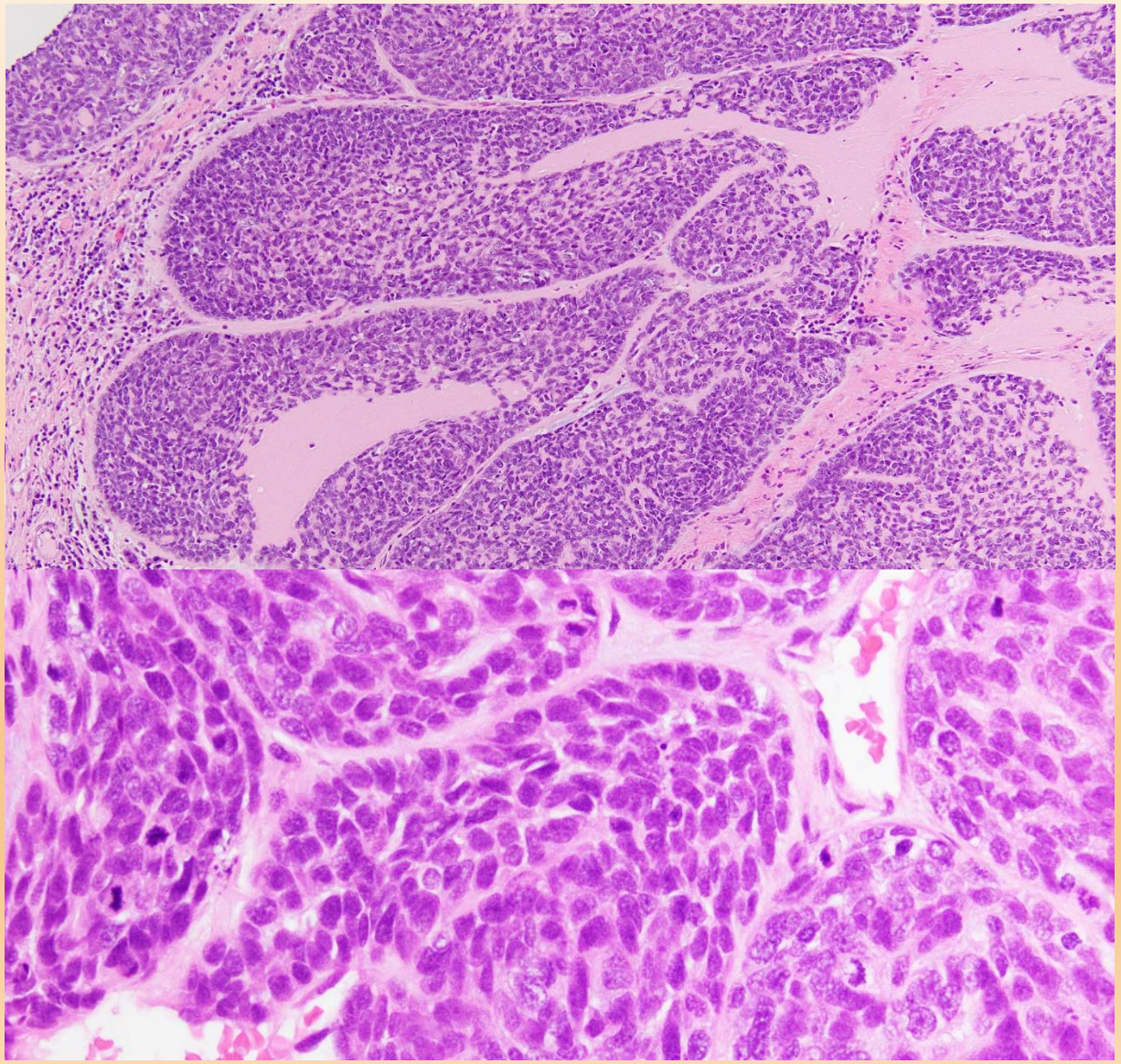
Rule out EBV+ Carcinoma

Other Histologic Patterns of HPV+ OPSCC:

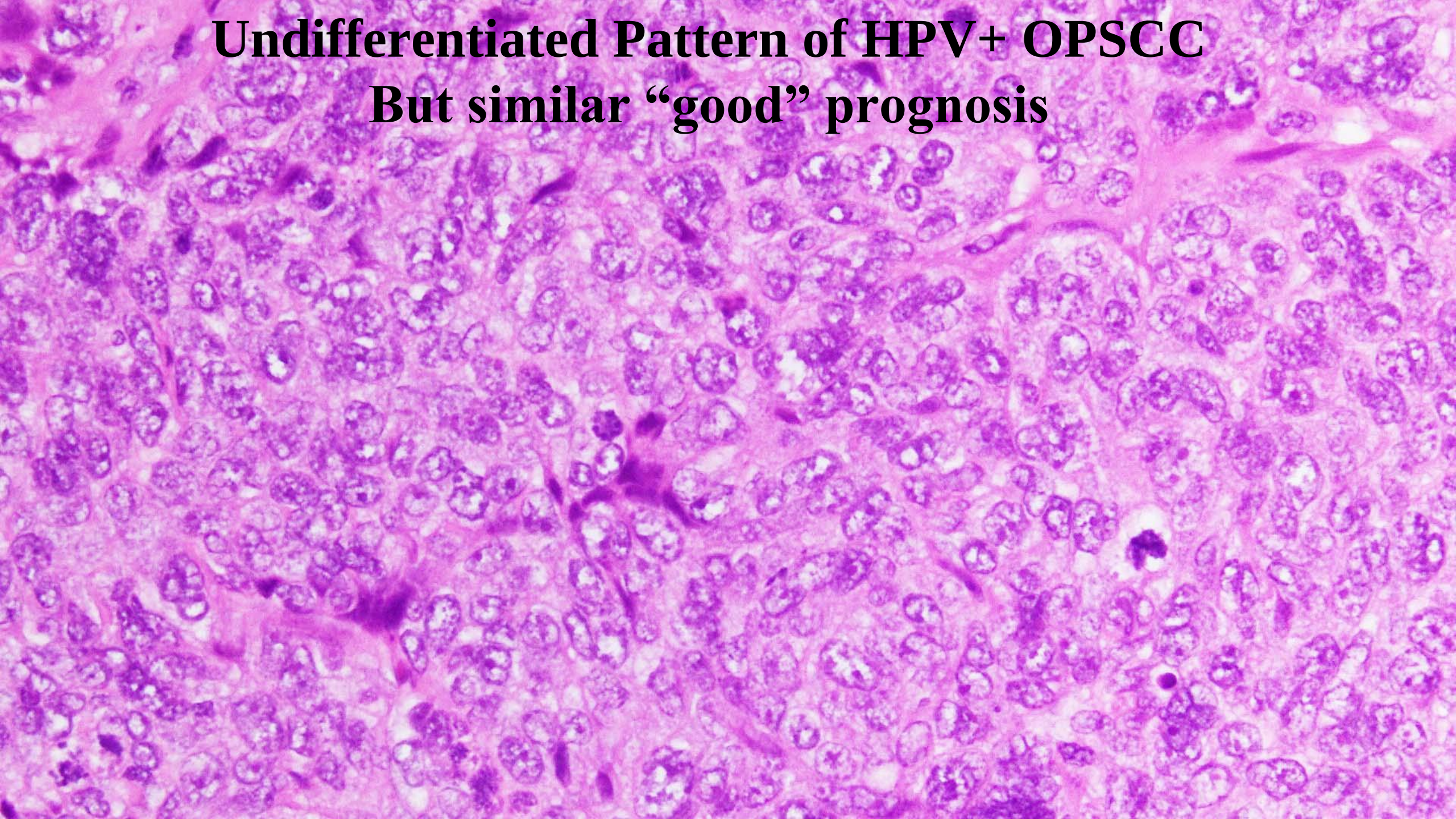
Can resemble a salivary gland neoplasm

Basaloid





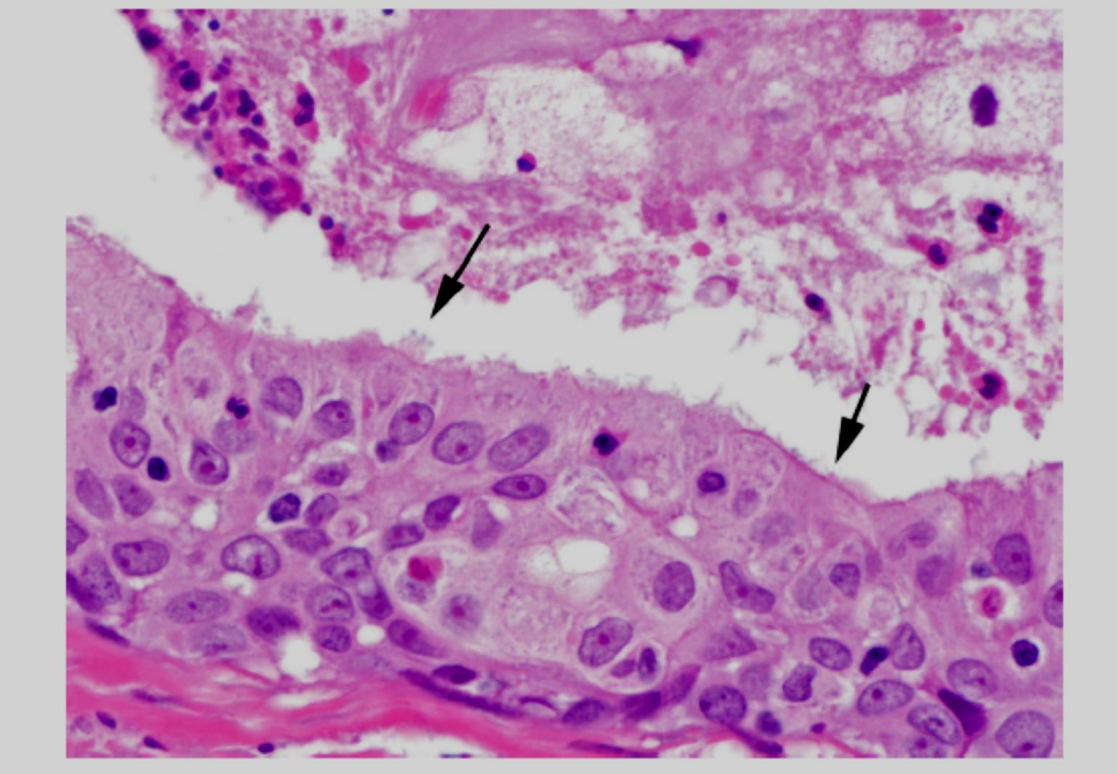
Undifferentiated Pattern of HPV+ OPSCC
But similar “good” prognosis



OP HPV+ Ciliated Non-Keratinizing Adenosquamous Carcinoma

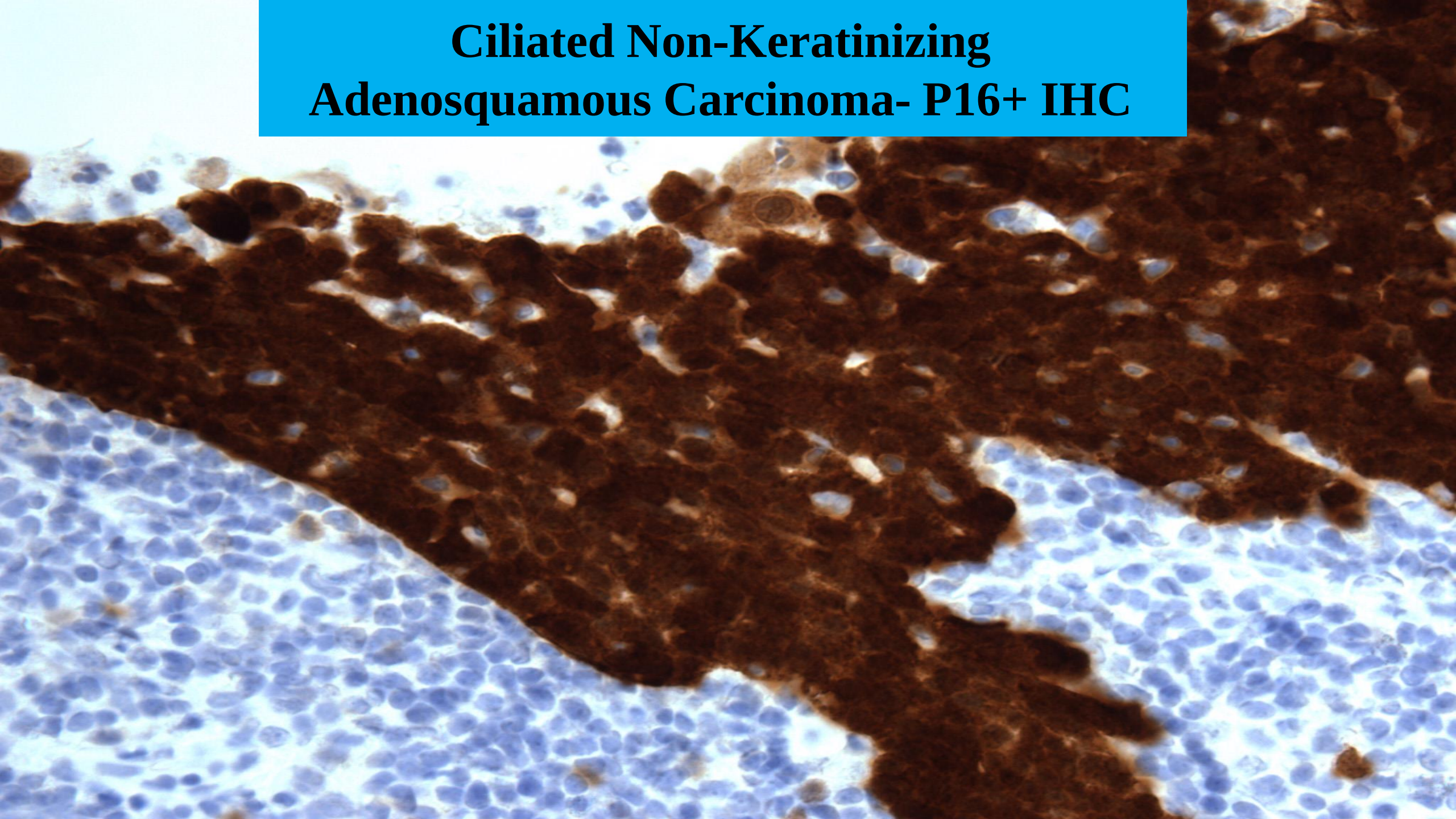
Ciliated Adenosquamous Carcinoma: Expanding the Phenotypic Diversity of Human Papillomavirus-Associated Tumors

Lisa Radkay-Gonzalez[1] · William Faquin[2] · Jonathan B. McHugh[3] · James S. Lewis Jr.[4,5] · Madalina Tuluc[6] · Raja R. Seethala[1,7]



***Resembles MEC but lack MAML2 fusion**
***Lower grade than most AdSqCA**
***HPV type 16 by PCR and ISH**

Ciliated Non-Keratinizing Adenosquamous Carcinoma- P16+ IHC



Role of HR-HPV in HN Cancer

The oropharynx is the HN site with the strongest evidence-based information linking HPV-positivity and improved outcome.

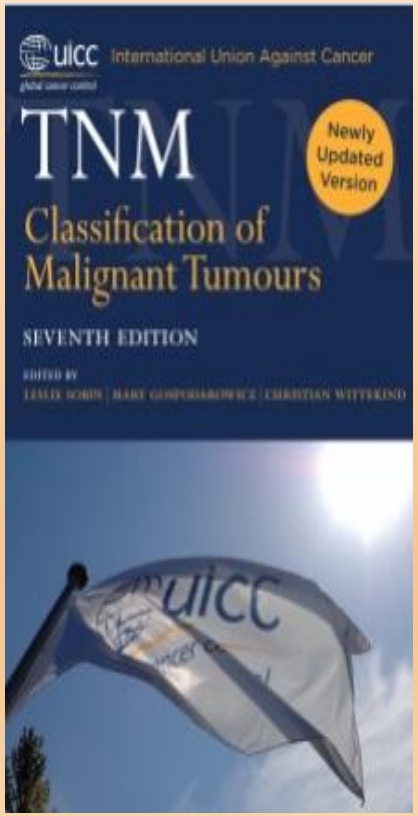
Should we do reflex testing for HR-HPV in HN SCC???

YES!!!

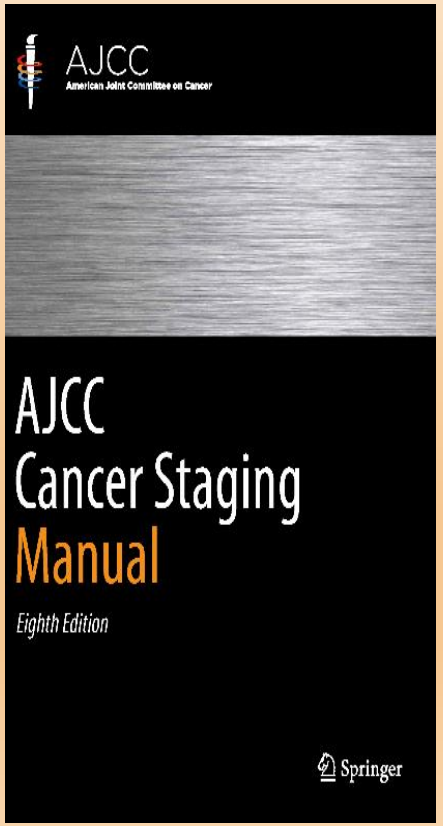
8th Edition: AJCC Staging Update for HPV-Positive OP Cancer

1) **Patient Prognosis and Etiology Counseling**

2) **UICC/AJCC Staging**



Specific, Separate Staging System for p16 Positive OPSCC



The CAP EBG HPV Testing Committee

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

CAP EBG HPV Testing Committee

Updated Testing Guidelines in 2023!!!

Summary: CAP Recommendations for HPV Testing in Head and Neck Cancer

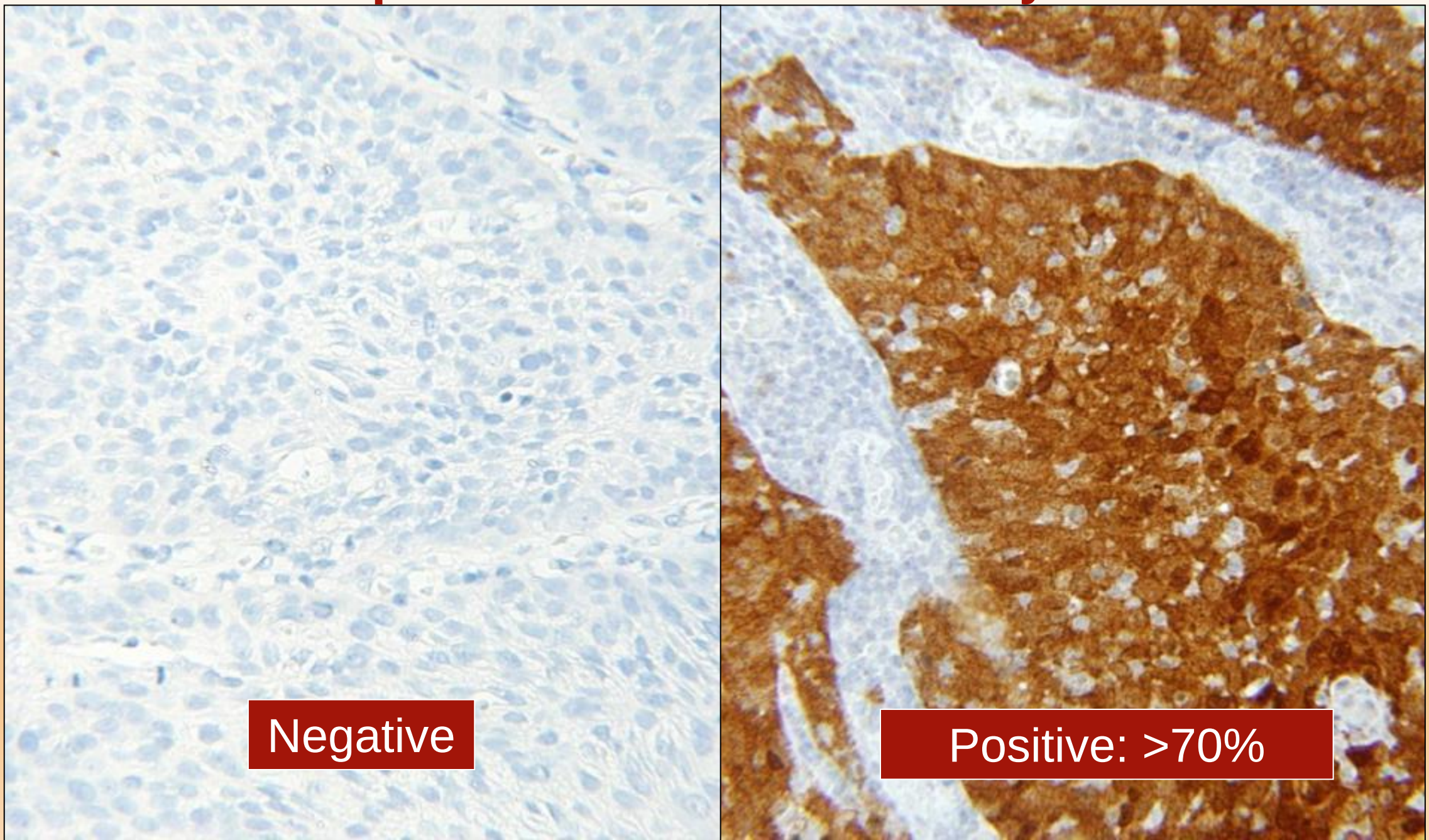
General Overview:

- **The tumors of all patients presenting with oropharyngeal SCC should be tested for HR-HPV**
- **Neck nodal tissue from all patients with metastatic SCC of unknown primary should be tested for HR-HPV**
- **Staining with p16 can be used as the sole initial screening method but confirmatory testing may be necessary in selected cases**
- **HR-HPV Testing of FNA specimens is recommended**

HPV in Oropharyngeal SCC: p16 Immunohistochemistry

- Sensitivity approaches 100%
- Specificity is high in OP (>90%) but low outside OP (79-82%)
- In the OP, p16 is sufficient
- In mets to level II/III and NK morphology, p16 is sufficient
- In other cases, HPV-specific testing may be needed

p16 Immunohistochemistry



ISH for HPV E6/E7 mRNA:

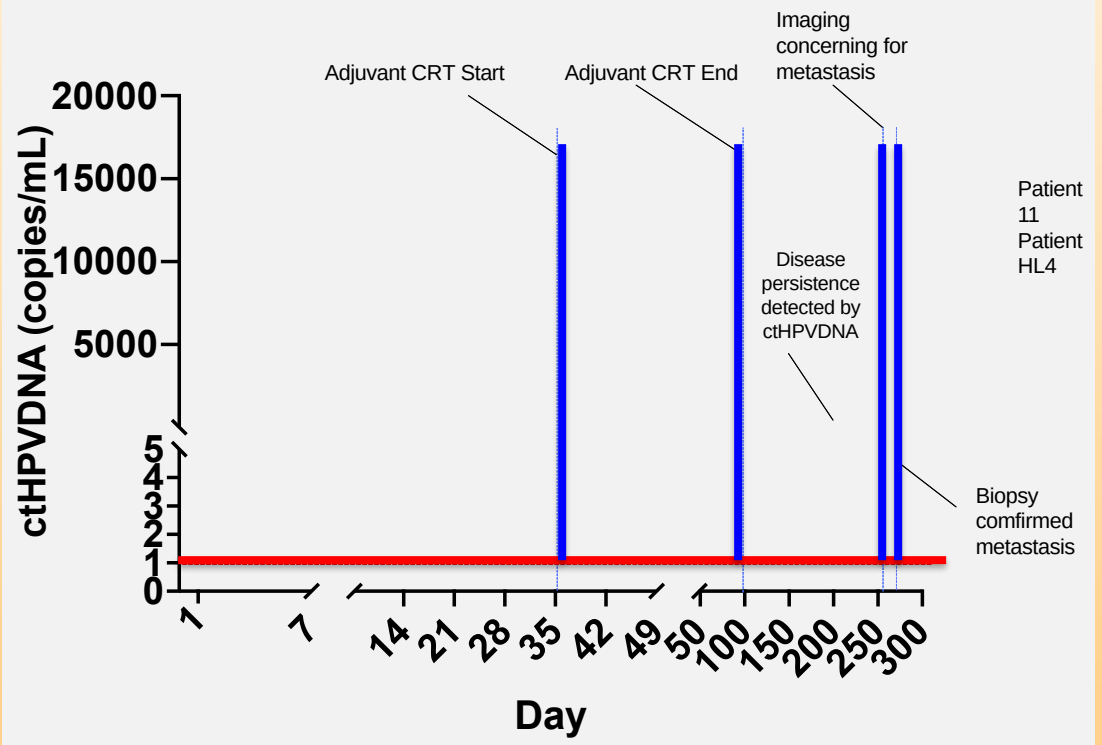
Potential to apply ISH for E6/E7 HPV mRNA to cytologic preparations.

Performance of a Branch Chain RNA In Situ Hybridization Assay for the Detection of High-risk Human Papillomavirus in Head and Neck Squamous Cell Carcinoma

Darcy A. Kerr, MD,† Kshitij S. Arora, MBBS,‡ Krishnan K. Mahadevan, MBBS,‡ Jason L. Hornick, MD, PhD,†§ Jeffrey F. Krane, MD, PhD,†§ Miguel N. Rivera, MD,*† David T. Ting, MD,†‖ Vikram Deshpande, MD,*† and William C. Faquin, MD, PhD*†*

Emerging Tests:
Cell Free DNA and HPV+ Cancer

- Circulating tumor HPV DNA detectable in blood
- Blood levels could be used to correlate with screening, disease stage, risk of recurrence following therapy, and overall survival.
- Blood-based molecular diagnostics – qPCR and droplet digital PCR
- Early results show high sensitivity and specificity



SUMMARY

- Keratinizing dysplasia is a common precursor in the UADT
- Microinvasive SCC is among the most challenging SCC diagnoses to make
- Beware of pitfalls: mal-oriented biopsy, pseudoepitheliomatous hyperplasia, inflammatory processes, etc
- Many variants of SCC can cause diagnostic problems:
  - Papillary SCC, basaloid SCC, spindle cell carcinoma, verrucous SCC
- HPV-associated OPSCC is unique/separate staging in the OP
  - Reflex HPV testing (p16 or HPV-specific) is performed in these cases


THANK YOU!