CSP06 Head and Neck Pathology: Challenges and Opportunities

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2011 Annual Meeting – Las Vegas, NV

AMERICAN SOCIETY FOR CLINICAL PATHOLOGY
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CSP06 Head and Neck Pathology: Challenges and Opportunities

This program will address some of the challenges that are faced by pathologists in their daily practice. The wide diversity of organs and tumors and their taxonomy in the head and neck region have resulted in the evolution of a variety of diagnostic problems and controversies. The program will highlight several areas in head and neck pathology including challenges in assessment of oncocytic lesion of the thyroid, common problems and controversies in salivary gland neoplasms specifically addressing a morphologic and immunochistochemical approach to common problems of the "biphasic" category of salivary gland tumors (tumors with both ductal and muoepithelial elements), polymorphous low grade adenocarcinoma, and high grade mucoepidermoid carcinoma. In addition, the program will also focus on challenges in diagnoses of squamous cell carcinoma of the head and neck and new insights gained in its development, specifically implications of association with high risk HPV types and their detection.

- Identify and approach common oncocytic lesions of the thyroid.
- Develop approach to diagnosis of select salivary gland tumors including those with biphasic patterns.
- Determine challenges in diagnostic of testing for high risk HPV.

FACULTY:

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Entire Pathology Team
Surgical Pathology
New Techniques
3.0 CME/CMLE Credits

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The Ever so Atypical Oncocytic Lesions of the Thyroid

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Disclosure

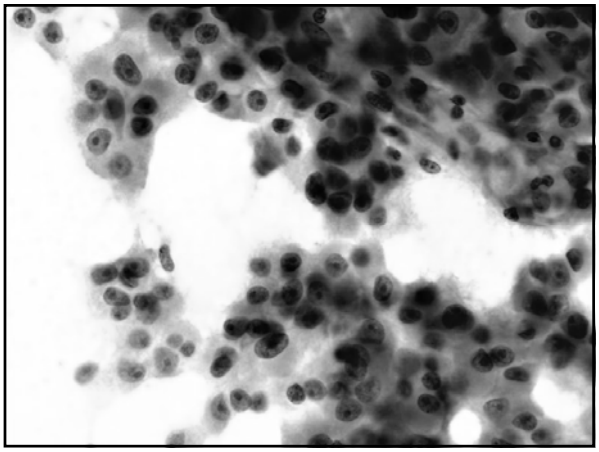
- Consultant
  - Veracyte, INC

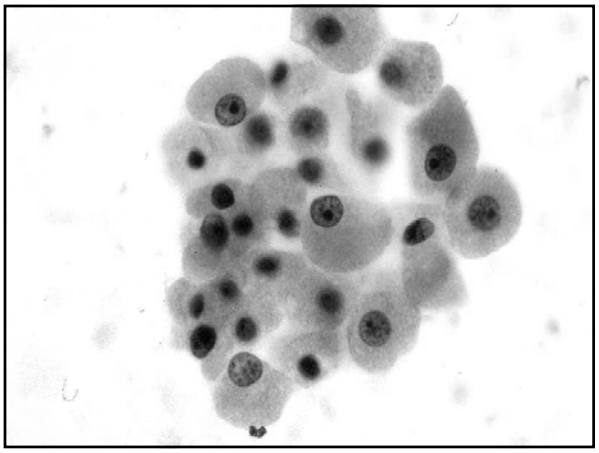
Presentation Objectives

- Oncocytic follicular lesions of thyroid
  - Oncocytic / Hürthle cell lesions
  - Oncocytic papillary lesions
- Mimickers of Oncocytic thyroid lesions
- FNA of oncocytic lesions
- Molecular analysis of FNA specimens

Case

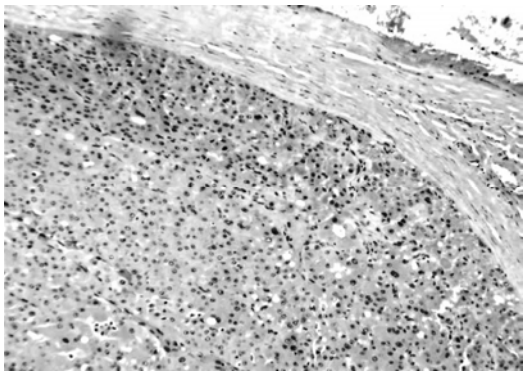
79 year old female with left thyroid mass

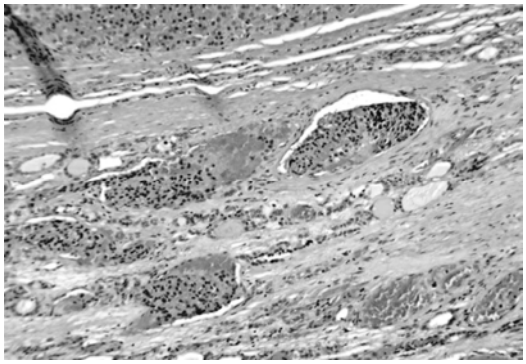




FNA Diagnosis

Hurthle cell Neoplasm





Diagnosis

Hürthle Cell Carcinoma
with Capsular and Vascular Invasion

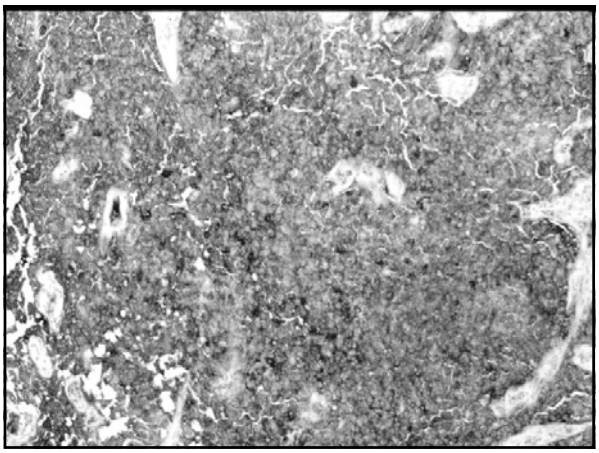
WHAT'S IN A NAME?

- **ONCOCYTES**
- **OXYPHILS**
- **HURTHLE CELLS**

- **My view about Oncocytic change**
  Oncocytes – eosinophilic and granular cytoplasm
  What is or has been called Hürthle cell is a cell with "granular cytoplasm, sharp cytoplasmic borders, round nuclei with prominent nucleoli"

Oncocytic /Hürthle Cells

- Follicular derived
- Express thyroglobulin not calcitonin
- EM
  - Increase number of mitochondria
  - Abnormalities of the mitochondria
    - increase size, dilated with disappearance of cristae
    - pleomorphic intra-mitochondrial dense bodies



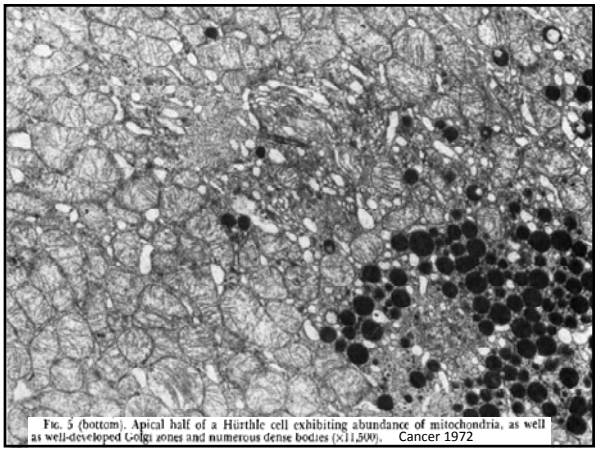


FIG. 5 (bottom). Apical half of a Hürthle cell exhibiting abundance of mitochondria, as well as well-developed Golgi zones and numerous dense bodies (×11,500). Cancer 1972

WHO Classification of Tumors of Endocrine Organs - 2004

Hurthle Cell Tumors Classified

as

Oncocytic Follicular Tumors

Oncocytic Lesions of Thyroid

Uncommon lesions

Controversial

- histologic interpretation
- biologic potential
- surgical management
- different than other follicular derived lesions

ONCOCYTIC TUMORS

- CYTOGENETICS
  - Relatively few cases of oncocytic thyroid tumors have been studied by conventional cytogenetic analysis, usually in general reports dealing with chromosomal alterations of thyroid neoplasia.
  - 42-47 chromosomes with structural and numerical changes have been demonstrated in one oncocytic carcinoma.

ONCOCYTIC TUMORS

- CGH
  - Chromosomal DNA unbalance and aneuploidy are present in 70-80% of oncocytic thyroid neoplasms.
  - Chromosomal DNA gains (+5, +7, +12, +17 , +19, +20) are more common than losses (-2, -9).
  - Aneuploidy is a feature of both oncocytic adenomas and carcinomas, sequential acquisition of numerical chromosomal changes (possibly beginning with trisomy 7) appears associated with tumor progression.
  - Carcinomas tend to have more chromosomal gains and losses then adenomas and a statistical association has been demonstrated between the degree of aneuploidy and loss of differentiation, extent of tumor invasion, and recurrence.

ONCOCYTIC TUMORS

- Genes and Proteins
  - ATP production appears defective in oncocytic thyroid tumors but no specific alterations have been demonstrated in the nuclear genes which code for most of the proteins involved in the mitochondrial oxidative phosphorylation process or which control mtDNA replication.
  - RAS mutations (frequently observed in follicular adenomas and carcinomas) and PAX8/ rearrangement (frequently observed in follicular carcinomas) are uncommon in oncocytic neoplasms.

ONCOCYTIC CELLS

- There may be a genetic predisposition of patients to develop oncocytic thyroid neoplasms.
- Gasparre et al. have recently shown that disruptive mutations in mitochrondrial DNA were found in some genes in Hurthle cell neoplasms and this finding appears to be a marker for thyroid oncocytic tumors

ONCOCYTIC FOLLICULAR TUMORS

- Maximo et al. have recently identified somatic missense mutations in **GRIM-19** in approximately 11% of sporadic Hurthle cell carcinomas.
- **GRIM-19** is located at 19p13.2. The TCO gene locus which has to been linked to familial Hurthle cell neoplasms has also been mapped to this locus.
- Hurthle cell carcinomas commonly express genes associated with mitochondrial and cellular metabolism.

ONCOCYTIC TUMORS

- **MULTIPLE FOLLICULAR AND ONCOCYTIC TUMOR SYNDROME**
- FAMILIAL; GERMLINE MUTATIONS IN PTEN
- MAY BE SPORADIC MUTATION (50%)
- HIGH RISK OF FOLLICULAR PATTERNED CANCERS
- ?COWDEN's SYNDROME

Oncocytic Lesions of the Thyroid

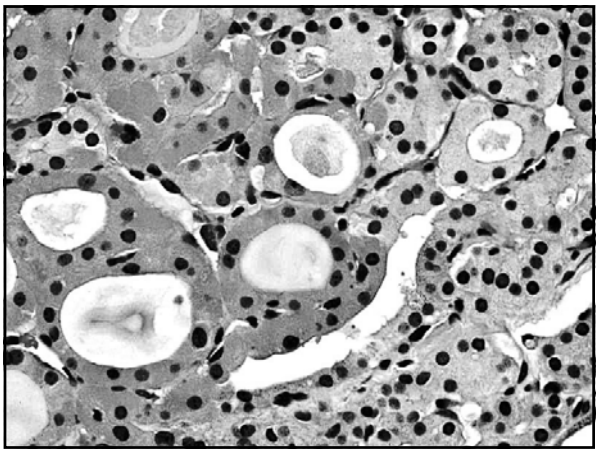
Benign

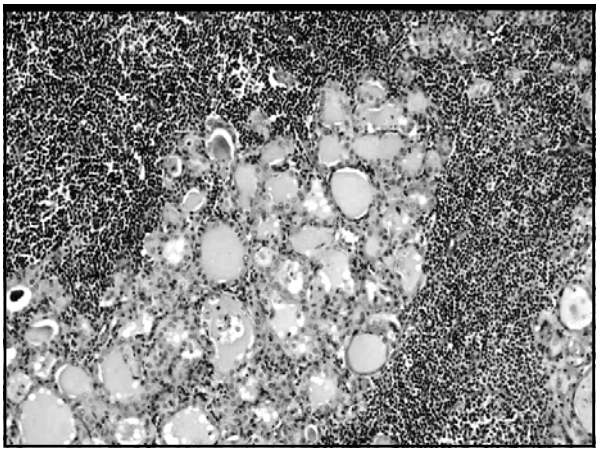
Malignant

Oncocytic Lesions

Benign

- Focal oncocytic change
  - Nodular goiter, Grave's disease
- Nodular oncocytic cell aggregates
  - Nodular goiter - hyperplastic nodule
  - Lymphocytic thyroiditis

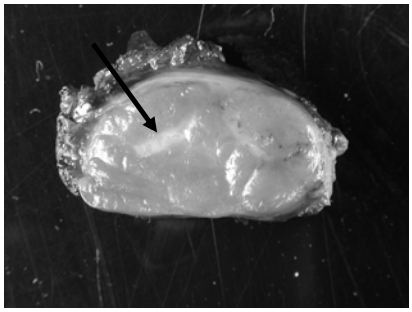




Oncocytic Lesions

Oncocytic Follicular Adenoma

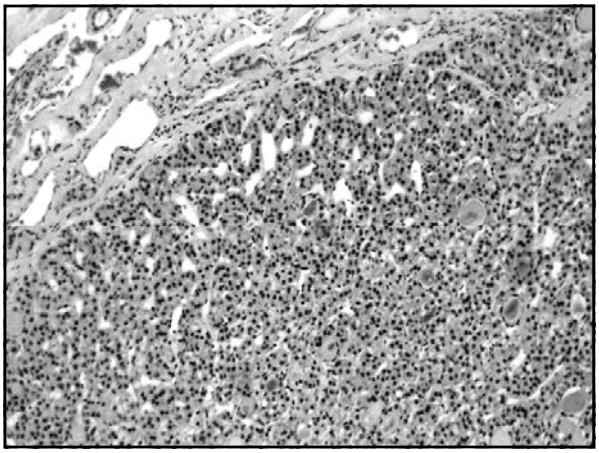
- Benign thyroid neoplasm composed exclusively or predominantly of oncocytes
- Completely encapsulated
- Brown or mahogany cut surface
- Secondary changes due to FNA
- Central scarring



Oncocytic Lesions

Oncocytic Follicular Adenoma

- Tumor confined within the capsule (no capsular or vascular invasion)
- Follicular, solid or trabecular growth pattern
- Random nuclear atypia, mitoses or multi-nucleation
- Infarction secondary to FNA



Oncocytic Lesions

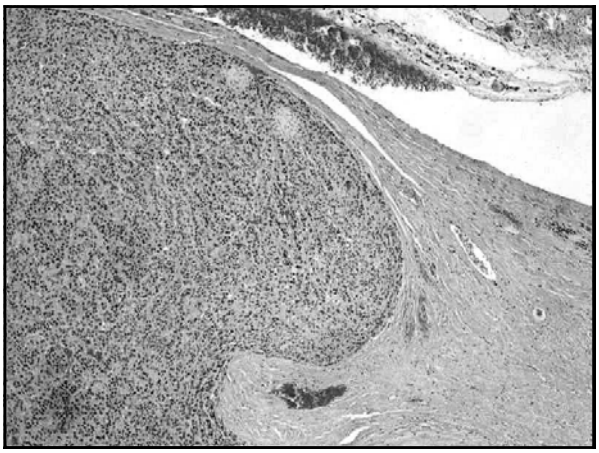
- *Random nuclear atypia - Indicator of malignancy?*
- "Atypical Hürthle Cell Adenoma"
  - Bronner and LiVolsi
  - – Marked nuclear atypia, mitoses, spontaneous infarction and necrosis
  - – Median follow-up 13 yrs - benign

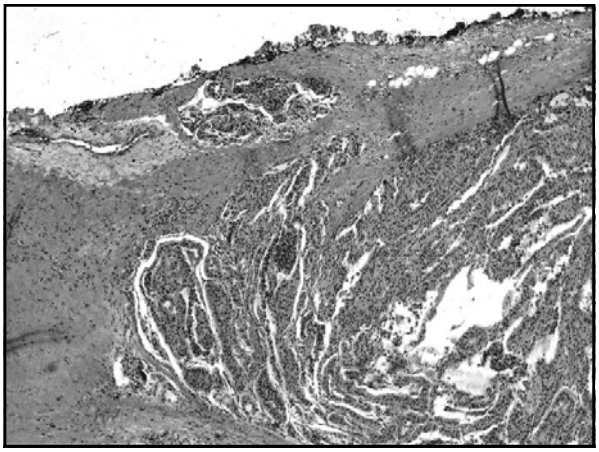
Hürthle Cell Lesions

- 35 cases - "Indeterminate"
  - Carcangui et al
  - – All cases behaved as adenomas
- *Criteria for Malignancy should be Capsular and/or Vascular Invasion*

Oncocytic Follicular Carcinoma

- Similar to oncocytic / follicular adenoma with capsular and/or vascular invasion.
- Increase tendency towards solid and/or trabecular growth pattern





Oncocytic Follicular Carcinoma

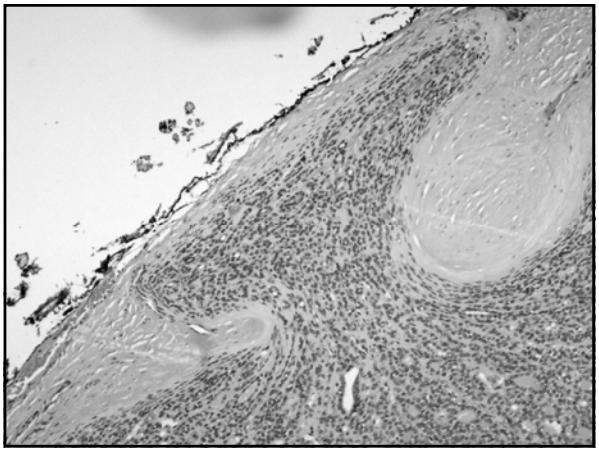
Features related to decrease survival rate

- Gender - male
- Older patient age (> 45-50 years)
- Tumor size (> 4-5 cm)
- DNA aneuploidy
- Distant metastases
- Solid and trabecular growth pattern

Oncocytic Follicular Carcinoma Diagnosis

Capsular invasion only

- Minimally invasive Hürthle cell or Follicular carcinoma
- Indeterminate biologic potential? (Williams et al)



Oncocytic Follicular Carcinoma Diagnosis

Capsular invasion only

- Associated with metastatic disease
  - Khan & Perzin; Evans et al
- Tumors with capsular invasion also demonstrate foci of vascular invasion on extensive sectioning of the tumor capsule
  - Yamashina et al

Oncocytic Follicular Carcinoma Diagnosis

Capsular Invasion – Diagnosis

- Tumor cells invading into and through the capsule into the surrounding thyroid parenchyma.

Oncocytic Follicular Carcinoma Diagnosis

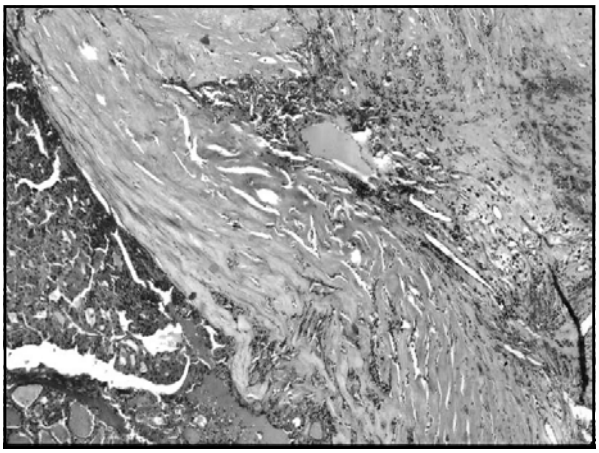
Capsular Invasion – Diagnosis

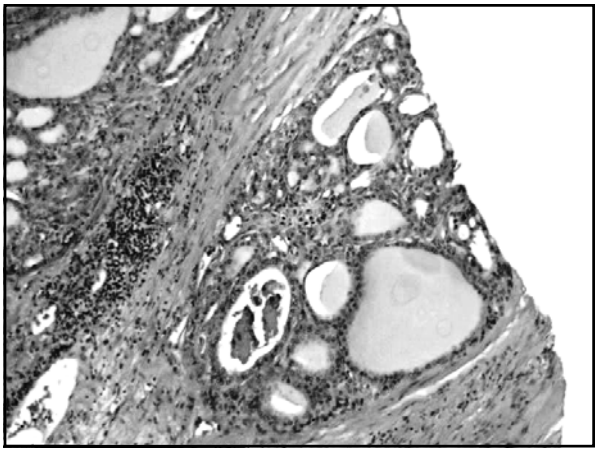
- Tumor cells invade into the tumor capsule only without invasion into surrounding thyroid.
  - Tumor cells mushroom out into the capsule
  - Tumor cell invade into a hook-like pattern, usually horizontally into the capsule.

Oncocytic Follicular Carcinoma Diagnosis

Capsular Invasion Mimics

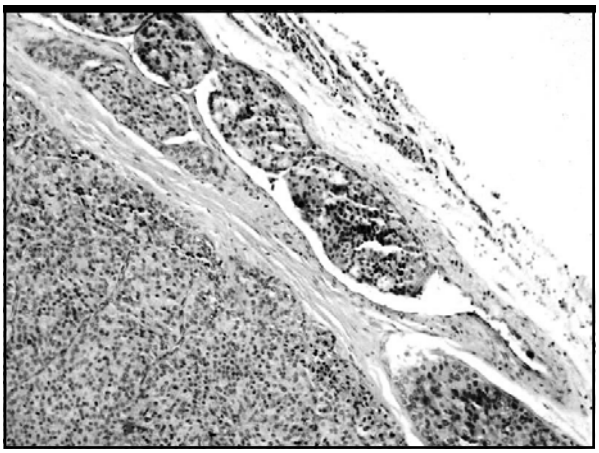
- Post FNA tracking of the tumor cells into the capsule
  - Vertical growth surrounded by hemorrhage, granulation tissue.
- Avoid diagnosing capsular invasion at the edge of the section (tissue curling effect).



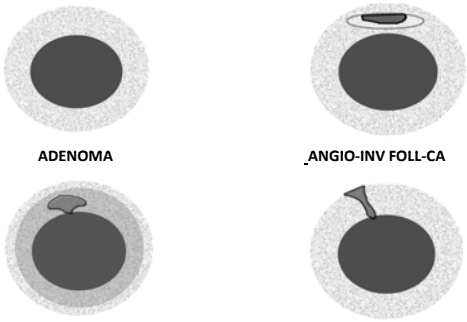


Oncocytic Follicular Carcinoma Diagnosis

- Vascular invasion with or without capsular invasion
  - Angio-invasive Hürthle cell / Follicular carcinoma



ENCAPSULATED FOLLICULAR LESIONS



Confirming Capsular and/or Vascular Invasion

- Morphology
- Stains (histochemical and immunohistochemistry)
  - Capsular Invasion
    - Elastic and Collagen stain
  - Vascular Invasion
    - Factor VIII, CD31

Oncocytic Lesions

Are Oncocytic and non-oncocytic follicular neoplasms are two separate entities?

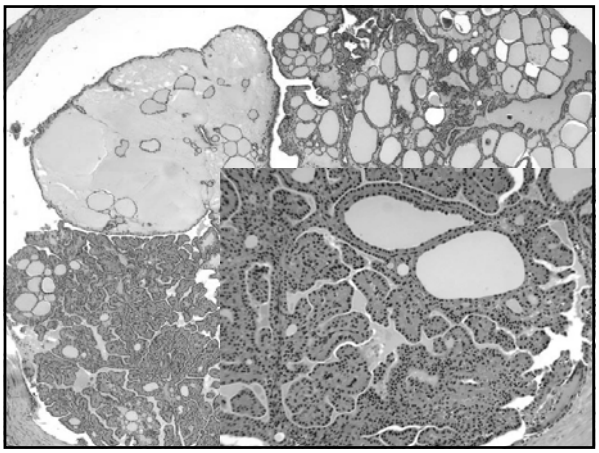
- Nodal and extranodal metastases
- Aggressive clinical course; increase in malignancy rate (35%)
- reduced or no uptake of radio-iodine, effecting further management
- Different genetic alterations

ONCOCYTES IN THE THYROID

- **OTHER**
- PAPILLARY HYPERPLASTIC NODULE
- WARTHIN-LIKE PAPILLARY CARCINOMA
- TALL CELL PAPILLARY CARCINOMA
- ONCOCYTIC PAPILLARY CARCINOMA
- ONCOCYTIC FOLLICULAR VARIANT PAPILLARY CARCINOMA
- ONCOCYTIC MEDULLARY CARCINOMA

PAPILLARY HYPERPLASTIC NODULE

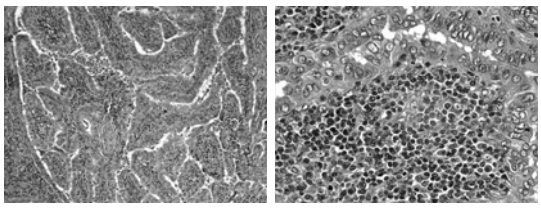
- **Usually solitary**
- **Modest size 2-3 cm**
- **Circumscribed, cystic**
- **Often young women (teenagers)**
- **May be hyperfunctional**



WARTHIN LIKE PAPILLARY CARCINOMA

- Similar age and sex incidence to usual PTC
- Almost always in background of thyroiditis
- May be circumscribed and partly cystic
- Tumor cells oncocytic/Hurthle as background
- Prognosis similar to usual PTC

Warthin Like Papillary Carcinoma

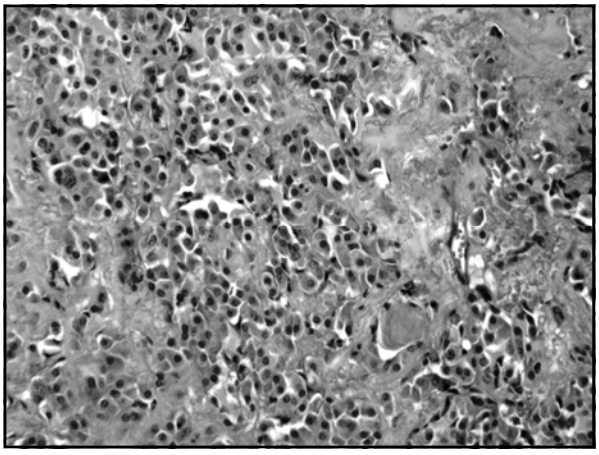


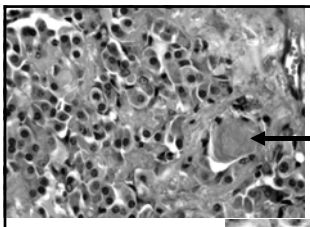
TALL CELL VARIANT of PAPILLARY CARCINOMA

- Often older patients (average age 57y)
- Large extrathyroidal lesions
- May have necrosis, easily found mitoses
- Often very papillary-may coalesce-look trabecular
- Prognosis 75% survival at 10 years
- May transform to anaplastic carcinoma

ONCOCYTIC MEDULLARY CARCINOMA

- RARE VARIANT
- SIMILAR PROGNOSIS TO OTHER MTC
- CALCITONIN IMMUNOSTAIN

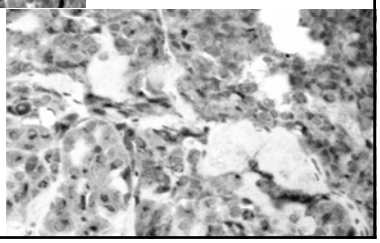




ONCOCYTIC MEDULLARY CARCINOMA

AMYLOID

IMMUNOSTAINS POSITIVE:
CALCITONIN,
CHROMOGRANIN,
CEA

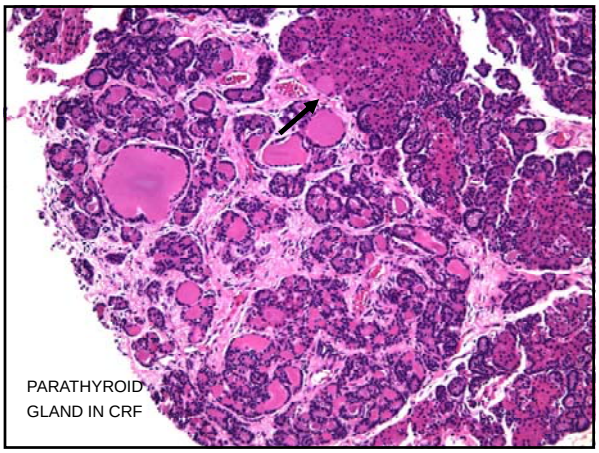


ONCOCYTES IN THE PARATHYROID

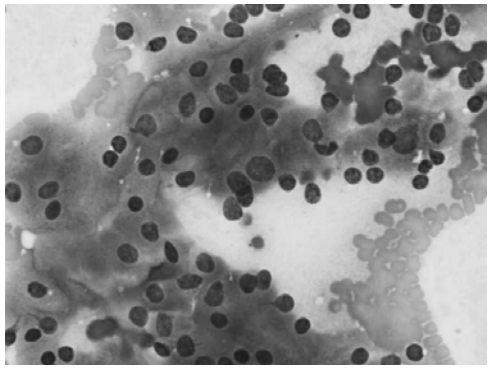
- If parathyroid gland is intra-thyroidal – can be mistaken for oncocytic lesion of the thyroid gland.

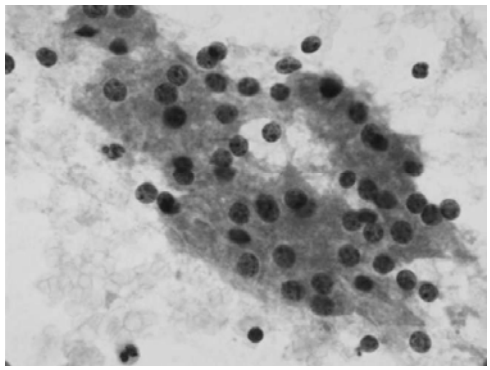
ONCOCYTES IN THE PARATHYROID

- All parathyroid parenchymal cells are alike.
- Metaplasia to oncocytes or clear cells.
- Oncocytes as isolated cells or small groups appear at or just after puberty.



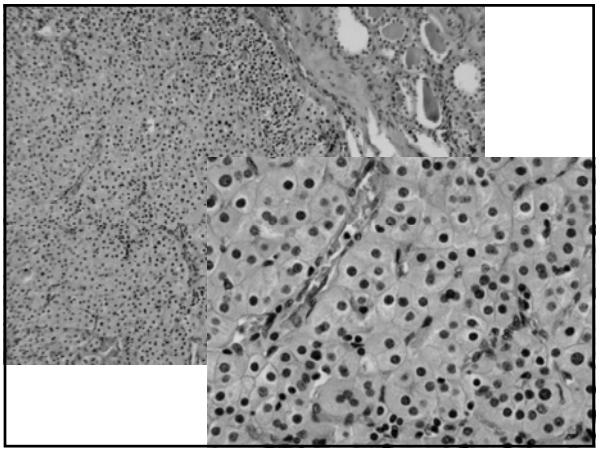
PARATHYROID GLAND IN CRF





FNA Diagnosis

Hürthle Cell Neoplasm



PTH levels

- Intact PTH assay 1984
  - All patients with primary hyperparathyroidism
    - Elevated PTH levels
    - Upper third of normal range
  - Rarely low-normal or sub-normal serum intact PTH in surgically proven hyperparathyroidism has been reported

Low PTH in Parathyroid Adenoma

- PTH is a heat labile/fragile peptide
- Coexistent sarcoidosis and/or Vitamin D toxicity might suppress intact PTH levels.
- Hypomagnesaemia
- Variability in intact PTH assay
- Mutated form of PTH molecule

Low PTH in Parathyroid Adenoma

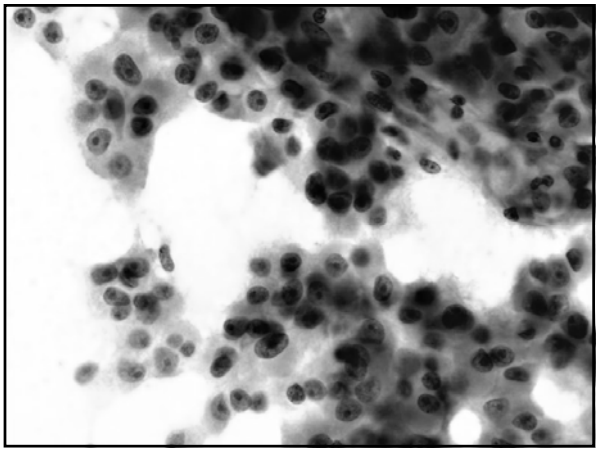
- Difference in the PTH release between the cells within the individual adenoma
  - Oxyphilic cells are virtually insensitive to changes in ambient calcium concentration.
    - Nygren et.al. 1988
    - Johansson H et.al. 1989

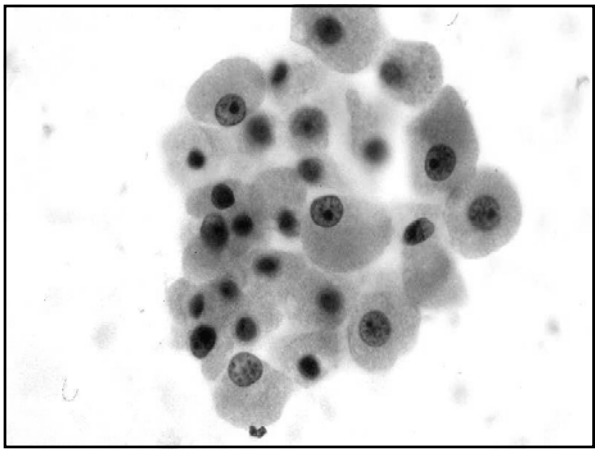
Oncocytic Follicular Lesions

Cytology

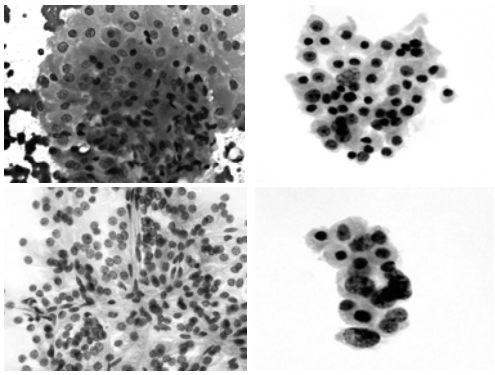
Oncocytic follicular lesions (AKA Hurthle cell lesions)

- FNA
  - Can only render the diagnosis of neoplasm
  - Specimen:
    - One cell population of oncocytic cells
    - Scant colloid
    - Cellular groups and single cells
    - Cellular dys-cohesion
    - Transgressing vessels
- Nuclear atypia does not differentiate between benign and malignant lesions
- Really don't know what a dysplastic oncocytic follicular cell is?





Oncocytic follicular lesions



Oncocytic Follicular Lesion Follow-up

Study	# Cases	Surgical F/U	% Malignant
Giorgadze et.al – 2004	206	169 (82%)	45%
Pu et.al. – 2006	87	87 (100%)	31%
Zhang et.al – 2008	55	55(100%)	16%
Sippel et.al – 2008	57	57(100%)	21%
Sorrenti et.al – 2009	140	140 (100%)	18.6%
Raparia et.al – 2009	37	37(100%)	41%
Kim et.al – 2010	57	57(100%)	46%
Strazisar et.al – 2010	279	279 (100%)	50%
Keskek et.al. – 2010	37	37(100%)	22%
Roh et.al – 2011	401	287 (71.6%)	24%

Oncocytic Follicular cells & Chronic Lymphocytic Thyroiditis (CLT)

- Roh et.al. (AJCP 2011)
  - Positive predictive value of malignancy in oncocytic lesion with or without CLT (clinical or pathologic evidence)
    - With CLT – malignancy risk 9.5%
    - Without CLT – malignancy risk 25.2%

The Atypical Category in Bethesda Thyroid FNA Classification

The main culprit for nuclear atypia is:
Oncocytic Follicular Cell

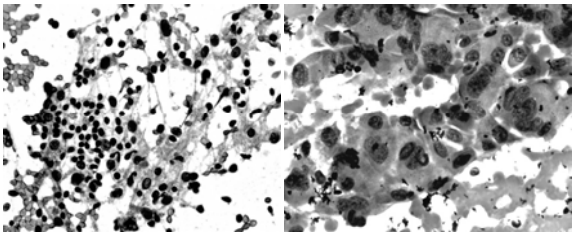
Atypia in Thyroid FNA Specimens

1. *Nuclear Atypia*
2. *Architectural Atypia*

Nuclear Atypia in Benign Thyroid Lesions Containing Oncocytes

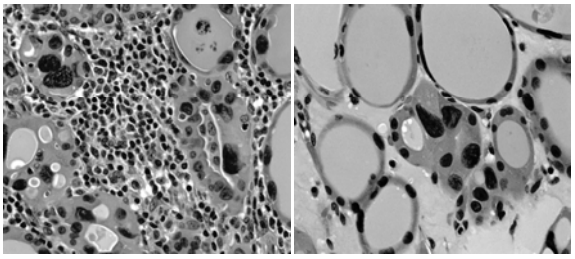
- Nuclear Pleomorphism
  - Chronic Lymphocytic thyroiditis (CLT)
  - Long Standing Goiter
  - Post FNA Change
  - Graves' Disease
    - Post Radioactive Iodine Treatment
    - Post Tapazole Treatment
  - Dyshormonogenetic Goiter

43-year-old with history of breast carcinoma underwent ultrasound guided FNA of a suspicious poorly circumscribed vascular area in right thyroid.



Surgical Excision

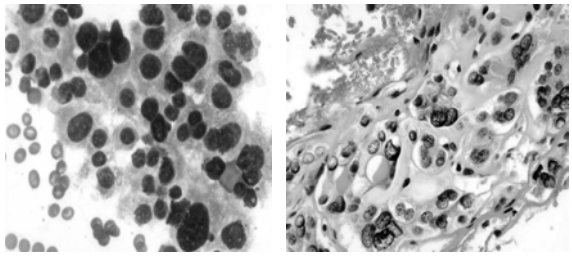
Chronic lymphocytic thyroiditis (CLT) with random nuclear atypia



Random Nuclear Pleomorphism in CLT

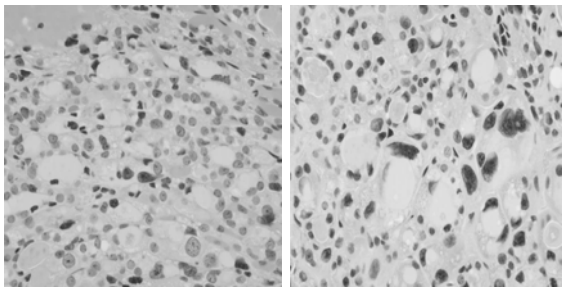
- Long standing history of hypothyroidism treated with thyroid hormone replacement.
- Distributed throughout the thyroid gland affected by CLT, however, can be concentrated in a nodule or nodular area.
- Seen in oncocytic cells (Thyroglobulin +ve)

32-year-old woman underwent FNA of a hypoechoic 2.2 cm right thyroid nodule

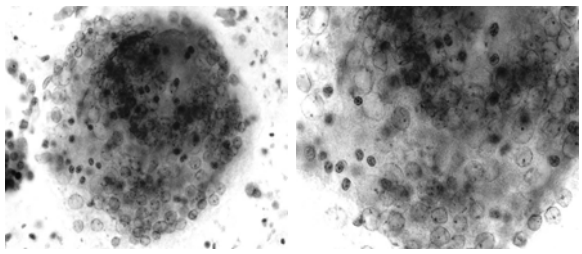


Surgical Excision

History of Graves' disease, treated with radioactive iodine



43-year-old female with long standing history of Hashimoto's thyroiditis-FNA



Total Thyroidectomy

Can Molecular Analysis of Thyroid FNA Specimens be Helpful in Further Classification of Atypical Cases?

Cost effectiveness of a molecular test

- The key drivers of cost effectiveness are:
- Cost of the test
- Cancer prevalence in cytologically indeterminate nodules
- The likelihood of surgery being performed on patients with such nodules
- Specificity of the novel molecular test.

Testing for Multiple Mutations in Thyroid FNA Samples
Now same panel available commercially

- Prospective study, 2003-2006, two centers (Univ. of Cincinnati, Univ. of Colorado)
- Thyroid nodule tested: 470
- Mutation detected: 32

	Risk of Cancer
BRAF (18)	**100%**
RAS (8)	**87%**
RET/PTC (5)	**100%**
PAX8/PPARg (1)	**100%**

Nikiforov et al. *JCEM* (2009)

Commercially Available Tests

1. Assuragen
2. Veracyte, INC

Asuragen

- **Austin, Texas – April 6, 2011. Asuragen, Inc. announced today the launch of *Inform™Thyroid, a panel of molecular markers used on Fine Needle Aspirates (FNA) of thyroid nodules to aid physicians in the management of thyroid cancer.***
- ***The FNAs are analyzed in Asuragen's CAP accredited CLIA Laboratory.***
- ***The Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer has stated, "The use of molecular markers (e.g., BRAF, RAS, RET/PTC, Pax8-PPARy) may be considered for patients with indeterminate cytology on FNA to help guide management."***

Afirma
Thyroid FNA Analysis

Indeterminate* results on thyroid FNA samples are a common and significant problem for physicians and their patients. FNA samples can be challenging to interpret and produce inconclusive results in up to 30 percent of cases.[1] Current guidelines recommend that most of these patients go to surgery.[2-3] However, the majority of these cases end up being benign.[1] Now, the Afirma Thyroid FNA Analysis delivers physicians an improved solution to better assess thyroid nodules.[4-6] The Afirma Thyroid FNA Analysis combines expert cytopathology and the novel Afirma Gene Expression Classifier.

Conclusions

- Most oncocytic lesions of the thyroid can be classified easily
- Chronic lymphocytic thyroid and nuclear pleomorphism can be problematic in thyroid FNA specimens
- Molecular analysis can definitely be helpful in oncocytic thyroid lesions diagnosed as atypical or neoplasm

Common Problems and Controversies in Salivary Gland Pathology

Raja R. Seethala, M.D.
Assistant Professor of Pathology and Otolaryngology
University of Pittsburgh Medical Center

Notice of Faculty Disclosure

In accordance with ACCME guidelines, any individual in a position to influence and/or control the content of this ASCP CME activity has disclosed all relevant financial relationships within the past 12 months with commercial interests that provide products and/or services related to the content of this CME activity.

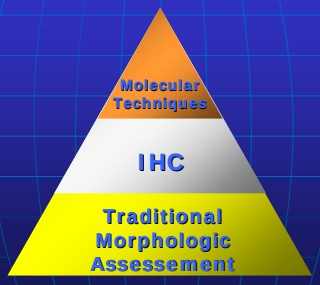
The individual below has responded that he has no relevant financial relationship with commercial interest to disclose:

Raja R. Seethala, MD, FASCP

The Challenges in Salivary Tumor Diagnosis

- Over 40 recognized epithelial tumor types
- Benign and malignant tumors show significant morphologic overlap
- Metastases need to be included occasionally in the differential diagnosis

Approaches to Facing These Challenges

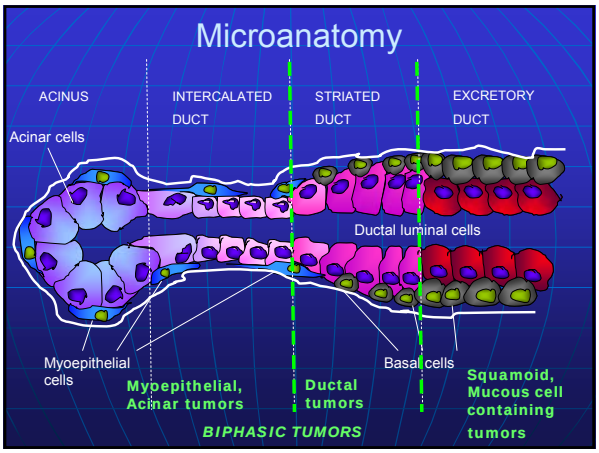


Topics for Discussion

- Normal Salivary Gland Phenotype
- Select 'Biphasic' Salivary Gland Tumors
- The Problem of Polymorphous Low Grade Adenocarcinoma (PLGA)
- Mucoepidermoid Carcinoma – Morphology meets molecular

Normal Salivary Gland Phenotype

Microanatomy



Immunophenotype by Cell Compartment

Myoepithelial

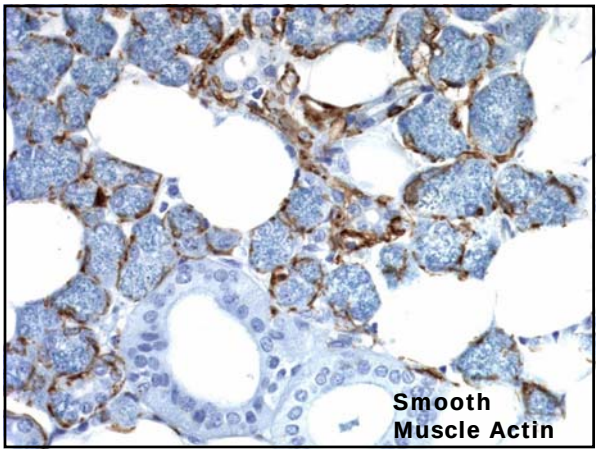
- Morphology
  - Varied, spindled to epithelioid, scant to abundant cytoplasm
  - Normal - Outermost layers of intercalated ducts and acini
  - Tumor – numerous patterns, surrounds ducts in biphasic tumors
- IHC
  - P63: positive
  - High MW keratins (CK5/6, 34βE12): positive
  - Muscle markers (actin/calponin): positive
  - Low MW keratins (CAM 5.2, CK 7,CK 19): weak positive

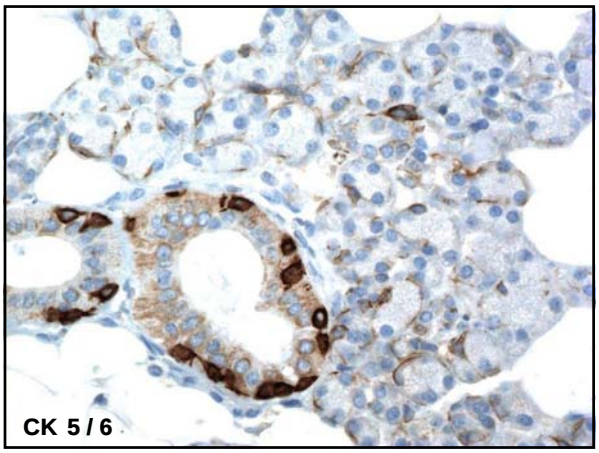
Basal

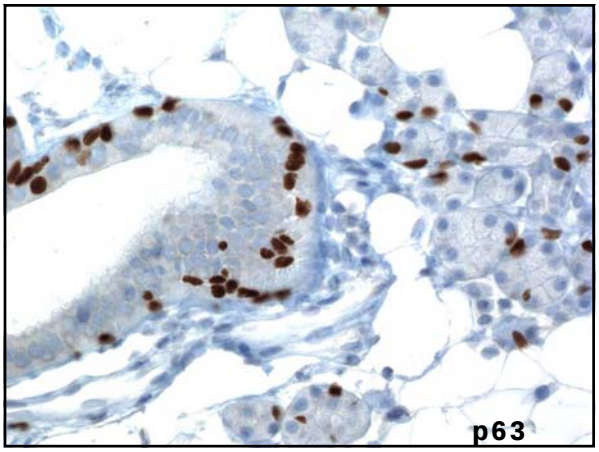
- Morphology
  - Scant cytoplasm, high N/C ratio
  - Normal - Outermost layers of large ducts
  - Tumor – Peripheral palisading in tumor nests
- IHC
  - P63: positive
  - High MW keratins (CK5/6, 34βE12): positive
  - Muscle markers (actin/calponin): weak positive to negative
  - Low MW keratins (CAM 5.2, CK 7,CK 19): weak positive to negative

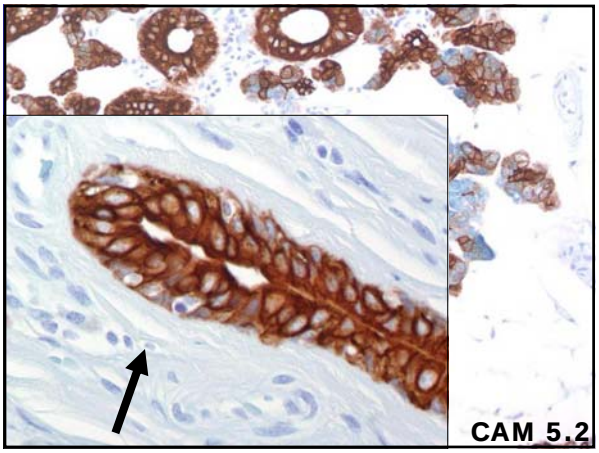
Ductal (and Acinar)

- Morphology
  - Cuboidal to columnar slightly eosinophilic to oncocytic and more prominent cytoplasm
  - Normal – luminal layer of all ducts
  - Tumor – tubules with secretions, central/inner layer in biphasic tumors
  - Acini – depends on type (serous vs mucinous)
- IHC
  - P63: negative
  - High MW keratins (CK5/6, 34βE12): focally positive to negative
  - Muscle markers (actin/calponin): negative
  - Low MW keratins (CAM 5.2, CK 7,CK 19): strongly positive (acini are weaker)



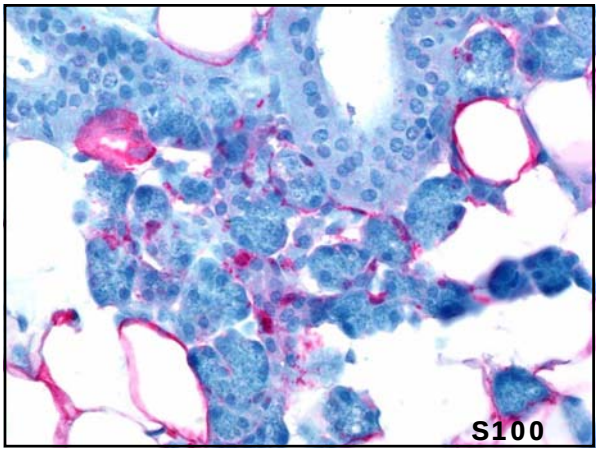

CK 5 / 6

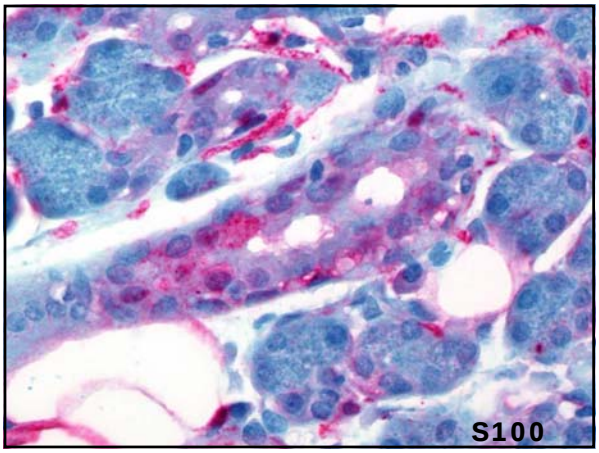

p63


CAM 5.2

S100 and Vimentin

- S100
  - Historically a myoepithelial marker
  - Has its uses
  - High infidelity (often stains intercalated ducts and sinonasal acini)
- Vimentin
  - Historically a myoepithelial marker
  - Strictly speaking not specific for myoepithelial
  - But still may be most sensitive (even more than p63)
  - Can support myoepithelial if morphology fits





Select Biphasic Tumors

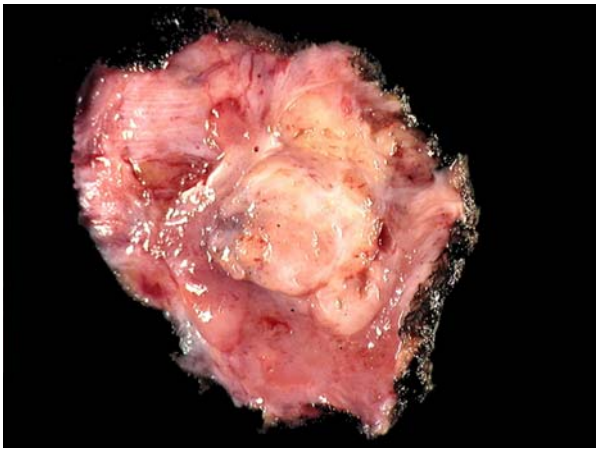
Definition

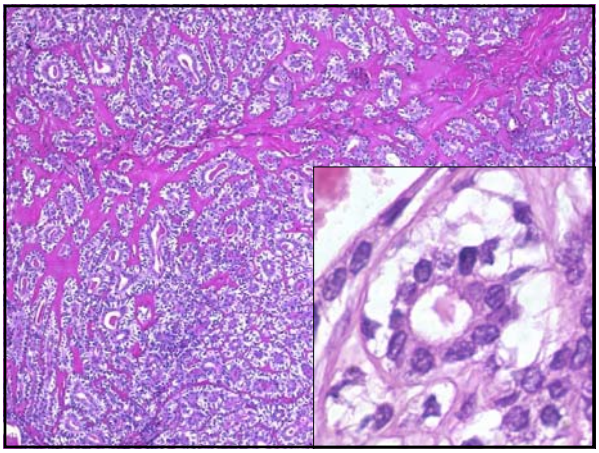
- Bilayered arrangement of luminal (ductal) cells and abluminal (basal and/or myoepithelial cells)
- Components often visible on H&E
- Delineation between cell components is sharp and organized
- IHC: pronounced phenotypic distinction between components

Prototypical Biphasic Tumors

- Benign
  - Pleomorphic Adenoma
  - Basal Cell Adenoma
  - Warthin Tumor
- Malignant
  - Epithelial Myoepithelial Carcinoma
  - Adenoid Cystic Carcinoma
  - Basal Cell Adenocarcinoma

Tumor types



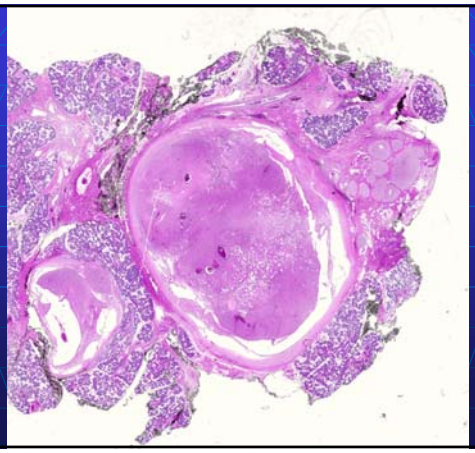


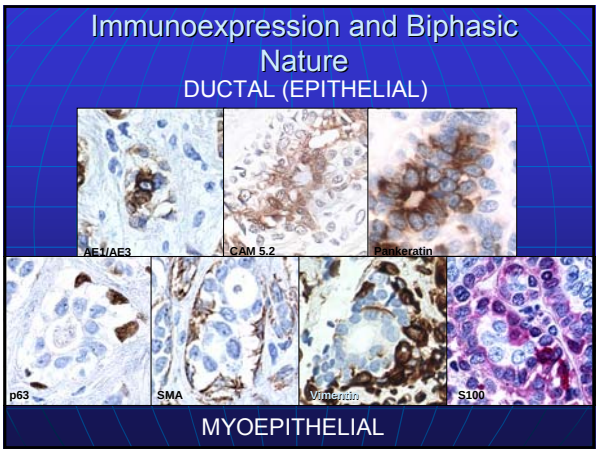
Epithelial Myoepithelial Carcinoma

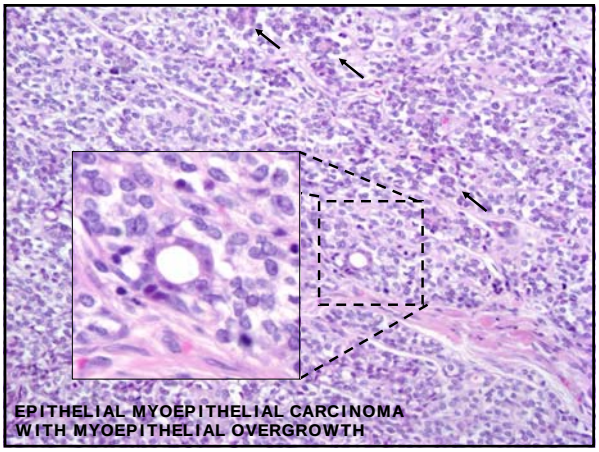
- Formally described by Donath et al 1972
- Age – 6th decade
- Female to male ratio - ~1.5:1.
- Site
  - parotid – 60-80%
  - submandibular – 8-15%
  - sinonasal – 5-10%
  - other – up to 5%
- Outcome very favorable (5 yr survival - 94%)

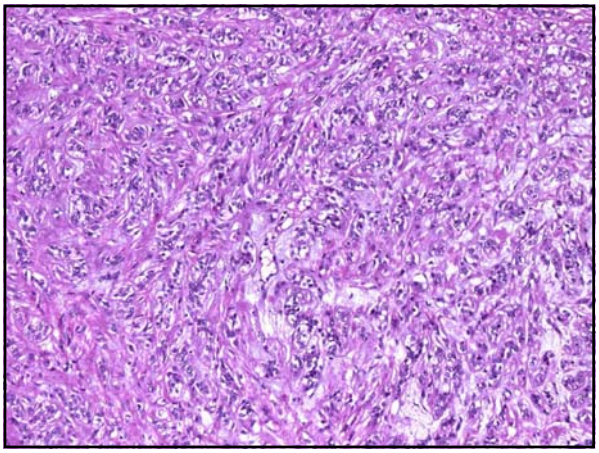
Histologic Features

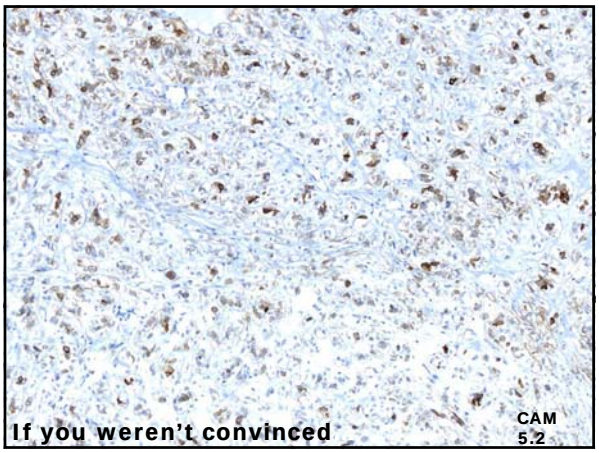
- Multinodular growth (can be partly encapsulated)
- ***Biphasic*** tubules with clear polygonal outer myoepithelial cells and inner eosinophilic cuboidal ductal cells
- Hyaline stroma
- Can have overgrowth of either component
- 'Non- clear cell' variants (i.e. oncocytic) exist

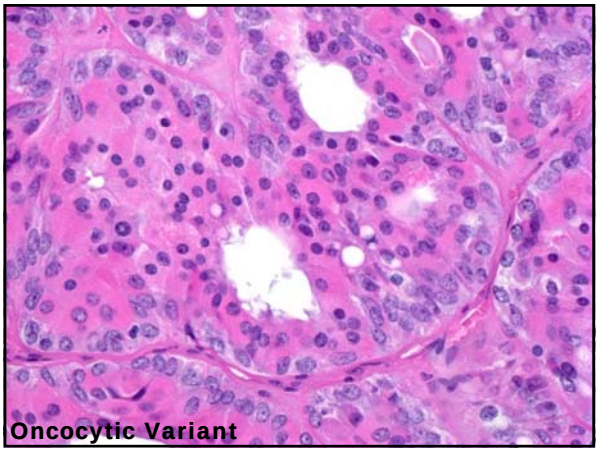



Immunoexpression and Biphasic Nature
DUCTAL (EPITHELIAL)
AE1/AE3
CAM 5.2
Pankeratin
p63
SMA
Vimentin
S100
MYOEPITHELIAL


EPITHELIAL MYOEPITHELIAL CARCINOMA
WITH MYOEPITHELIAL OVERGROWTH

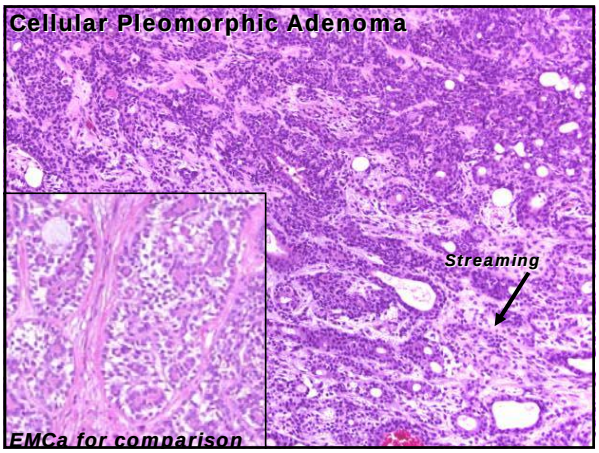


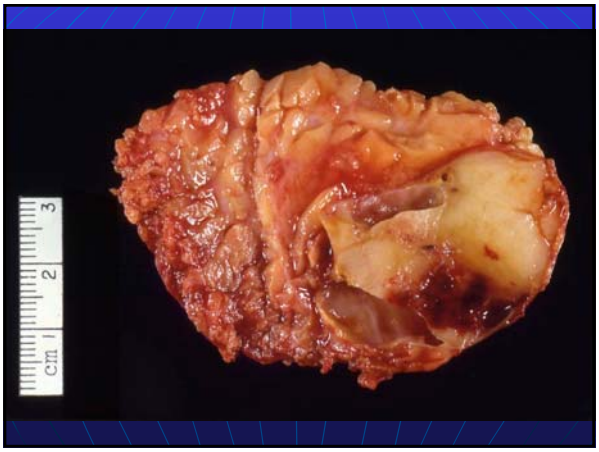


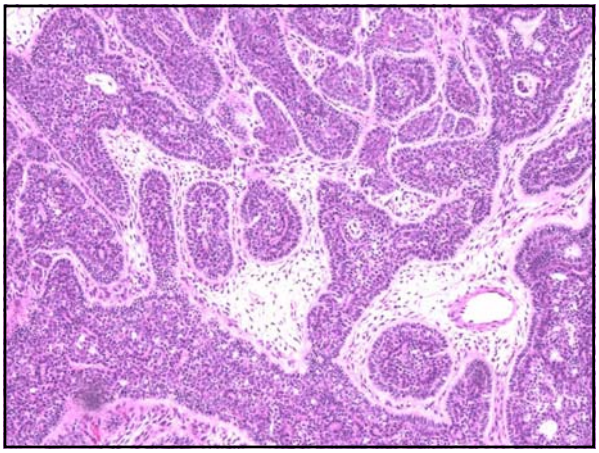


Distinction from Cellular Pleomorphic Adenoma

Cellular Pleomorphic Adenoma	Epithelial-myoepithelial Carcinoma
▪ Encapsulated non infiltrative	▪ Multinodular permeation
▪ Small indistinct myoepithelial cells that 'stream' into a myxoid stroma	▪ Larger Polygonal myoepithelial cells embedded in hyaline stroma with no 'streaming'
▪ Chondroid elements	


Cellular Pleomorphic Adenoma
Streaming
EMCa for comparison


cm 1
2
3



Basal Cell Adenoma (historic – monomorphic adenoma)

- Age 5th decade, F:M 2:1
- Parotid>>>submandibular>>>other sites
- Solitary slow growing mass

Basal Cell Adenoma

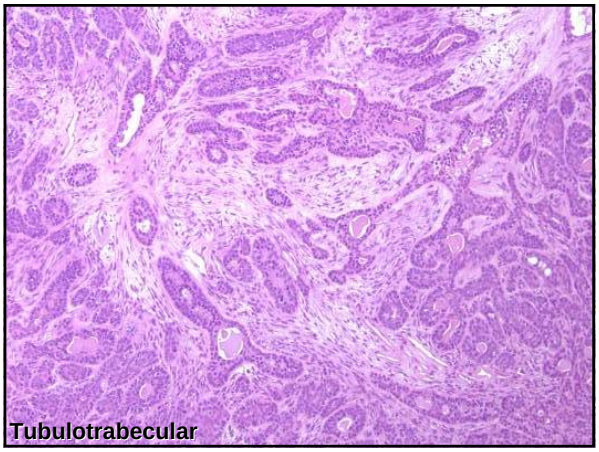
- Special variant – Dermal analogue (Membranous type)
  - Often Multifocal
  - Can be associated with Brooke Spiegler syndrome (multiple trichoepithelioma, cylindroma)
  - Molecular findings: *CYLD1* gene, chromosome 16q12-13. Presumed tumor suppressor gene, mutated or lost in sporadic and germline tumors

Basal Cell Adenoma

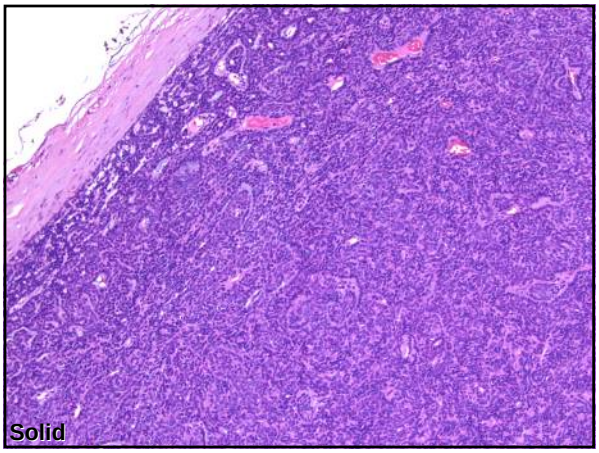
- Recurrence rate
  - Very low <2%
- Exception –Dermal analogue – 25%
  - May really be second primary rather than recurrence

Histologic Features

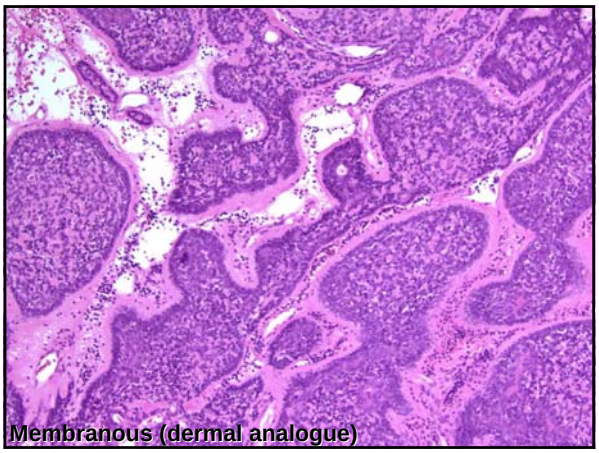
- Patterns: Tubulotrabecular, Solid, Cribriform, Membranous
- Basal cells
  - Dark cells – outermost palisaded layer
  - Pale cells – immediately adjacent to dark cells and can have squamoid features
- Ductal cells -vary in proportion
- Squamous and sebaceous elements can be present
- *Peculiar S100+ spindled 'myoepithelial derived' stroma in tubulotrabecular tumors*

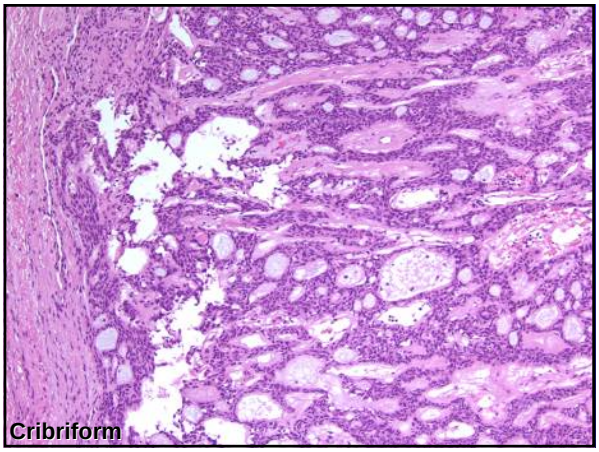


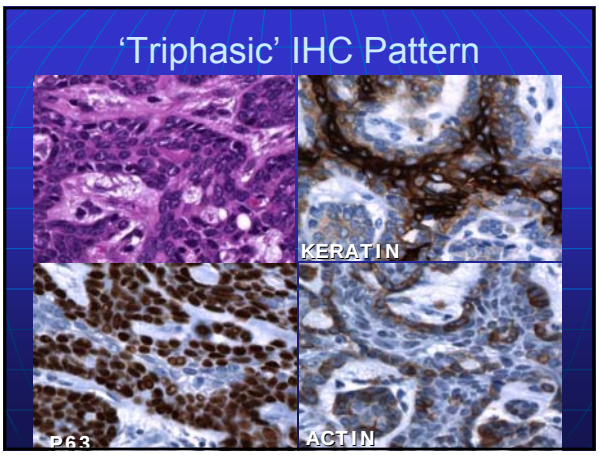
Tubulotrabecular

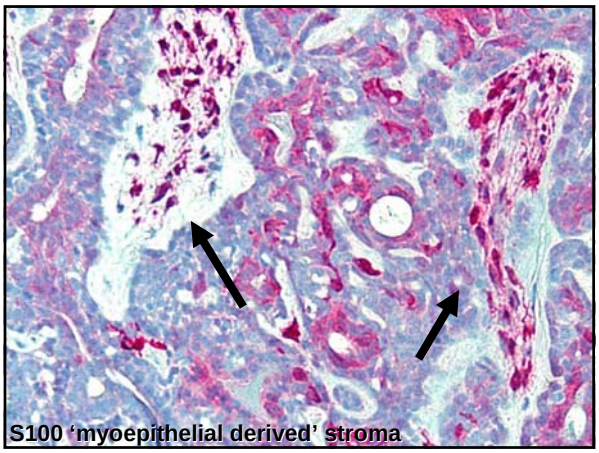


Solid


Membranous (dermal analogue)


Cribriform

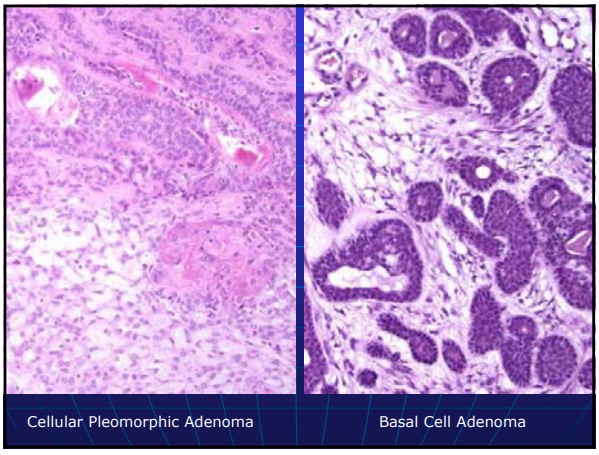

'Triphasic' IHC Pattern
KERATIN
P63
ACTIN



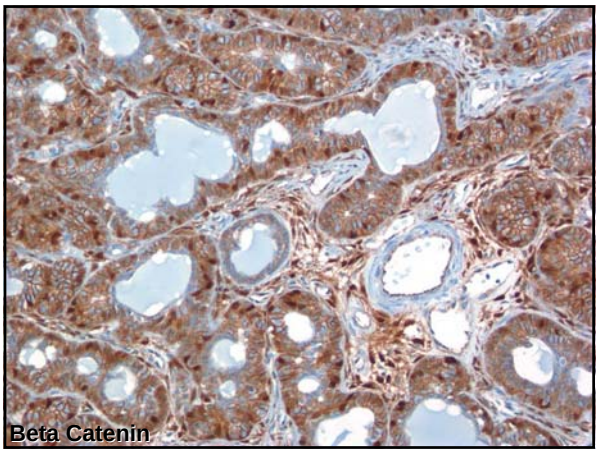
S100 'myoepithelial derived' stroma

Distinction from Cellular Pleomorphic Adenoma

Cellular Pleomorphic Adenoma	Basal Cell Adenoma
▪ No prominent palisading	▪ Prominent peripheral palisading
▪ Small indistinct myoepithelial cells that 'stream' into a myxoid stroma	▪ Distinct from surrounding hyaline or cellular 'myoepithelial derived' stroma
▪ Chondroid elements	▪ Sebaceous elements ▪ ***Nuclear Beta Catenin***



Cellular Pleomorphic Adenoma | Basal Cell Adenoma

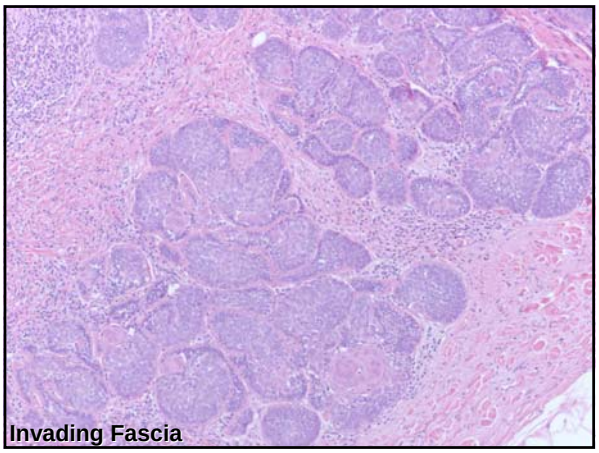

Beta Catenin

Basal Cell Adenocarcinoma

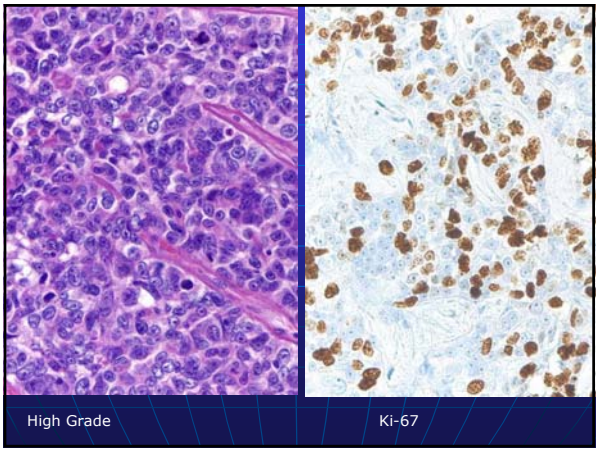
- Same morphologic patterns but invasive
- Age ~ one decade older than BCAC, M=F
- Usually de novo, but can arise from BCA (usually membranous type)
- Solid and membranous most common patterns

Histologic Features

- ***Infiltrative***
- Mitosis>4/10hpf
- Ki-67 >5%
- PNI (~1/3)
- High grade histology *rare*



Invading Fascia



High Grade Ki-67

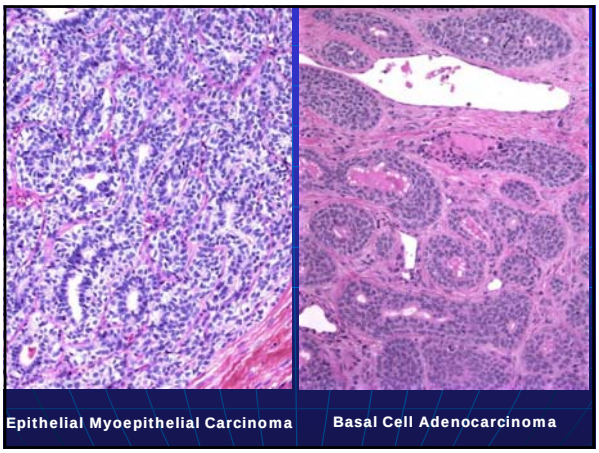
Basal Cell Adenocarcinoma vs Epithelial-Myoepithelial Carcinoma

Epithelial-Myoepithelial Carcinoma

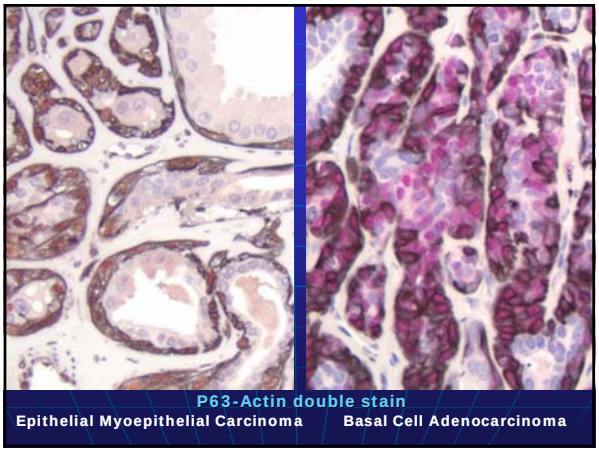
- No prominent palisading
- Abundant (clear) cytoplasm in outer layer
- P63 ≈ actin

Basal Cell Adenocarcinoma

- Prominent peripheral palisading
- Outer layers can be subdivided into dark and pale cells with scant cytoplasm
- P63> actin (only dark layer)
- ***Nuclear Beta Catenin***

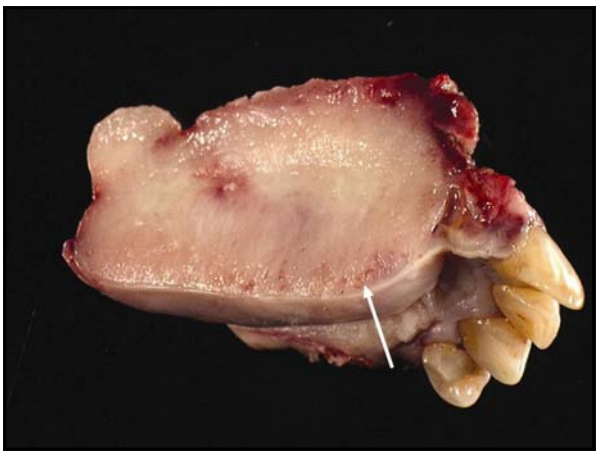


Epithelial Myoepithelial Carcinoma Basal Cell Adenocarcinoma



P63-Actin double stain

Epithelial Myoepithelial Carcinoma Basal Cell Adenocarcinoma



Adenoid Cystic Carcinoma (ACC)

- Biphasic Salivary Gland Tumor
  - (Ducts surrounded by myoepithelial cells)
- Tubular, Cribriform and Solid growth patterns
- Slow but relentless progression
  - 5 year survival = 75-80%
  - 15 year survival = <15%

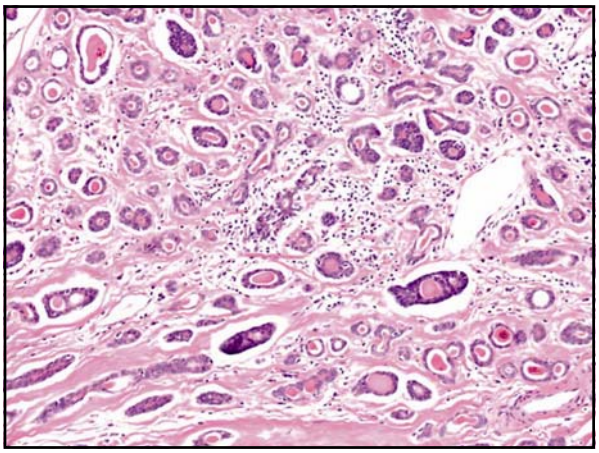
Odd things about ACC 'Risk'

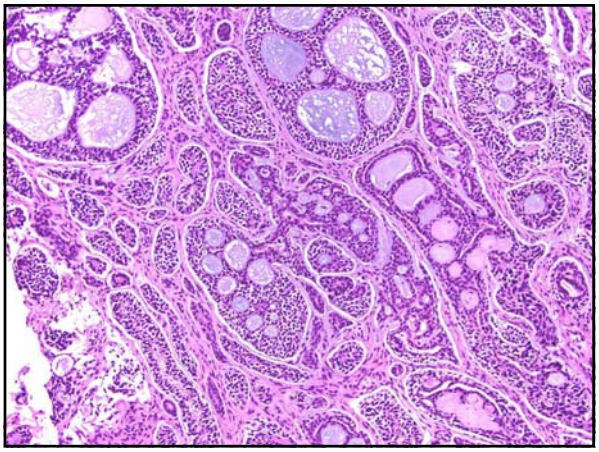
- Regardless of grade…
  - Infiltrative and locally aggressive thus considered *high risk* for XRT
  - But LN metastasis rate is low ~5%, thus considered *low risk* for neck dissection
- Grade is useful prognostically

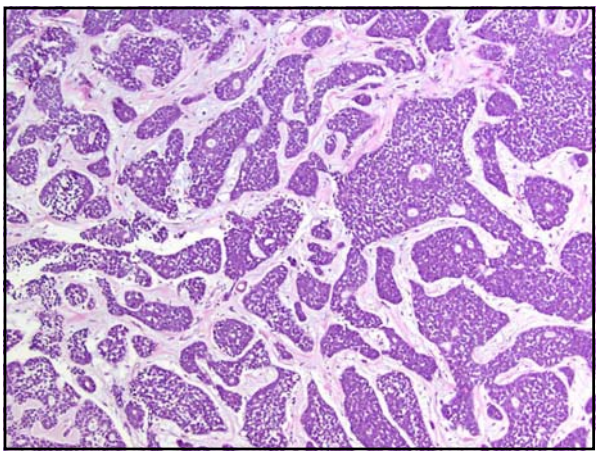
Grading Scheme

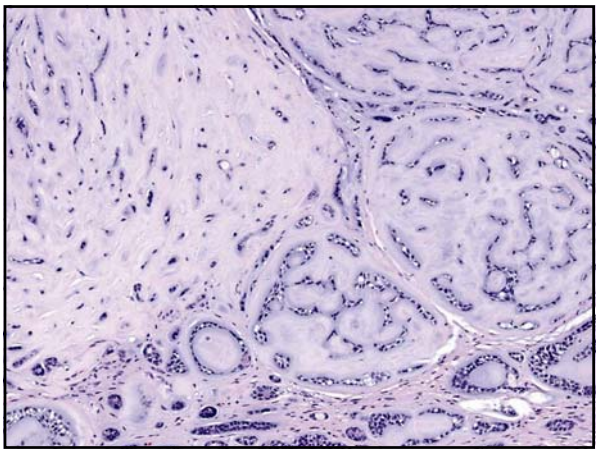
- WHO scheme (2005)
  - tubular
  - cribriform
  - solid*

  *30% or more portends a worse prognosis
- *Sclerosing Variant*



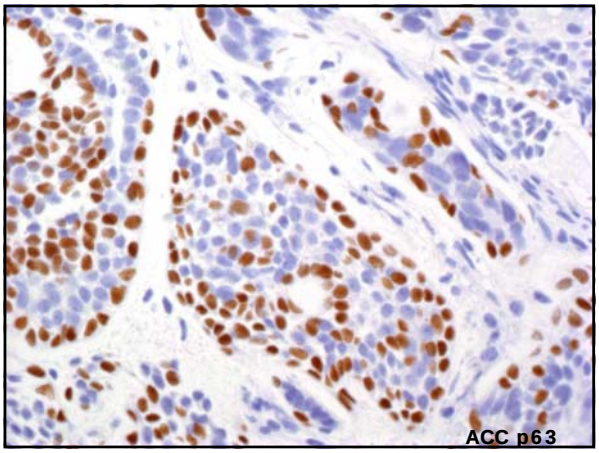


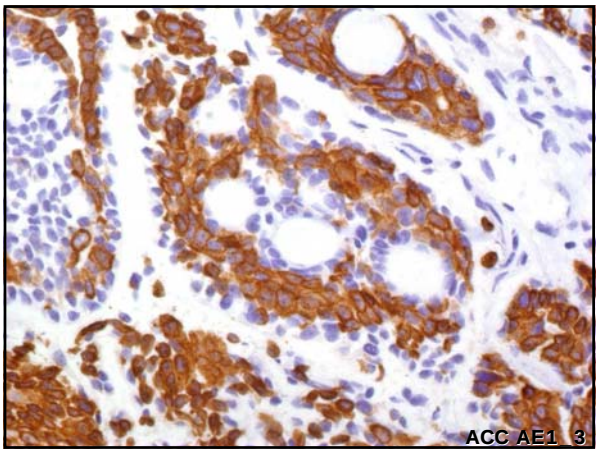


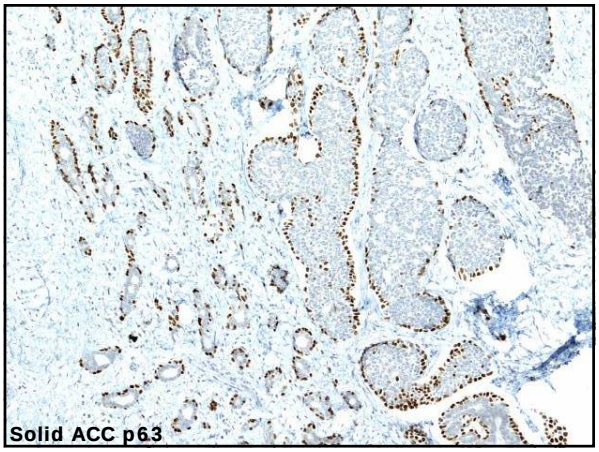


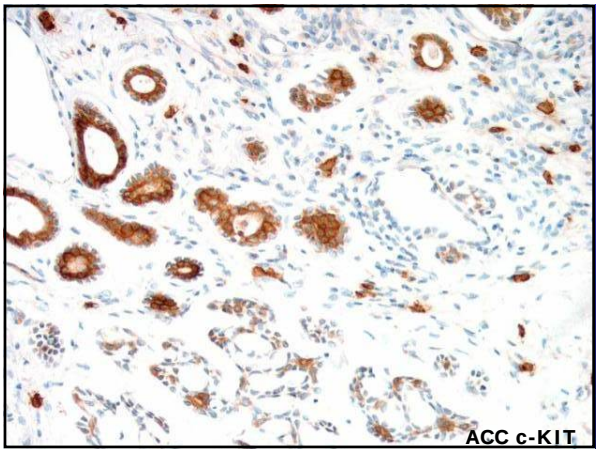
Immunophenotype

- Biphasic
  - Inner ductal
  - Outer myoepithelial
- C-kit strongly positive (mainly ductal)




ACC AE1_3

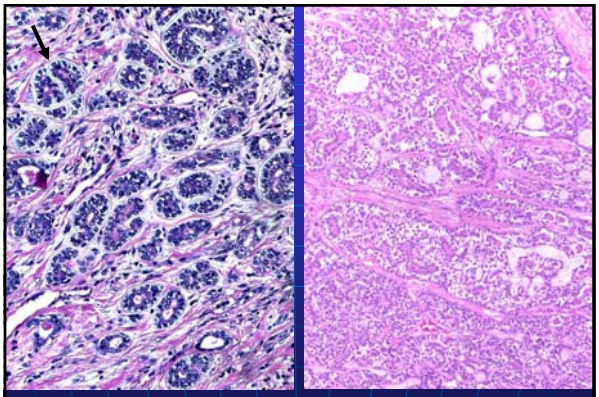

Solid ACC p63


ACC c-KIT

Adenoid Cystic Carcinoma (Tubular) vs Epithelial-Myoepithelial Carcinoma

Adenoid Cystic Carcinoma	Epithelial-Myoepithelial Carcinoma
▪ Very infiltrative	▪ Typically multinodular pushing permeation
▪ Small dark angulated myoepithelial cells, scant cytoplasm	▪ Large polygonal myoepithelial cells
▪ Clefting between tumor nests and stroma	▪ Occasional single cell dyshesion but no clefting between tumor and stroma

Both can be c-Kit +!!

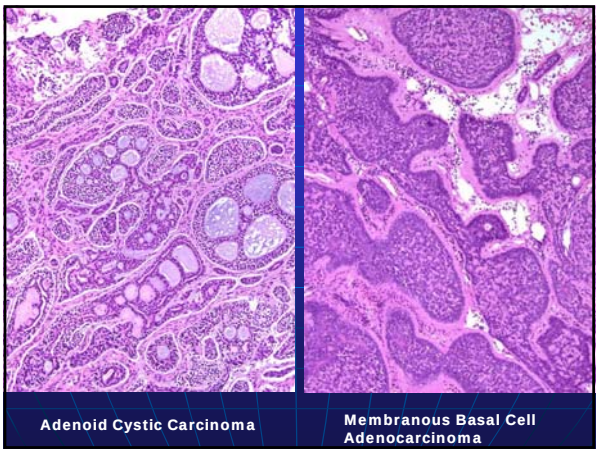


Adenoid Cystic Carcinoma | **Epithelial Myoepithelial Carcinoma**

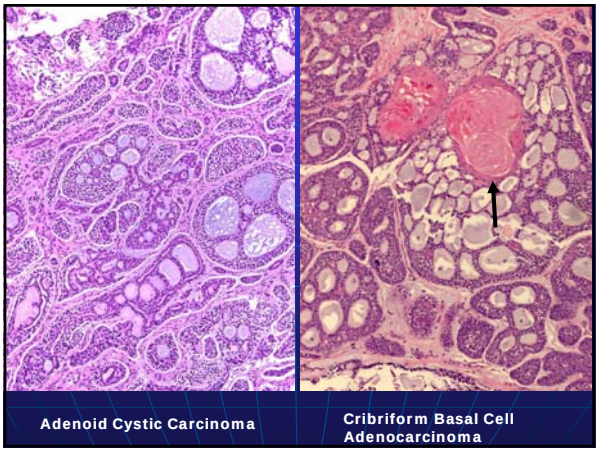
Adenoid Cystic Carcinoma (Cribriform and Solid) vs Basal Cell Adenocarcinoma (Membranous and Cribriform)

Adenoid Cystic Carcinoma	Basal Cell Adenocarcinoma
▪ Highly infiltrative	▪ Variable border often cystic or partly encapsulated
▪ Cylinders are thicker	▪ Small droplets of matrix in membranous pattern
▪ Small dark angulated myoepithelial cells, scant cytoplasm	▪ Vesicular with peripheral palisading, 'triphasic' staining frequent
▪ 'Pure,' rarely any metaplasia	▪ Squamous and sebaceous elements

Both can be c-Kit +!!



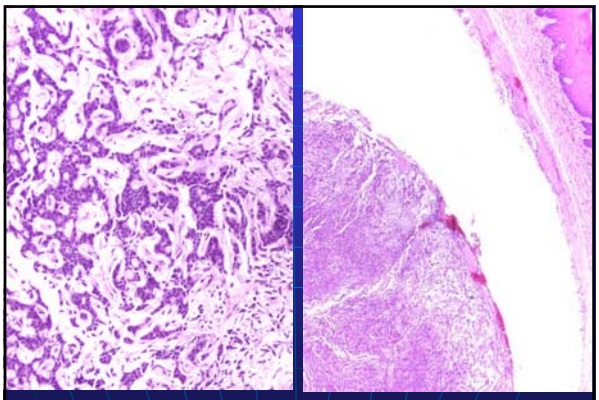
Adenoid Cystic Carcinoma | Membranous Basal Cell Adenocarcinoma



Adenoid Cystic Carcinoma | Cribriform Basal Cell Adenocarcinoma

Final Words on Biphasic Tumors: Biopsies

- Tremendous overlap
- Classification best done on resection
- Benign vs Malignant
  - Requires tumor normal interface with invasion
  - OR Perineural or angiolymphatic invasion
  - OR high grade histology
  - OR must have perfect features for a given tumor type



Biphasic tumor 1986 –
called Adenoid Cystic Carcinoma

Resection – Cellular PA
Recurrence free as of 2007

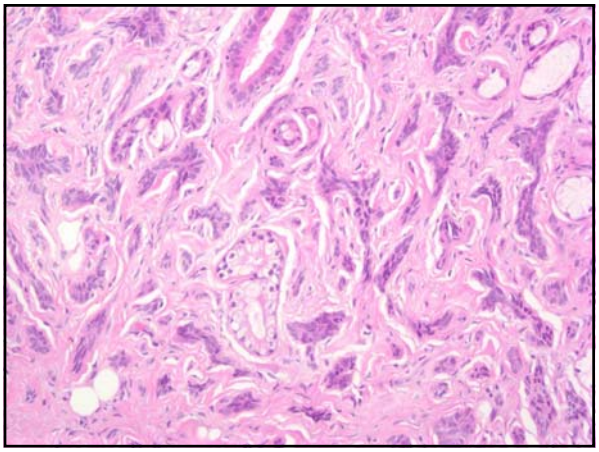
The Problem of Polymorphous Low Grade Adenocarcinoma (PLGA)

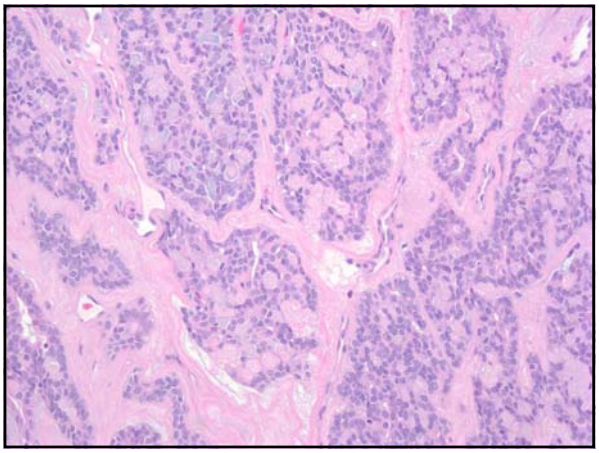
PLGA

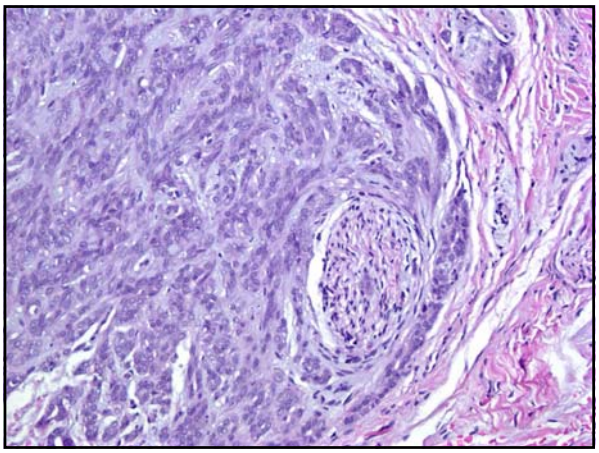
- Originally coined by Evans and Batsakis - 1984
- F:M – 2:1, Age: 5th - 6th decade
- Almost exclusively minor salivary (palate 60-80%)
- *Historically confused with Adenoid Cystic Carcinoma*
- Recurrences in 1/3 of patients
- 0-17% nodal metastasis rate
- Distant metastases and deaths from disease rare

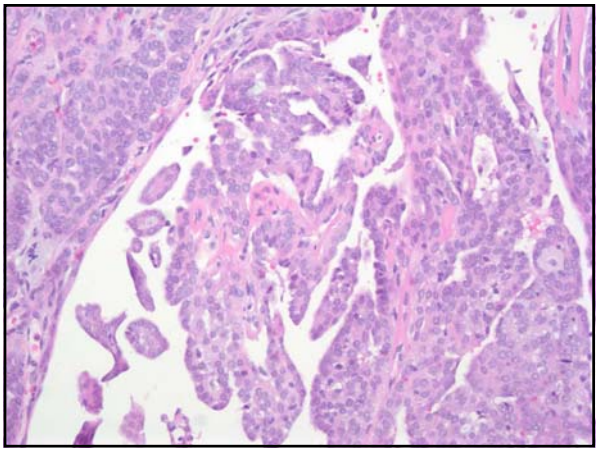
Histologic Features and Immunophenotype

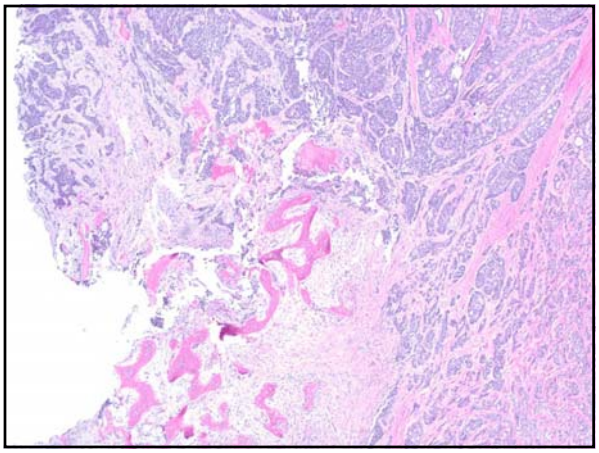
- Tubular, Cribriform, Solid and Papillary Growth patterns
- Bone invasion in ¼ of patients
- 'Activated' intercalated duct phenotype (S100+, AR-, GCDFP 15 -, Her-2/neu:0-1+)
  - ***Polymorphous Low Grade Adenocarcinoma***
  - *Low Grade Salivary Duct Carcinoma*
  - *Cystadenocarcinoma (subset)*
  - *Mammary Analogue Secretory Carcinoma (NEW!!!)*











Important Facts about PLGA

- Low grade carcinoma
- Polymorphous in pattern
- BUT monomorphic cytologically
- Ductal (epithelial) phenotype with only occasional myoepithelial features
- NOT truly biphasic

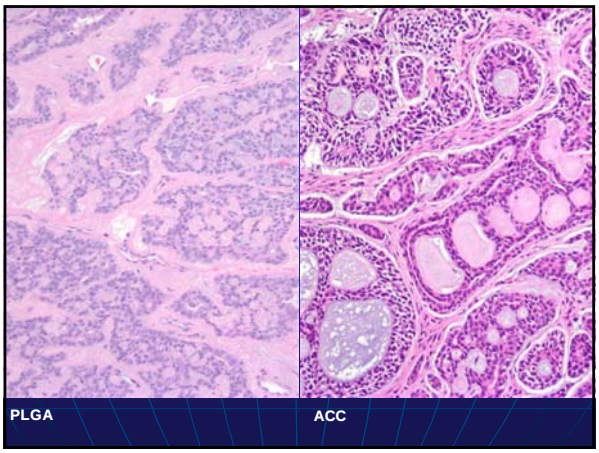
Polymorphous low grade adenocarcinoma vs Adenoid cystic carcinoma

An Overrated Differential Diagnosis??

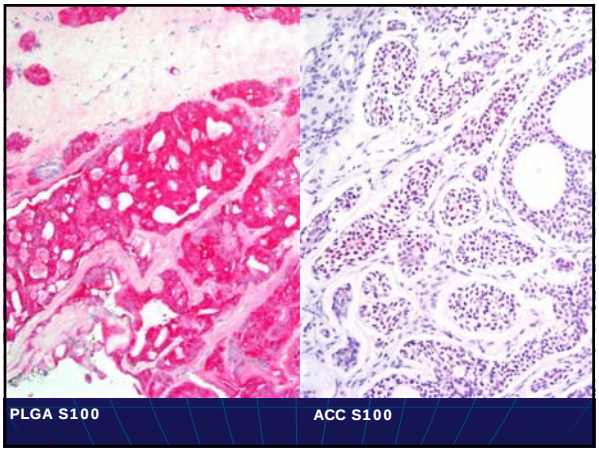
Distinction from Adenoid Cystic Carcinoma

- PLGA
  - Not biphasic
  - Classic vesicular clear 'papillary thyroid carcinoma' nuclei
- S100 – strong and diffuse
- Otherwise predominantly ductal immunophenotype
- Other markers – c-kit weakly positive, CD43 negative, ki-67 <10%

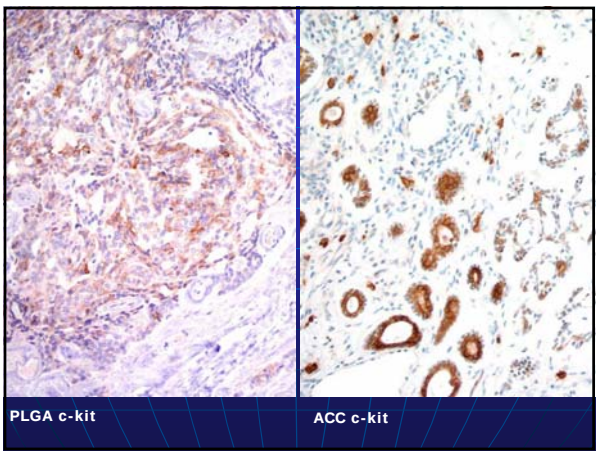
- ACC
  - Biphasic
  - Angulated hyperchromatic nuclei
  - Stromal clefting
- S100 – variable
- Otherwise biphasic phenotype
- Other markers – c-kit strongly positive, CD43 occasionally positive, ki-67 ~15%+



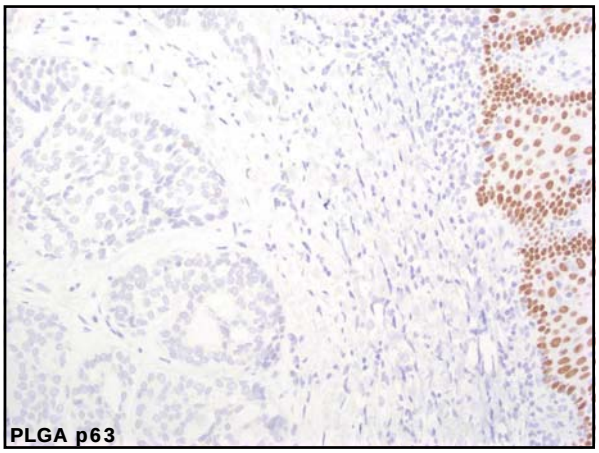
PLGA ACC

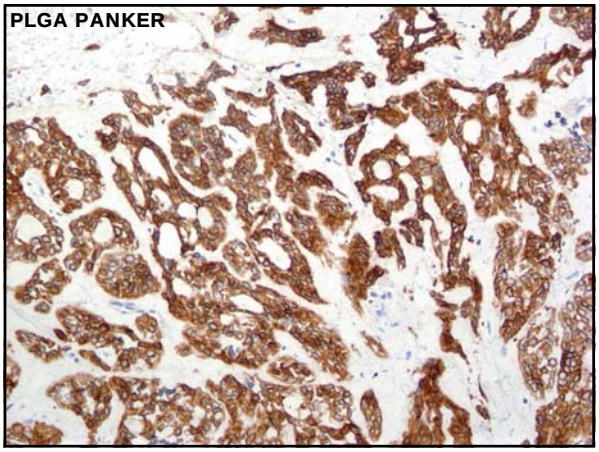


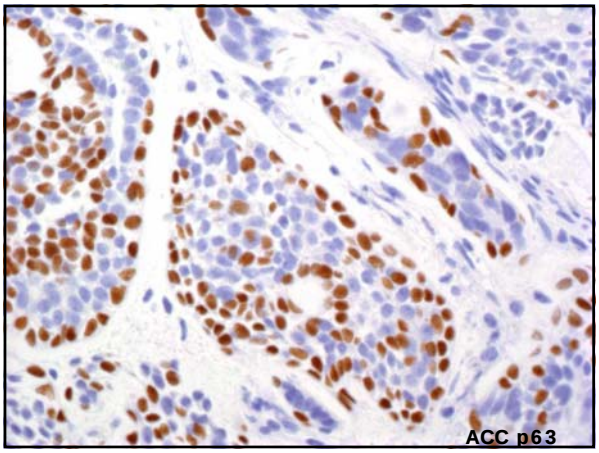
PLGA S100 ACC S100

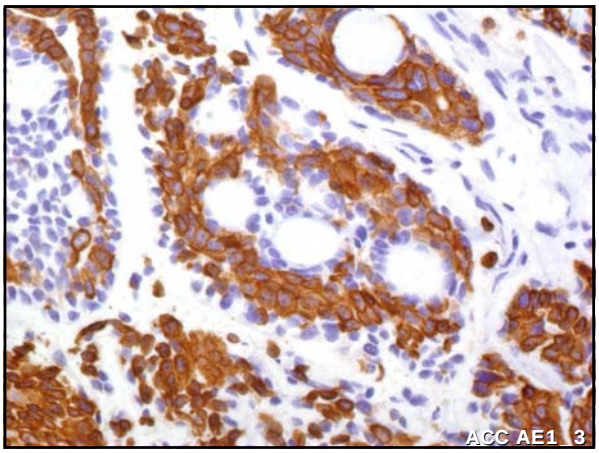


PLGA c-kit ACC c-kit


PLGA p63


PLGA PANKER


ACC p63



PLGA vs Other S100 positive 'Activated Intercalated Ductal' Tumors

Low grade salivary duct carcinoma (SDCA)

- AKA low grade intraductal carcinoma, low grade cribriform cystadenocarcinoma
- 6th-7th decades, almost always in parotid
- Resembles low grade DCIS or ADH of breast
- Unlike conventional salivary duct CA
  - Predominantly in-situ, very indolent behavior
  - Not apocrine but 'activated' intercalated duct
- Relationship between conventional and low grade SDCA unclear

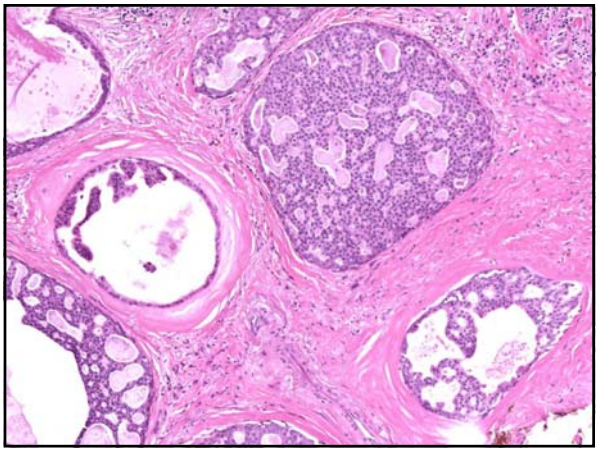
Distinction of PLGA from Low Grade Salivary Duct Carcinoma

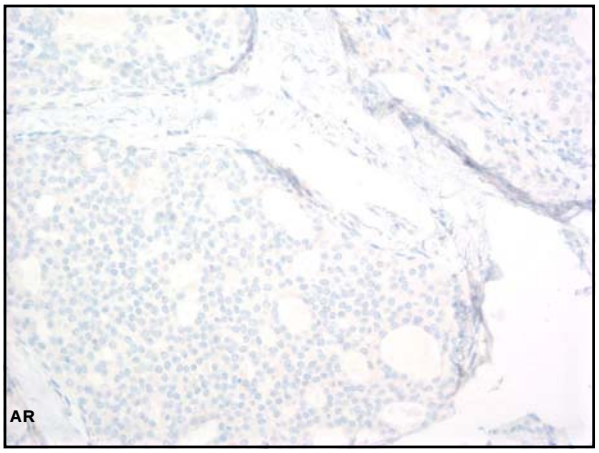
PLGA

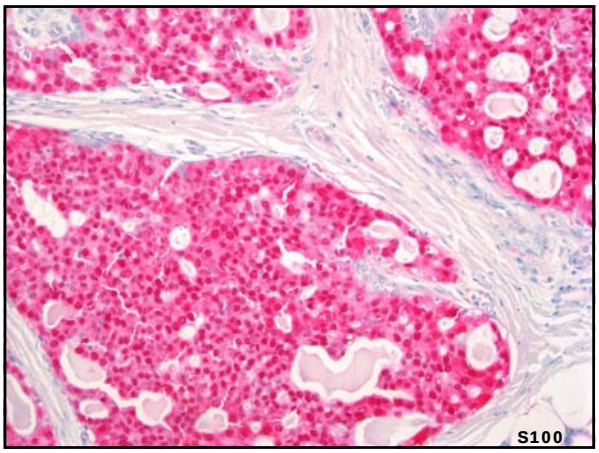
- Palate and Minor Salivary
- Infiltrative
- Ovoid vesicular nuclei

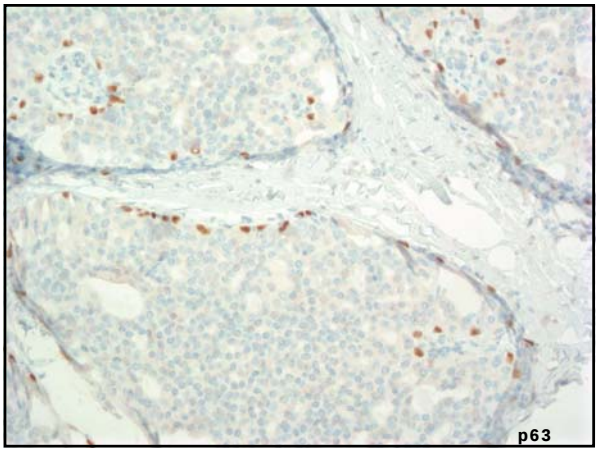
Low Grade Salivary Duct Carcinoma

- Parotid
- Well demarcated with a p63 + delimiting layer (intraductal)
- Small round nuclei







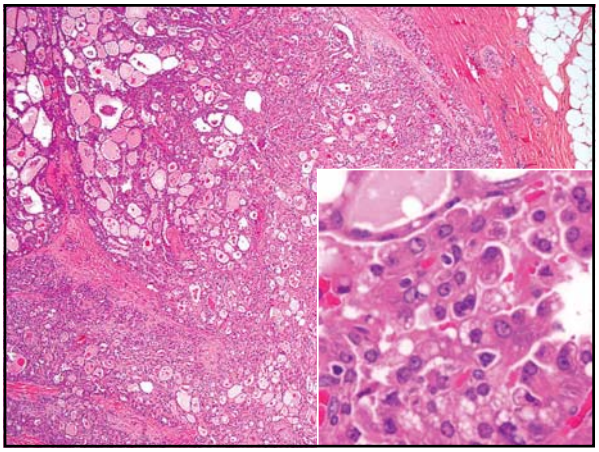


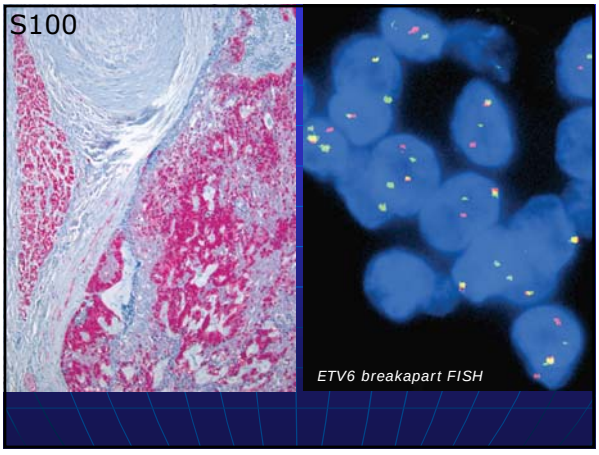
Mammary Analogue Secretory Carcinoma (MASC)

- Described by Skalova et al 2010
- Tumors culled from zymogen granule poor acinic cell carcinomas
- Identical to juvenile secretory carcnioma of breast
- Highly vacuolated eosinophilic cytoplasm, lobular cribriform growth and mucin
- S100+, STAT5a +, vimentin +
- Harbors a (12;15) (p13;q25) *ETV6-NTRK3* translocation
- Slight male predilection, 5th decade
- ~30% recurrence rate

Distinction of PLGA from MASC

PLGA	MASC
▪ Palate and Minor Salivary	▪ Mainly Parotid
▪ Infiltrative	▪ Lobular but permeative
▪ Ovoid vesicular nuclei	▪ Variable nuclei ▪ Abundant vacuolar cytoplasm ▪ Mucin ▪ ETV6-NRTK3 translocation





Unresolved Issues in PLGA

- Papillary predominant pattern
  - Adverse prognosticator
  - ?Separate entity
- Cribriform Adenocarcinoma of Minor Salivary Gland Origin
  - Cribriform predominant pattern favoring base of tongue site
  - PLGA variant vs Distinct entity
  - More aggressive than typical PLGA

Mucoepidermoid Carcinoma – Morphology meets molecular

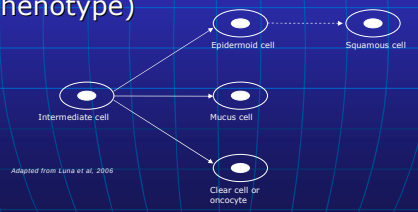
Molecular Profiles of Salivary Gland Tumors

Key Molecular Alterations in Salivary Gland Tumors

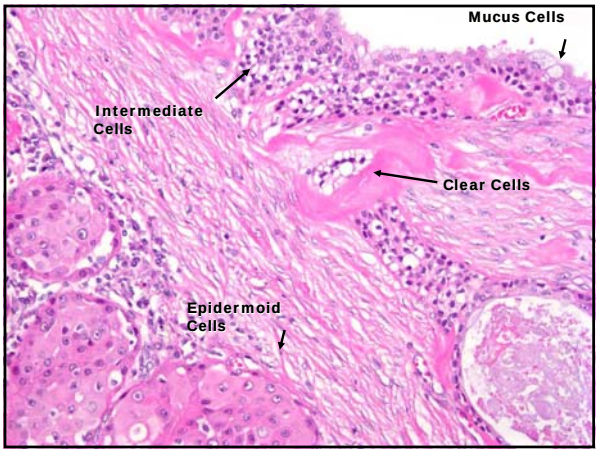
Tumor	Chromosomal Alteration	Gene	Prevalence
Pleomorphic Adenoma	8q12 12q13-15 rearrangements	*PLAG1* *HMGA2*	25-30% 10-15%
Membranous Basal Cell Adenoma/ Adenocarcinoma	16q12-13 Loss of heterozygosity/ mutation	*CYLD1*	75-80%
Mucoepidermoid Carcinoma	t(11;19)(q21;p13) t(11;15)(q21;q26)	*CRTC1-MAML2* *CRTC3-MAML2*	40-80% ~5%
Salivary Duct Carcinoma	17q21.1amplification	*ERBB2*	~40%
Adenoid Cystic Carcinoma	t(6;9)(q22-23;p23-24)	*MYB-NFIB*	25-50%
Mammary Analogue Secretory Carcinoma	t(12;15)(p13;q25)	*ETV6-NRTK3*	~100% (defining)
Hyalinizing Clear Cell Carcinoma	t(12;22)(q21;q12)	*EWSR1-ATF1*	~100% (defining)

Background

- MEC is the most common salivary gland malignancy
- Diverse cell types (excretory duct phenotype)



Adapted from Luna et al. 2006

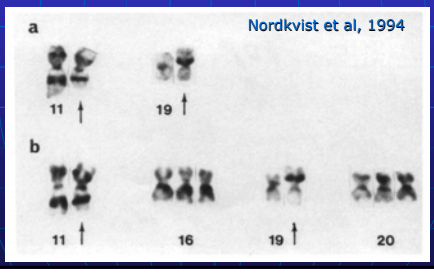


Grading

- *Arguably no other salivary gland tumor in which grading is as important to prognosis and therapy*
- However, reproducibility poor
- ***Intermediate grade outcome varies based on grading system***
- Objective Prognosticator Desirable

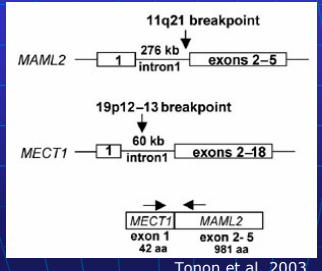
The Translocation

- Major breakthrough in MEC tumorigenesis
- t(11;19)(q14-21;p12) described in early 1990s by conventional karyotype



Characterization

- Tonon et al 2003 identify translocation partners as *MECT1 (now CRTC1)* (Ch 19) and *MAML2* (Ch 11)

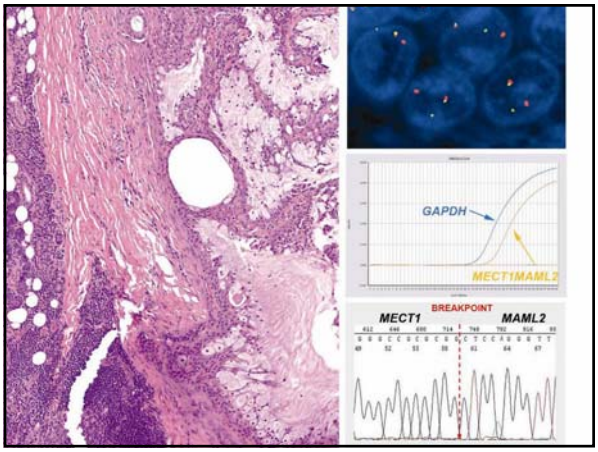


Tonon et al, 2003

- Fehr et al 2008 discover *CRTC3-MAML2* translocation

Prevalence of Translocation

Study	Overall	%	Low		Intermed		High	
Martins 2004	7/10*	70%	2/2	100%	4/5	80%	0/2	0%
Behboudi 2006	16/29*	55%	13/14	93%	2/3	67%	0/11	0%
Tirado 2007	18/22	82%	2/2	100%	11/13	85%	5/7	71%
Fehr 2008	48/67	72%	29/35	83%	14/21	66%	5/11	46%
Seethala 2010	**29/48 cohort 7/7 validation**	**60% 100%**	**12/15 3/3**	**80% 100%**	**6/9 2/2**	**67% 100%**	**11/24 2/2**	**41% 100%**
Chenevert 2011	**14/14**	**100%**	**5/5**	**100%**	**7/7**	**100%**	**2/2**	**100%**
Schwarz 2011	25/40	63%	22/27	81%	0/3	0%	3/10	30%
Okomura 2011	44/111	40%	40/72	56%	3/9	33%	1/26	4%
Overall	208/348	**60%**	128/175	**73%**	49/72	**68%**	29/86	**34%**



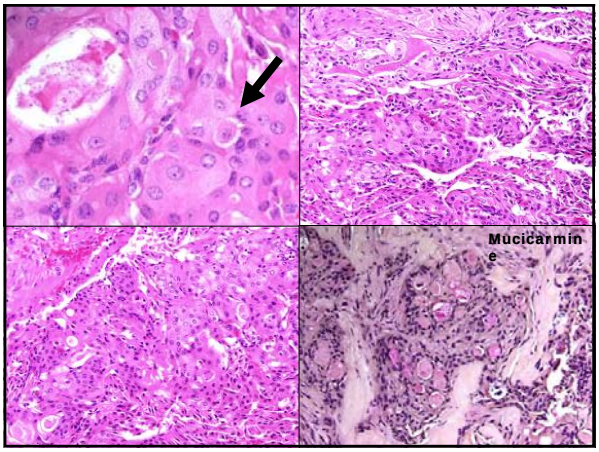
Prognostic Value – Replacement for Grade?

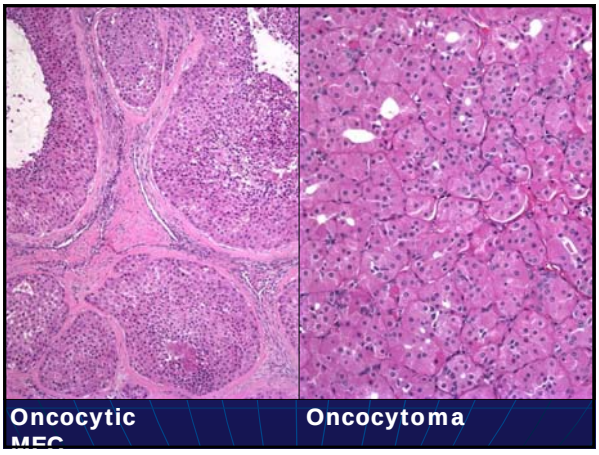
- (4 references, n=189) Overall survival
  - Translocation + MEC =96%
  - Translocation – MEC = 60%
- Okabe et al 2006
  - Translocation is independent favorable prognosticator (multivariate analysis)
- However at least 7 disease related deaths in Translocation + tumors reported
- Thus likely supplement but not entirely replace grade

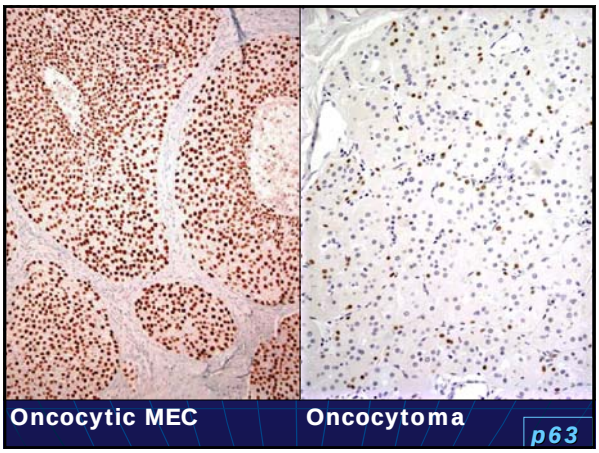
Diagnostic (rather than Prognostic) Utility: Oncocytic MEC

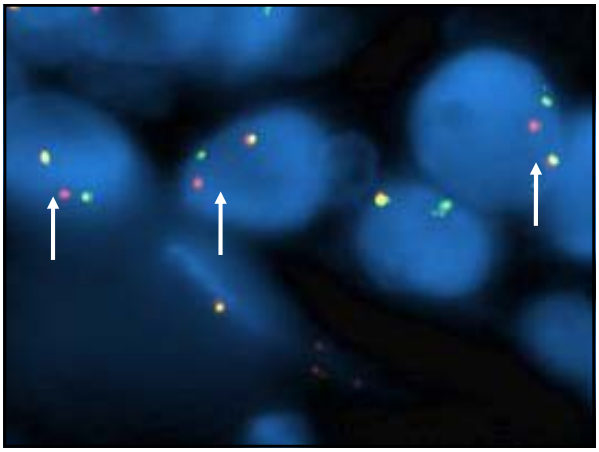
- Variant morphology: 3% of all MEC
- Main differential diagnosis – Oncocytoma

	Oncocytic MEC	Oncocytoma
H&E	Cellular fibrosis – epidermoid "cobblestoning"	+/- Sclerosis. Tubules
Mucus cells	Present	Absent
p63	Diffuse	Patchy and Basal
MECT/MAML	Subset + (70%)	Negative









Mucoepidermoid Carcinoma (MEC) vs Adenosquamous Carcinoma (AsqCA)

MEC
- Salivary gland tumor
- Variable behavior based on grade, etc
- Characterized largely by *CRTC1 (MECT1)-MAML2* or *CRTC3-MAML2* translocation

AsqCA
- SCC variant (in H&N)
- Generally very aggressive behavior
- No known defining gene alterations

Most common reason for misdiagnosis of high grade MEC in our institution: 1956 – present

(Seethala et al 2010, Chenevert et al 2011)

Criteria for AsqCA (Alos et al, 2004)*

- Presence of surface dysplasia
- Infiltrative growth pattern
- Pronounced keratinization
- Discrete adenocarcinomatous foci (often in deep portions of tumor),
- Pronounced nuclear atypia
- Absence of intermediate cells

*Alos L, Castillo M, Nadal A, et al. Adenosquamous carcinoma of the head and neck: criteria for diagnosis in a study of 12 cases. *Histopathology.* Jun 2004;44(6):570-579.

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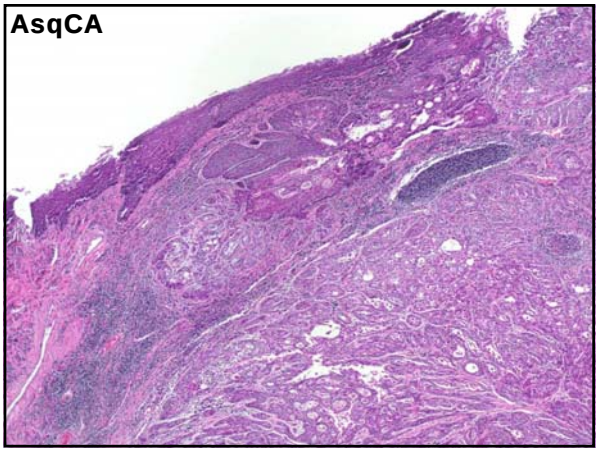

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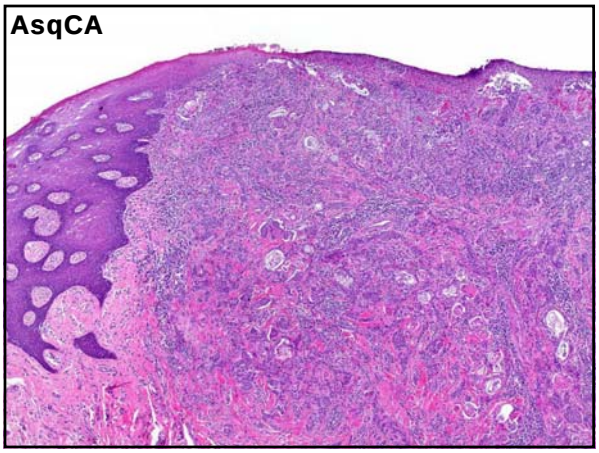

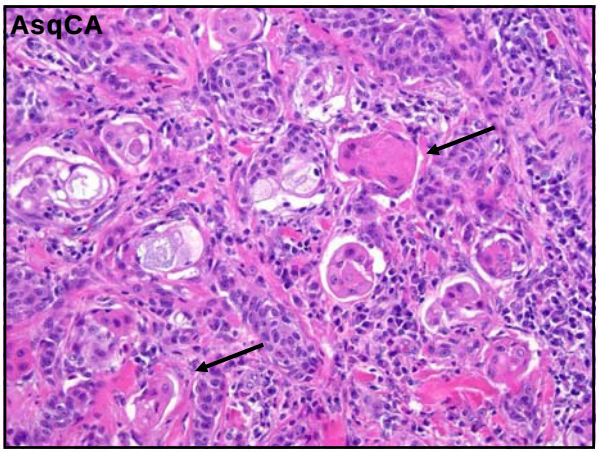
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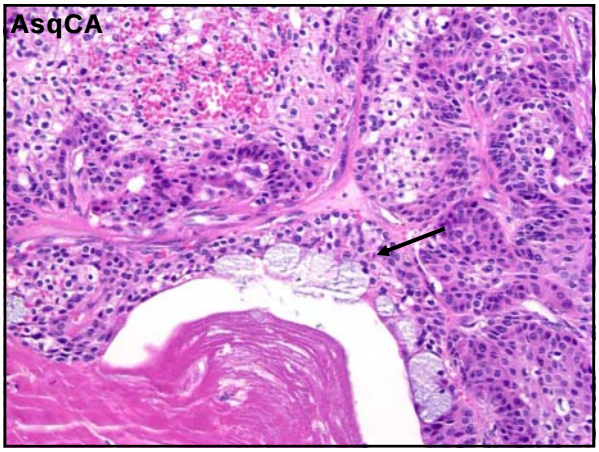
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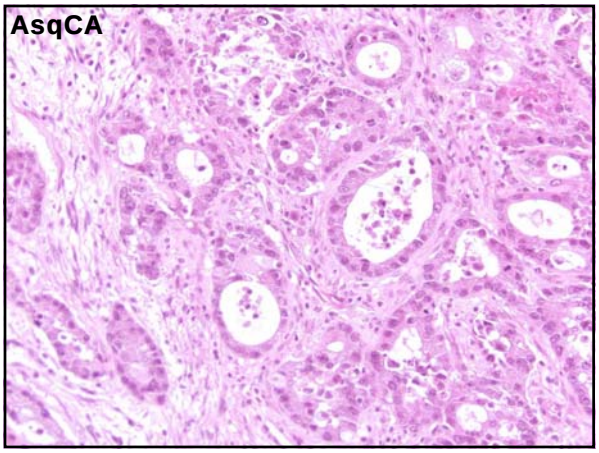
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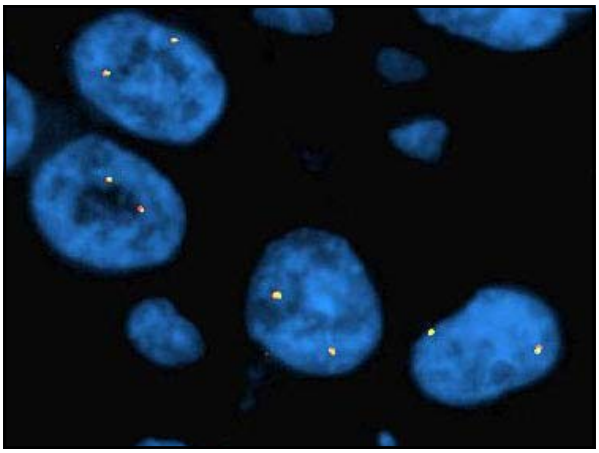


Summary

- Understanding normal salivary gland compartmental morphology, structure and immunophenotype is important for tumor classification
- Biphasic tumors show considerable histologic overlap, but can be distinguished using key clinical and immunohistochemical findings. Tumor interface is vital on biopsy for appropriate stratification.
- PLGA mimics adenoid cystic carcinoma in pattern though it is distinguished by its monophasic 'activated intercalated duct phenotype.' Papillary variants and the new entity cribriform adenocarcinoma of minor salivary gland origin are contentious entities.
- Several translocation associated salivary gland tumors exist, but MEC serves as the paradigm for a molecular finding translated into clinical use as a prognostic and diagnostic marker.

Squamous Cell Carcinoma of the Head and Neck: Diagnostic Dilemmas and Update on Pathogenesis

Walter C. Bell, MD
Associate Professor, Pathology
University of Alabama at Birmingham

Squamous Cell Carcinoma

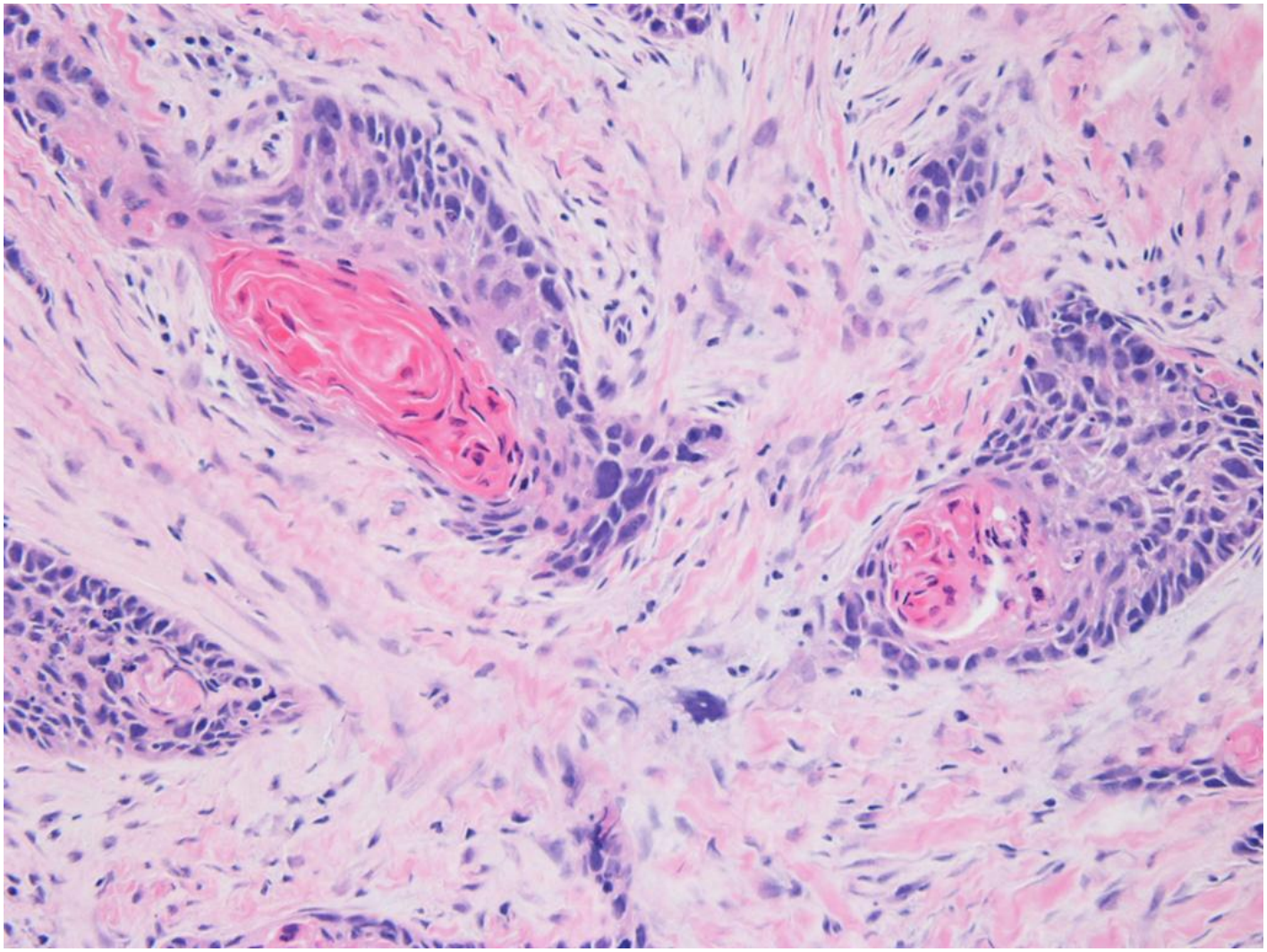
- Oral Cavity
- Nasal Cavity/Paranasal Sinuses
- Nasopharynx
- Oropharynx
- Hypopharynx
- Larynx

- Very common neoplasm in head and neck
- >95% of all head and neck carcinomas

Conventional Squamous Cell Carcinoma

- Risk factors: Alcohol, Tobacco
- Older individuals, > age 60
- More common in males

Conventional Squamous Cell Carcinoma



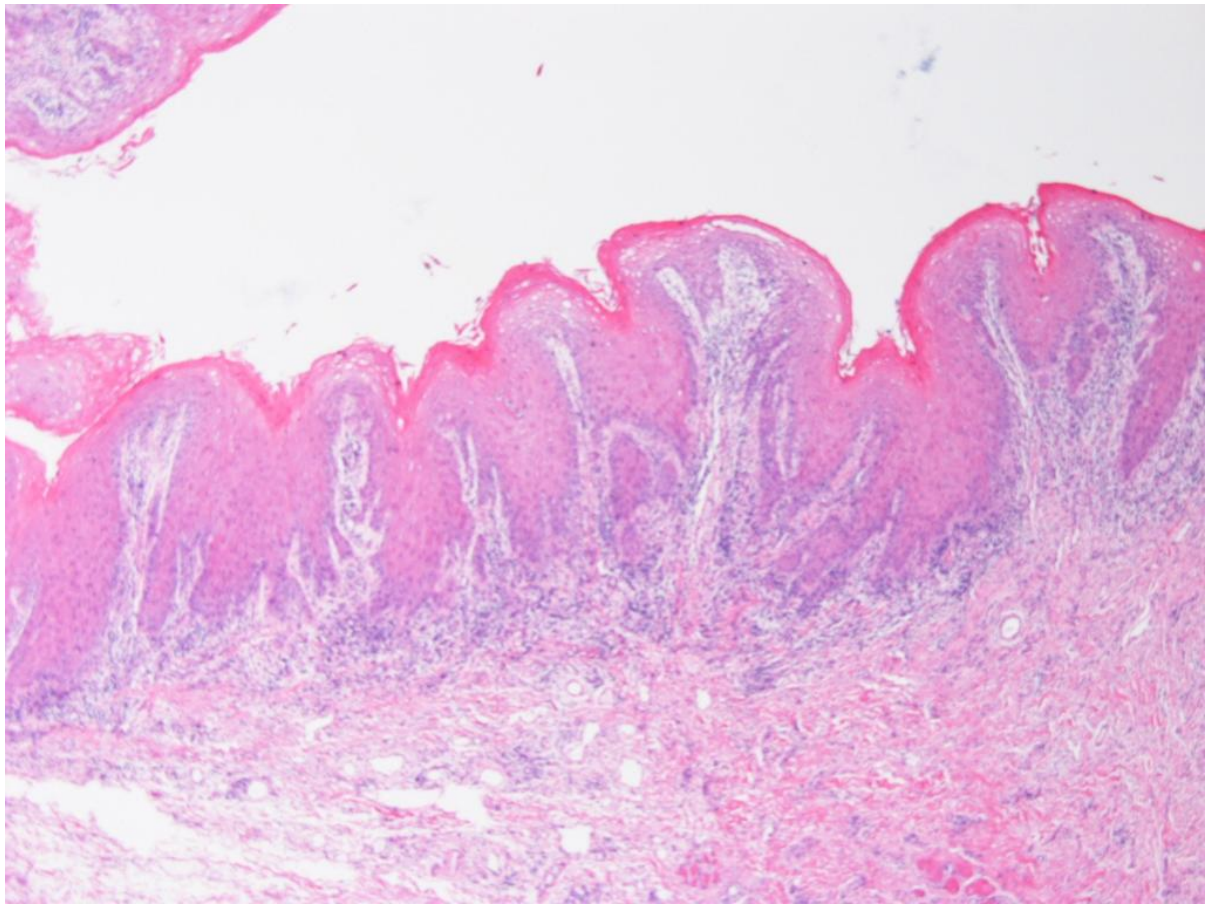
Mimics of Squamous Cell Carcinoma

- Pseudoepitheliomatous hyperplasia
- Sialometaplasia
- Radiation atypia
- Fungal infections

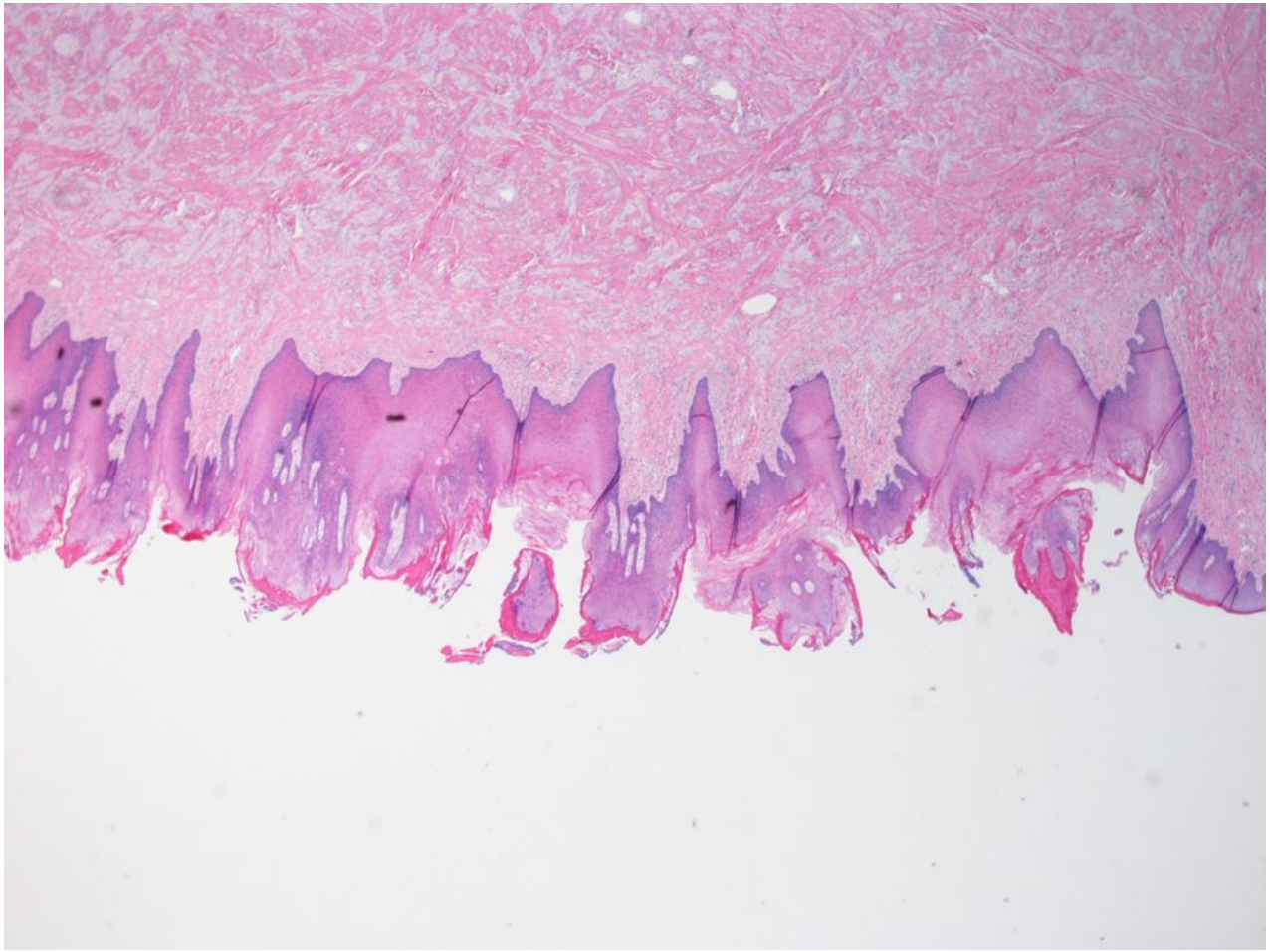
Pseudoepitheliomatous Hyperplasia

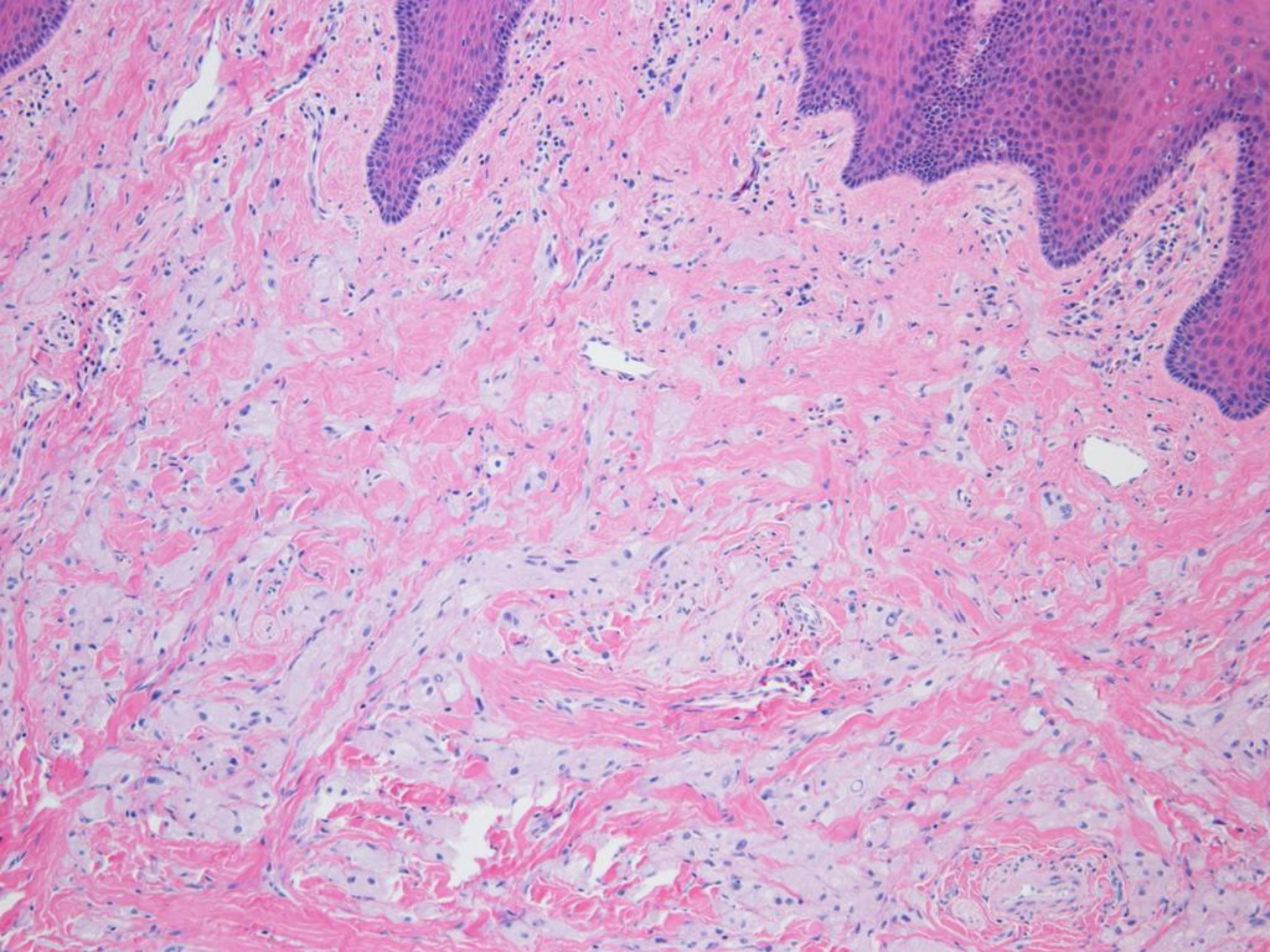
- Reactive proliferation of squamous epithelium into underlying stroma
- Histologically characterized by mild nuclear pleomorphism, mitotic activity, abrupt keratinization
- Marked pleomorphism, hyperchromasia, and atypical mitoses are absent
- Underlying causes: Infection, chronic irritation, granular cell tumor

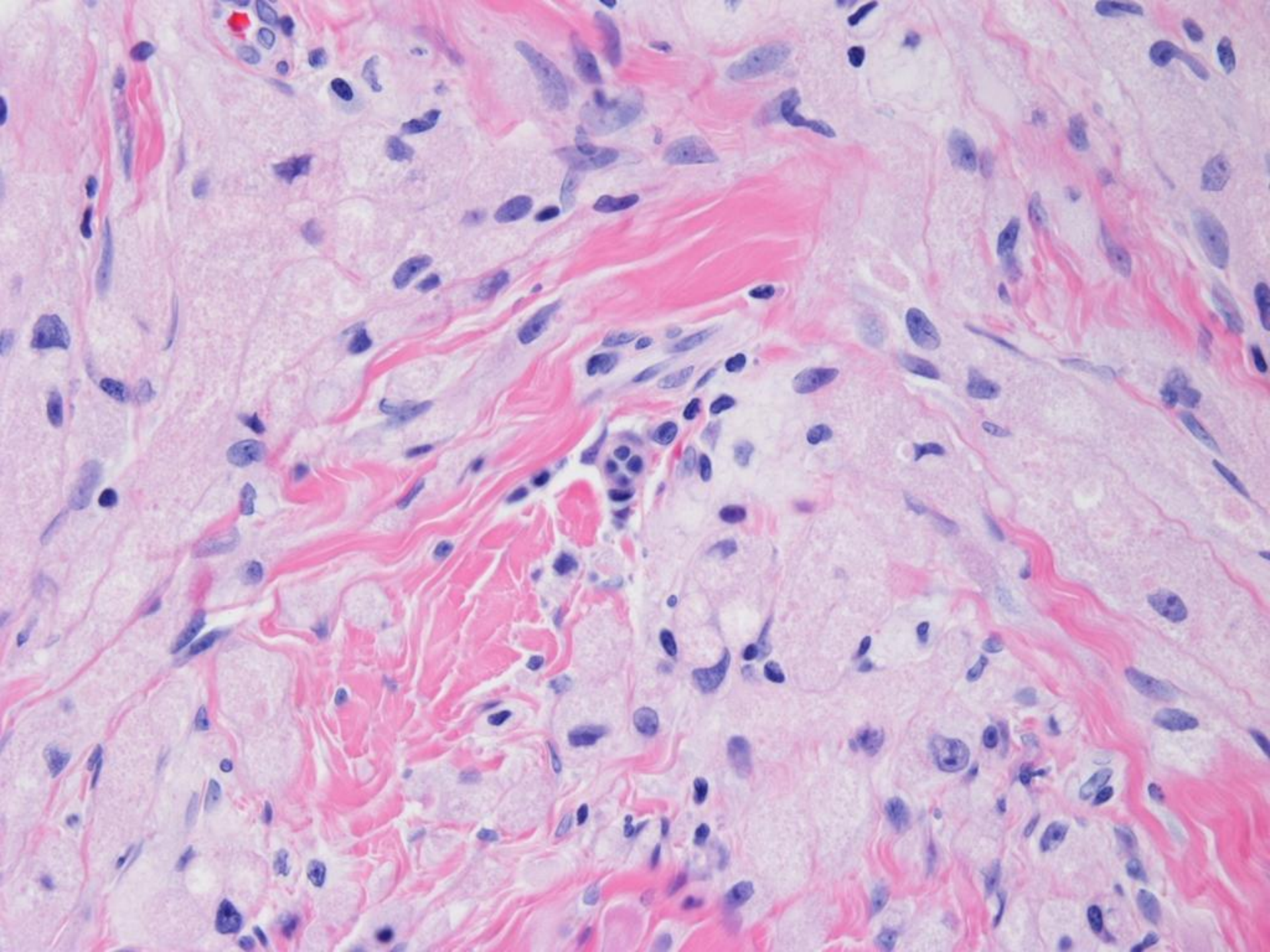
Chronic Irritation
Inflammatory Papillary Hyperplasia

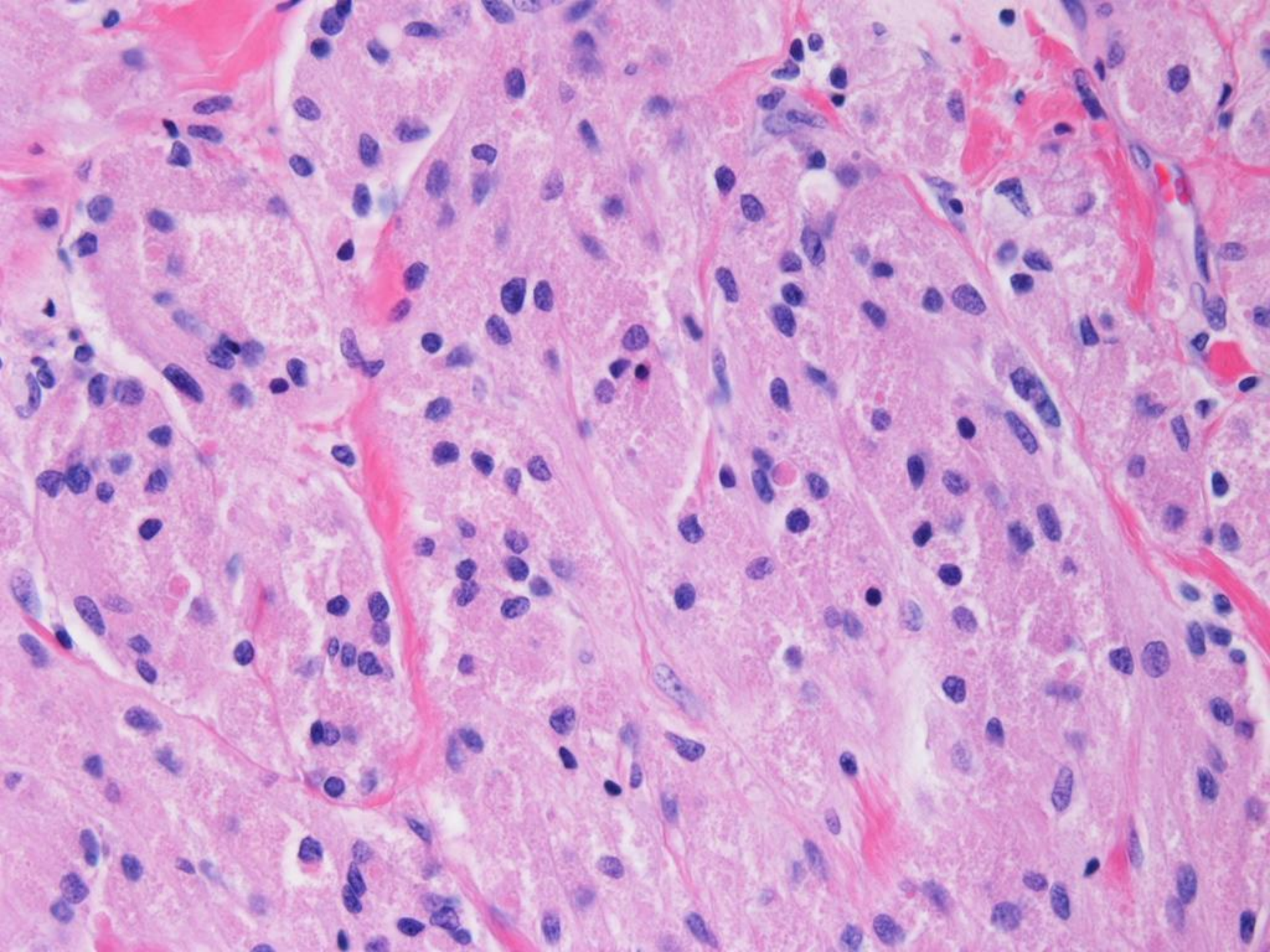


PEH Lateral Tongue

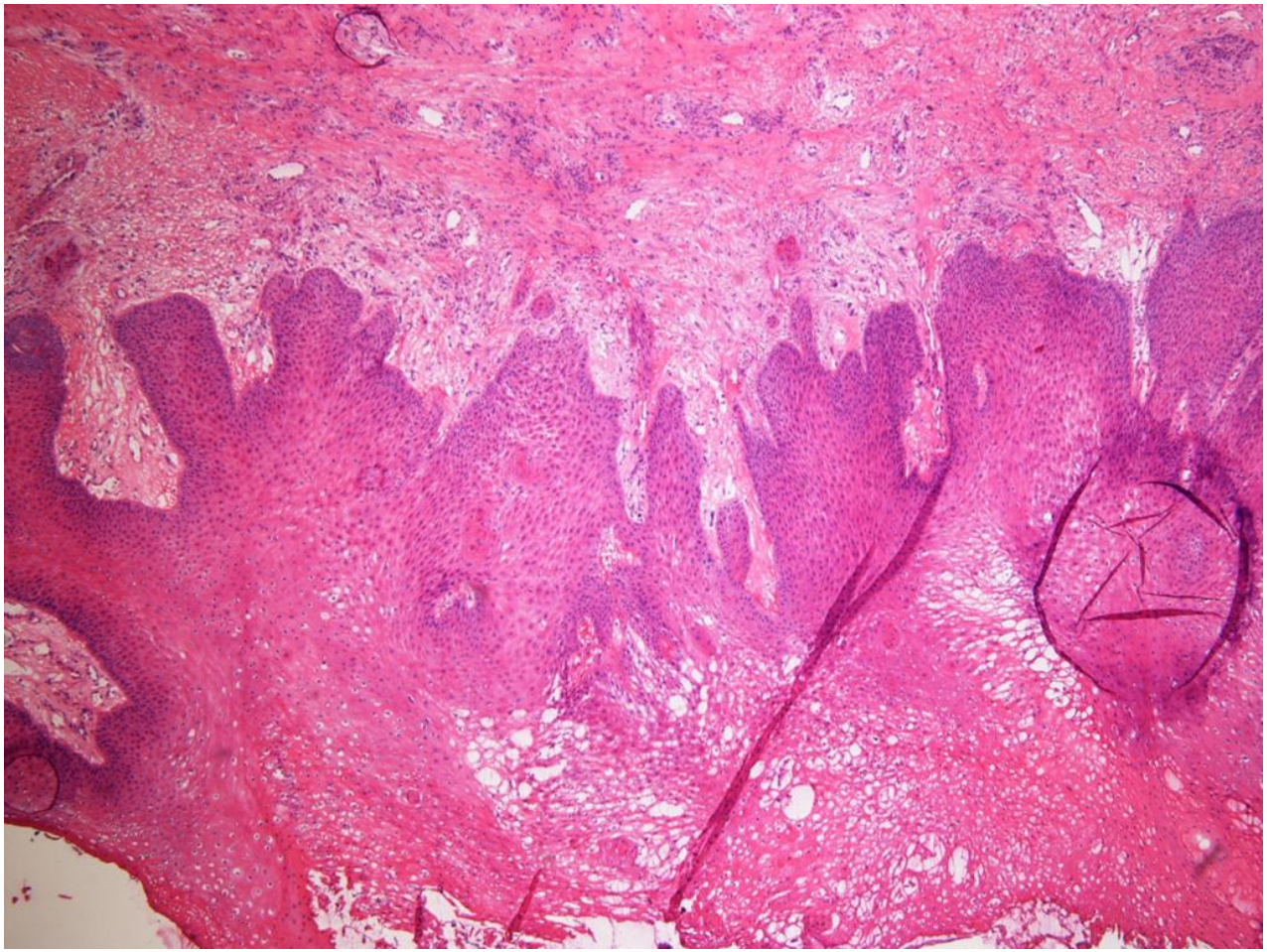




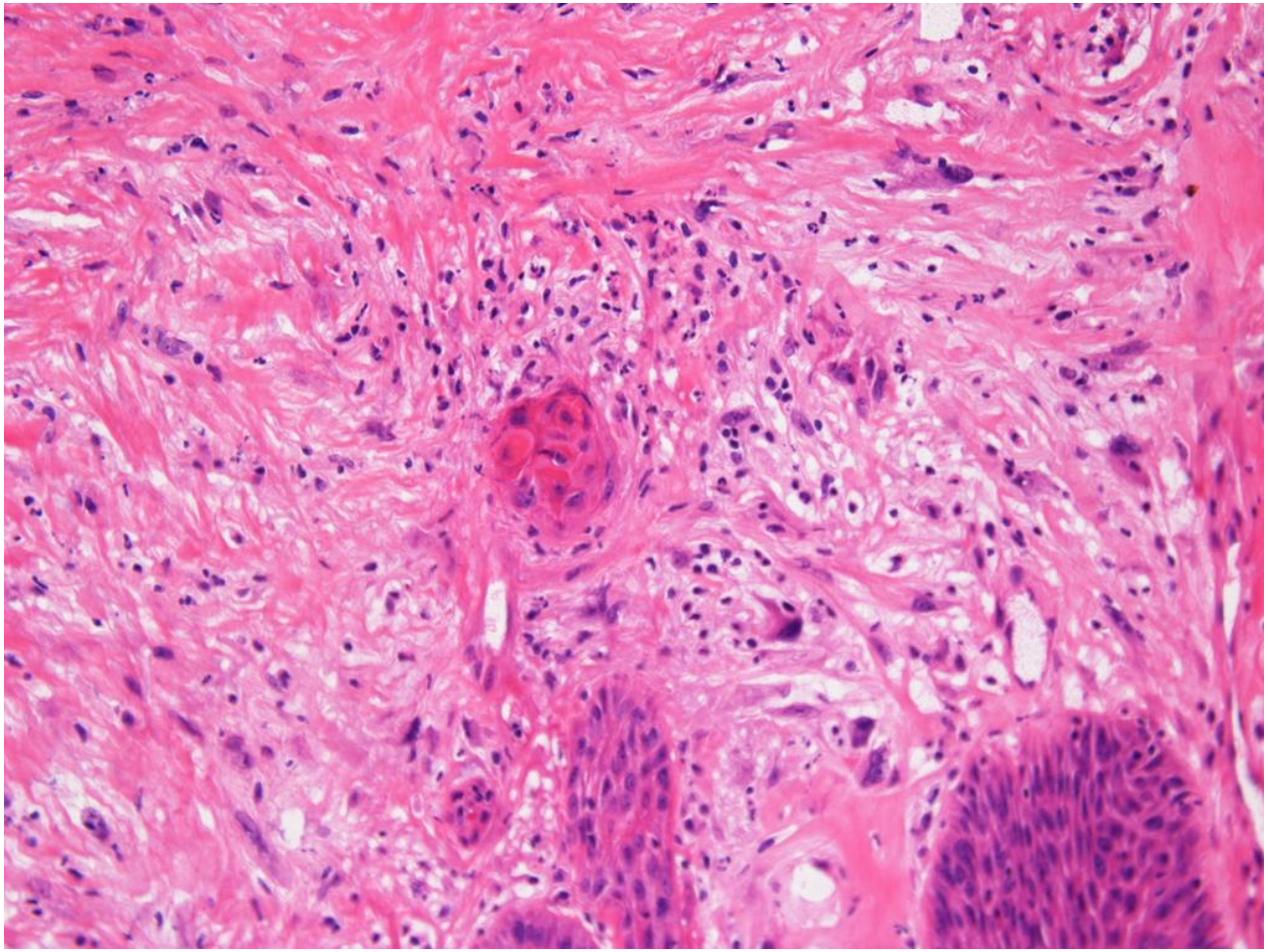


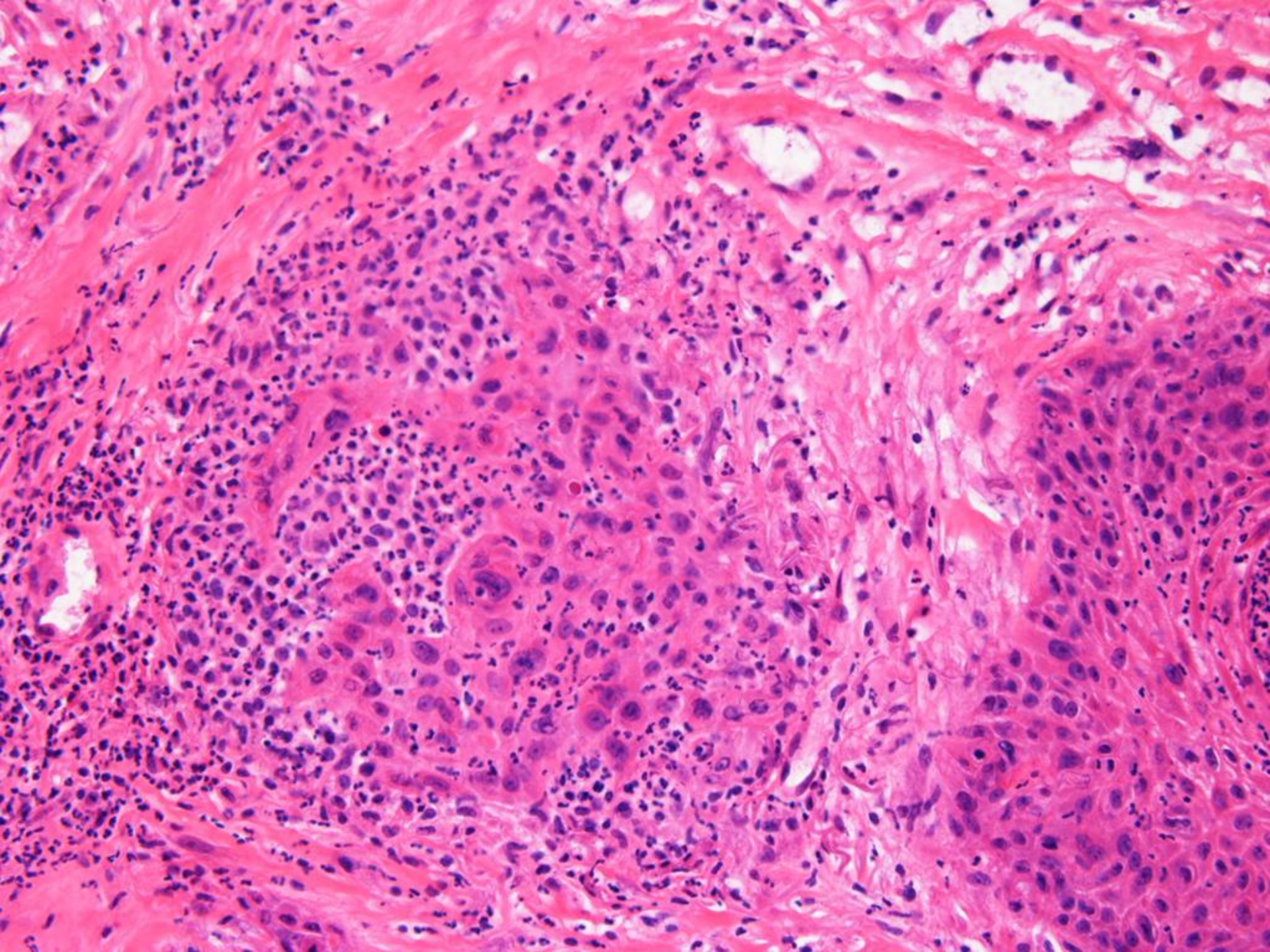


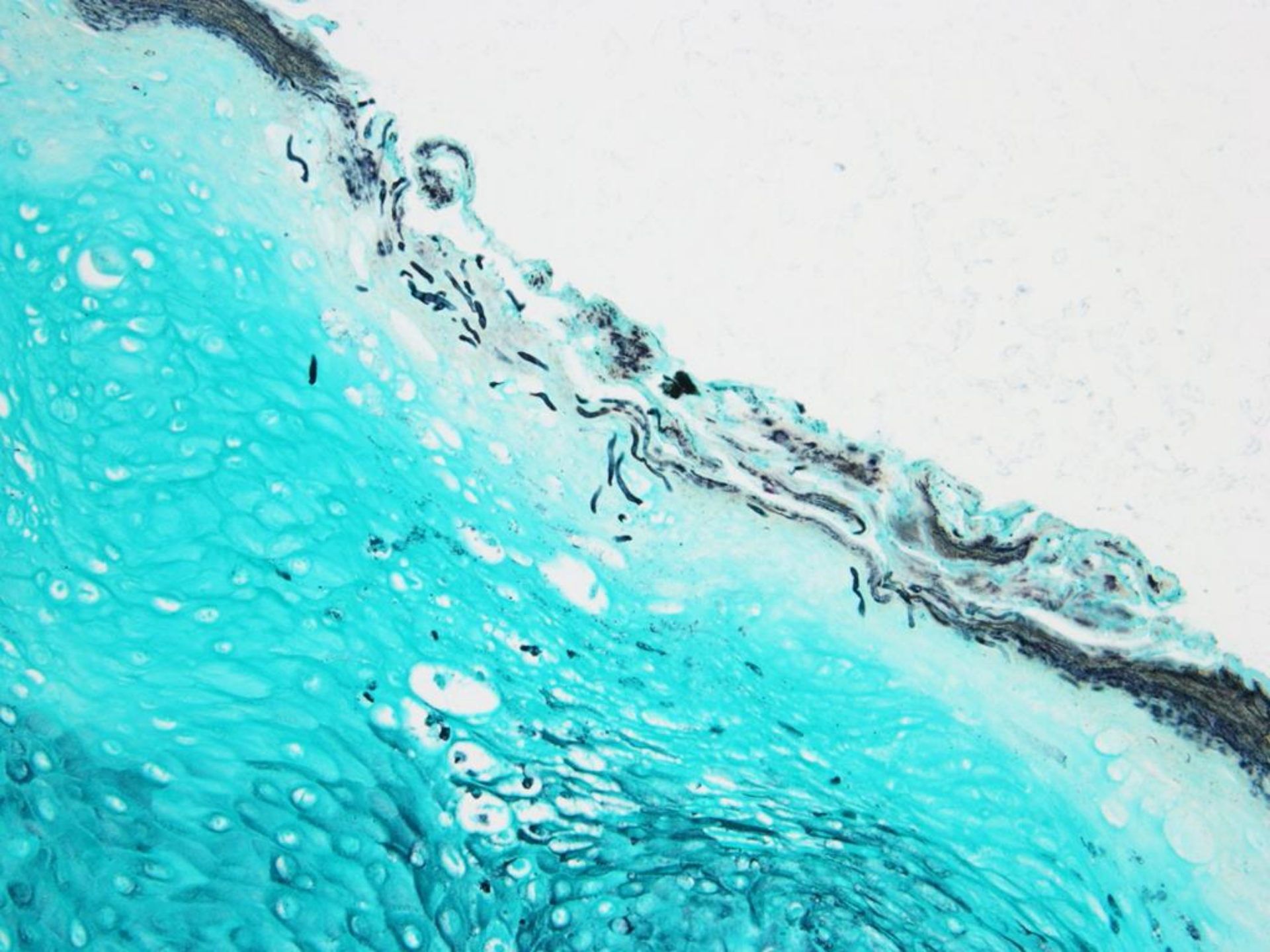
Buccal Mucosa
(Frozen Section)



Radiation Atypia



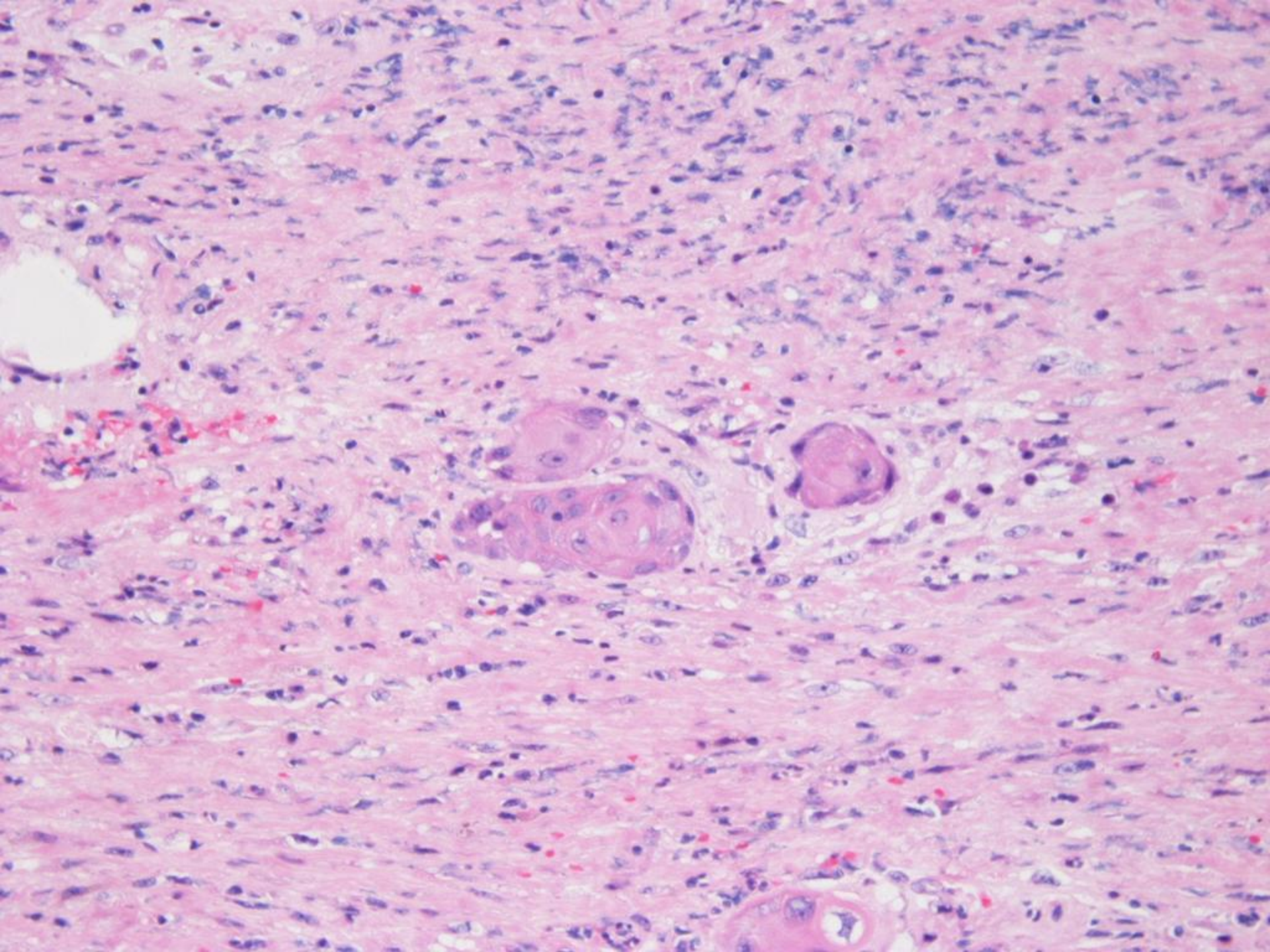


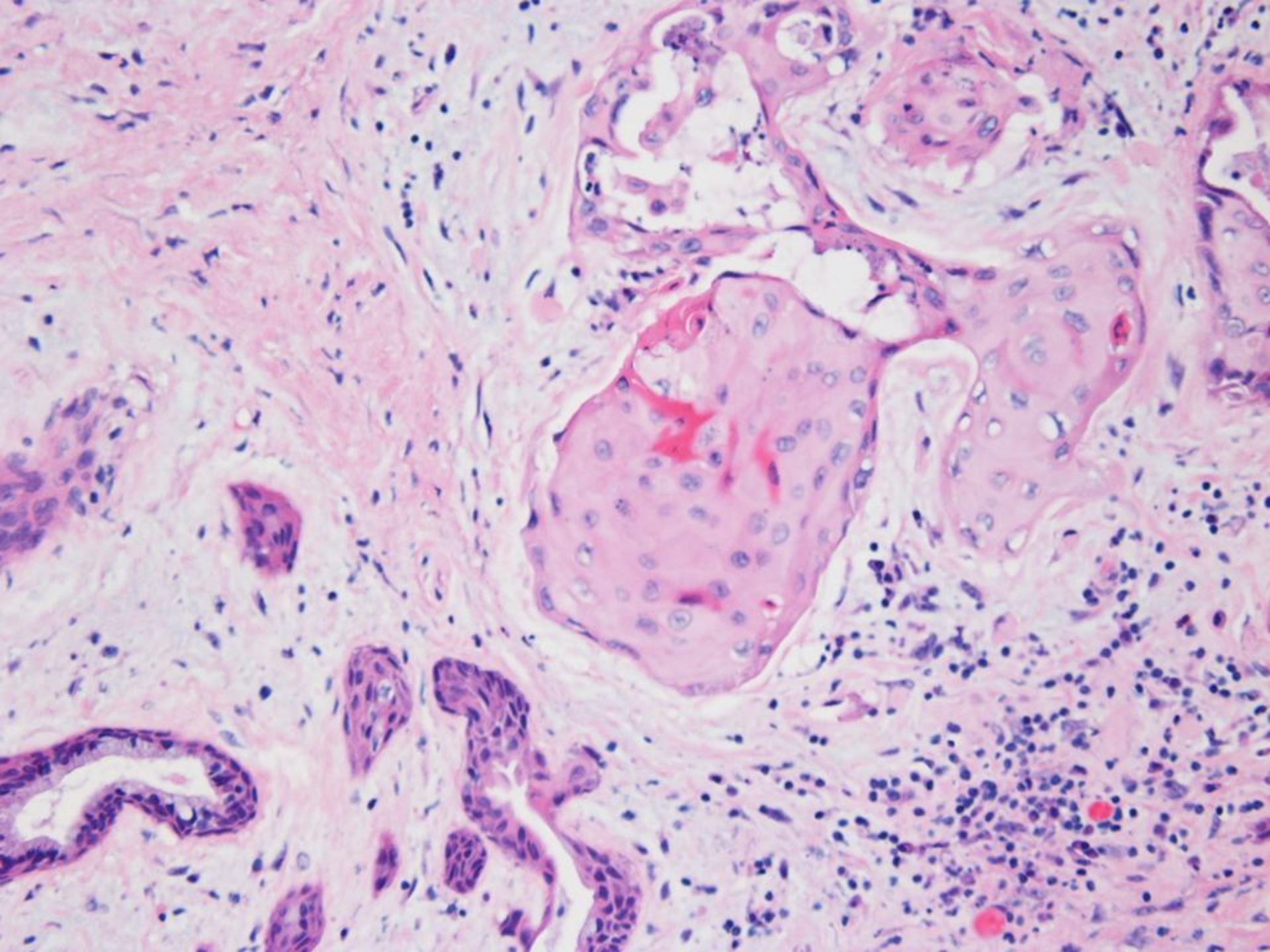


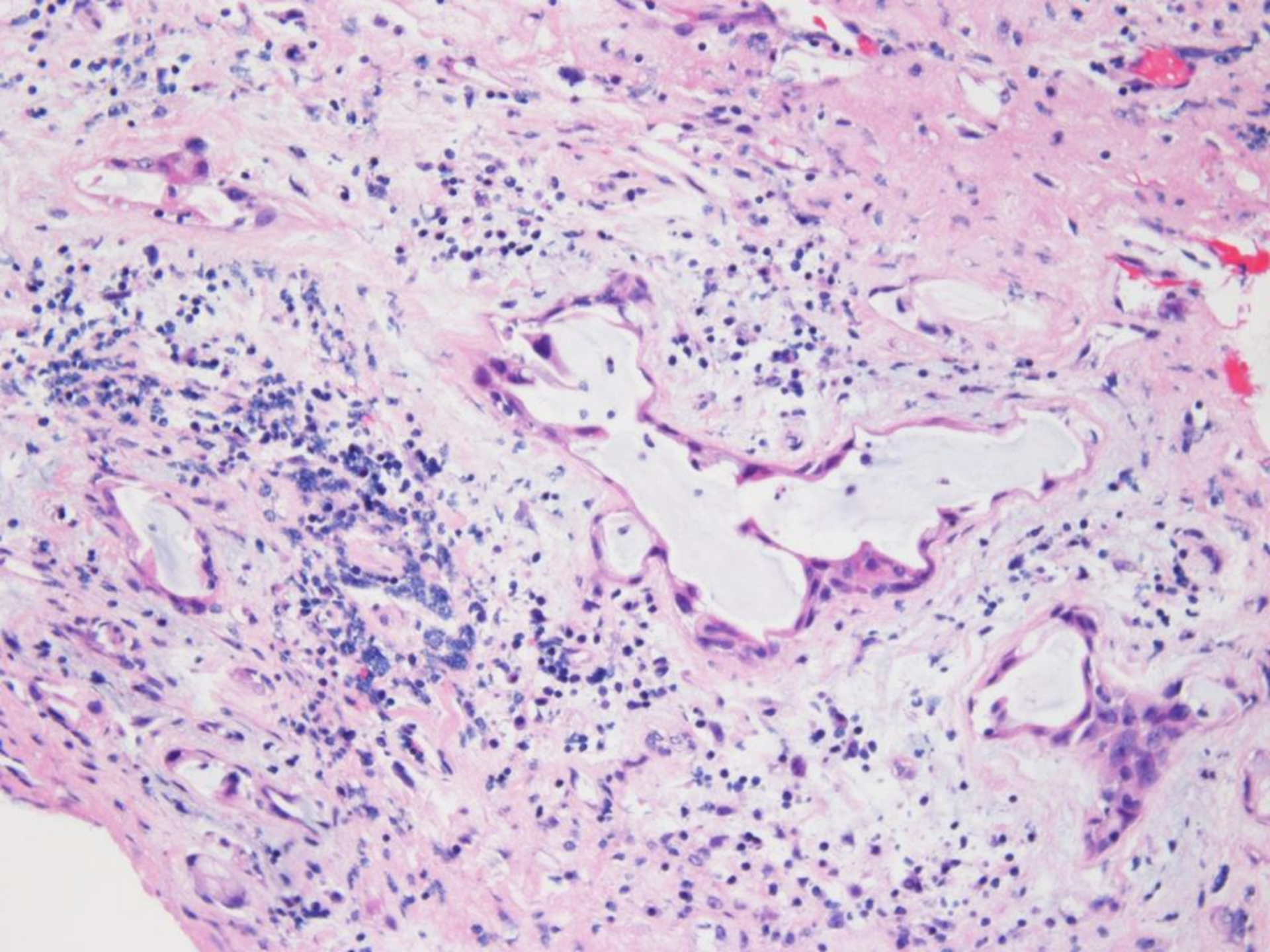
Sialometaplasia

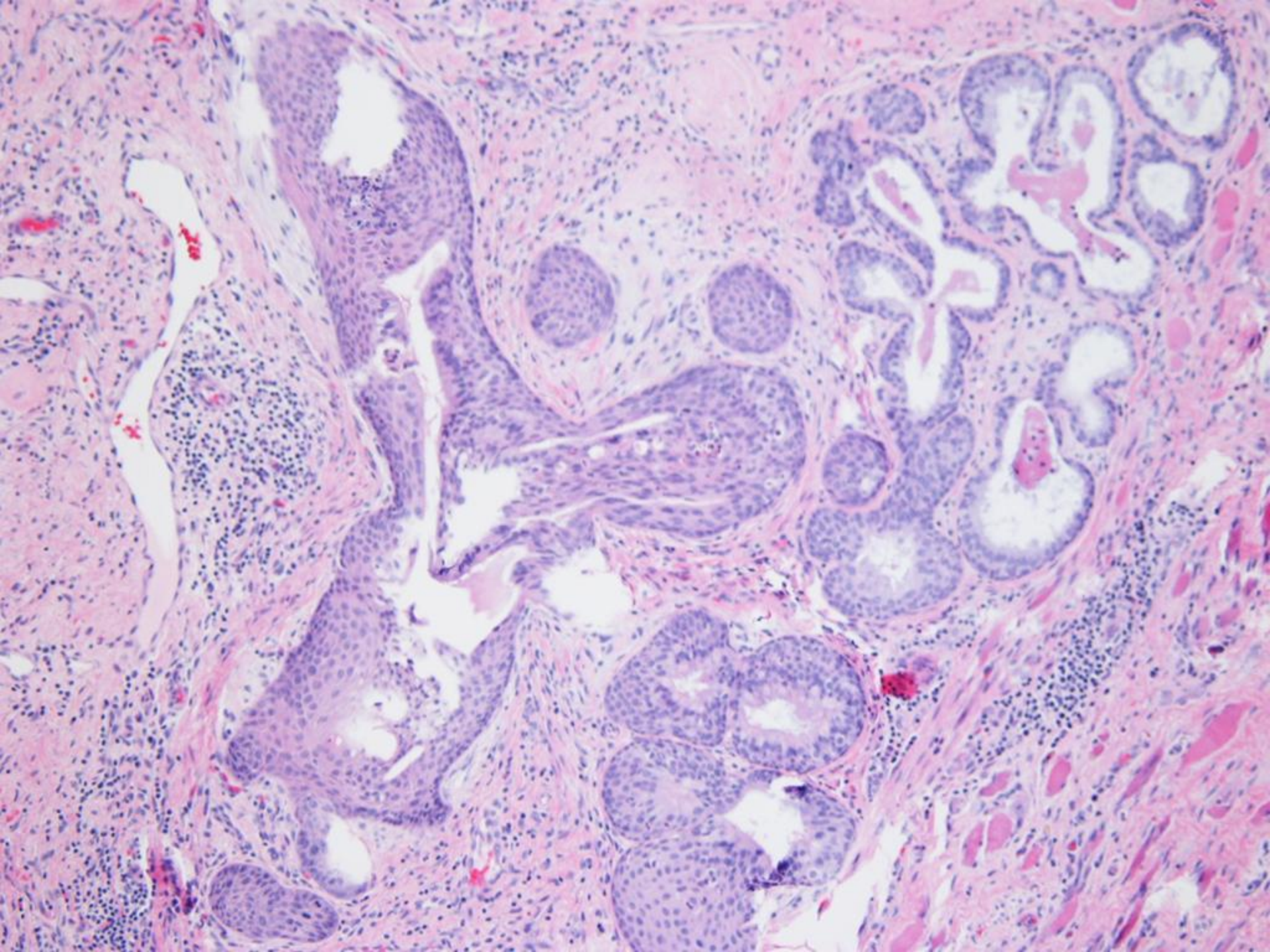
Sialometaplasia

- Squamous metaplasia of minor salivary glands secondary to inflammation, radiation, or surgery
- May mimic both squamous cell carcinoma and mucoepidermoid carcinoma









Squamous Cell CarcinomaVariants Causing Diagnostic Difficulty

- Verrucous Carcinoma
- Papillary Carcinoma
- Spindle cell / sarcomatoid carcinoma

Verrucous Carcinoma

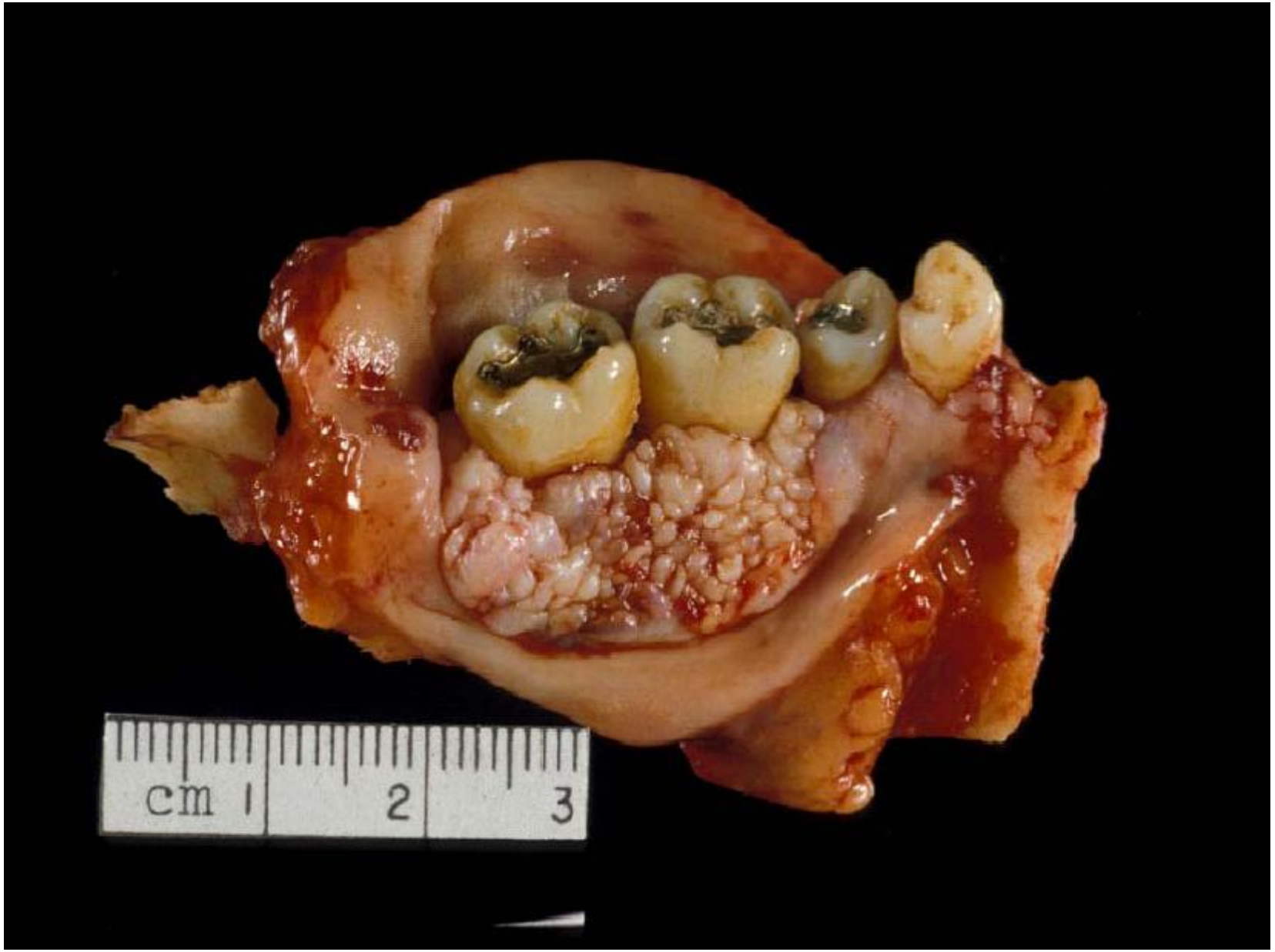
Verrucous Carcinoma of the Oral Cavity

- Represents 2-8% of all squamous carcinomas of the oral cavity
- Almost 75% occur on buccal mucosa or gingiva
- Predominantly males between 50-80 years of age

Verrucous Carcinoma of the Larynx

- **Accounts for 1-3% of all carcinomas**
- **Most are of glottic origin**
- **Patients average 58-60 years of age;**

majority are men who smoke.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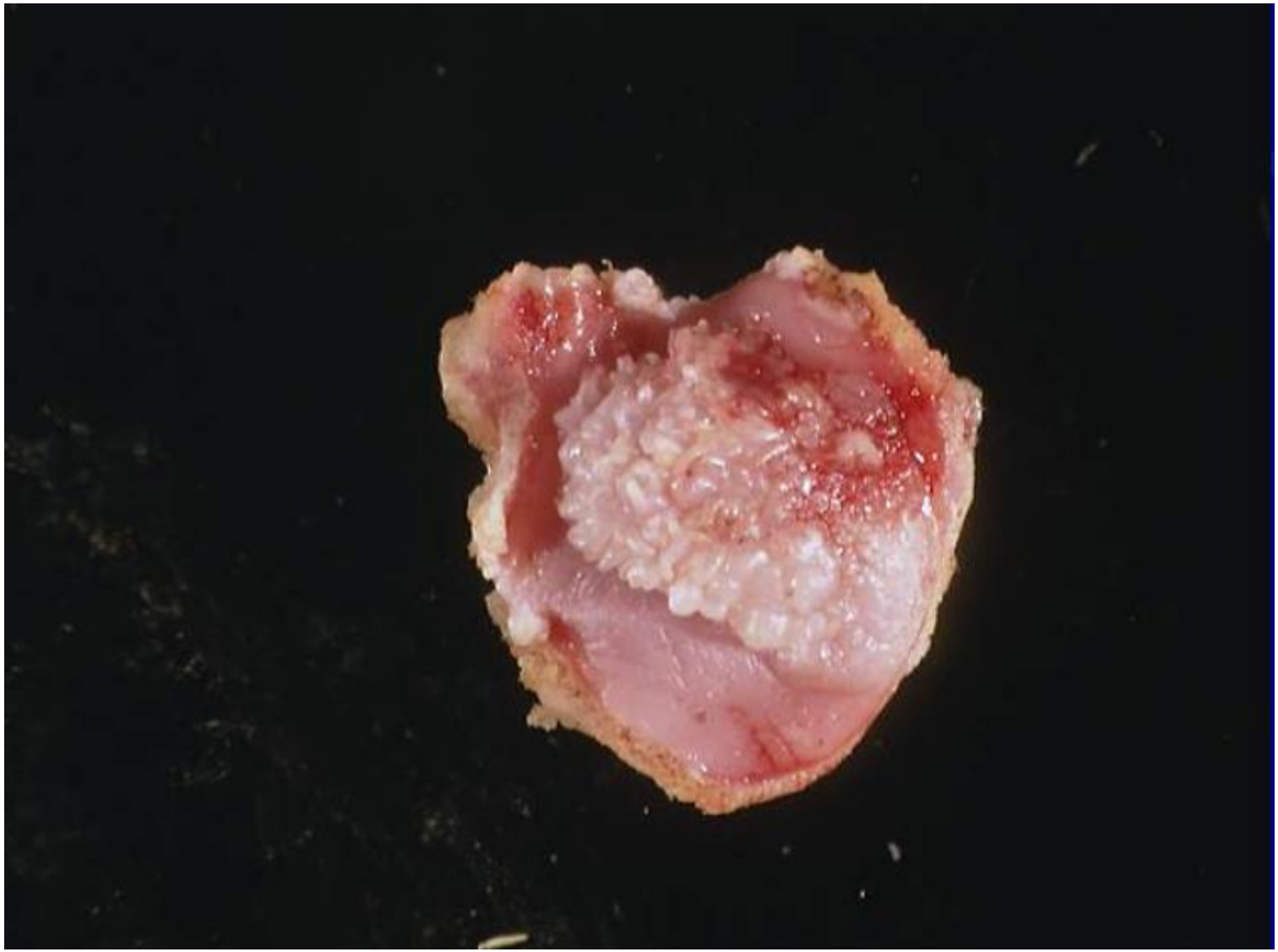
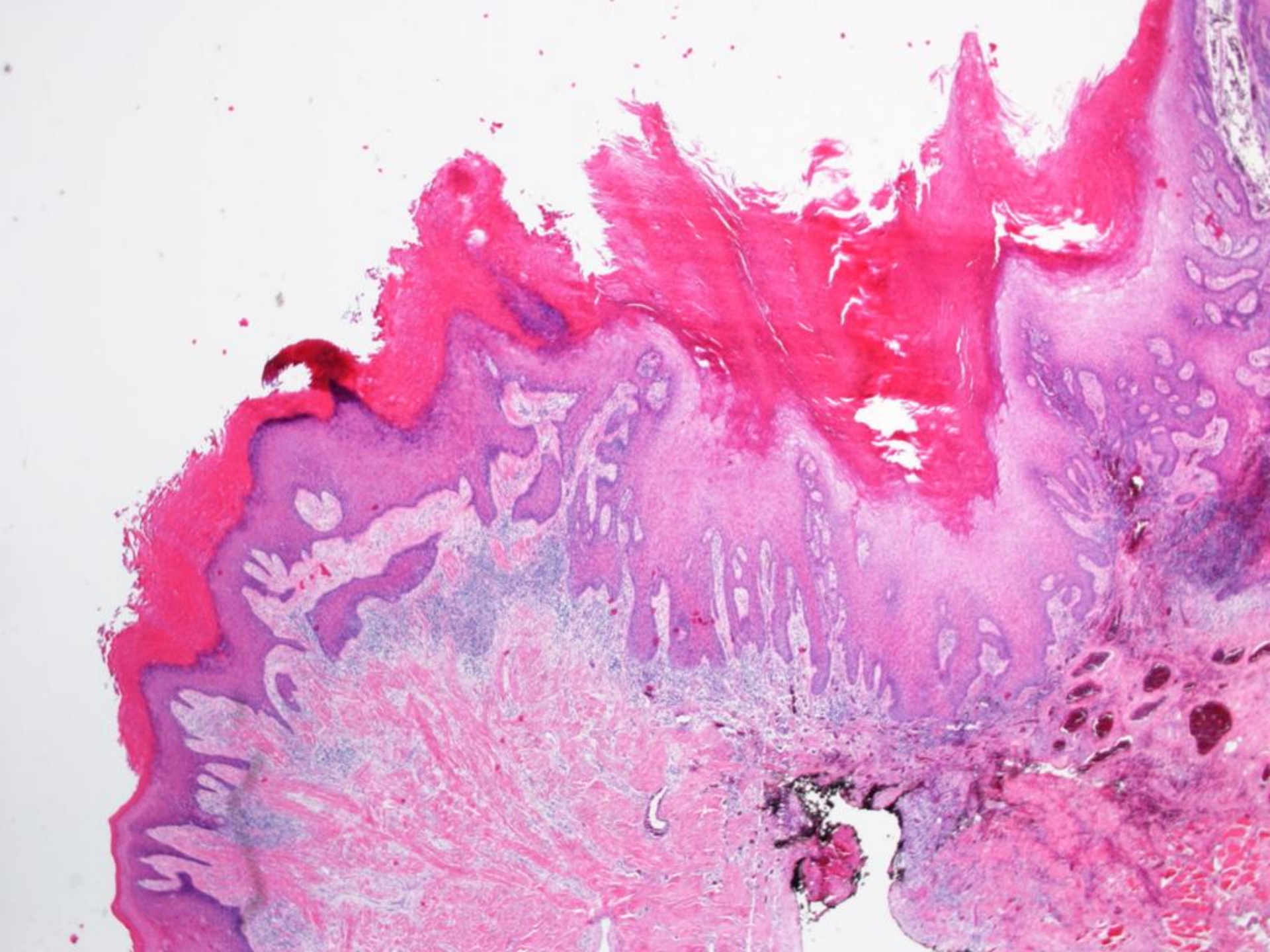
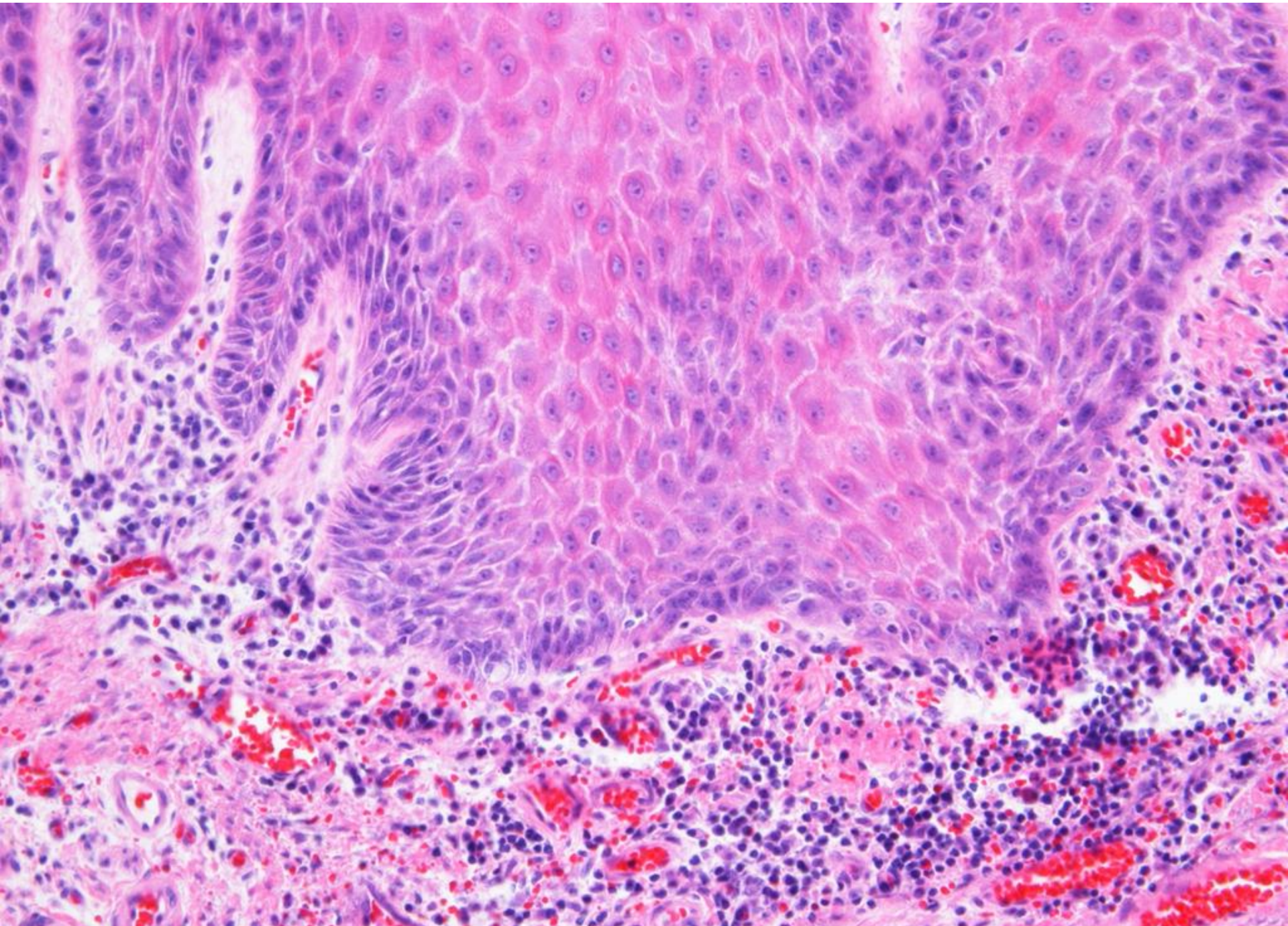






Hybrid Verrucous Carcinoma

- Of 104 verrucous carcinomas of the oral cavity, 19.2% were hybrid.
- No differences in clinical appearance between verrucous and hybrid carcinomas.
- Following surgery and/or radiation, 30% of hybrid tumors recurred versus 18.2% for verrucous.

Medina JE, et al. Arch Otolaryngol 110:437, 1984

Papillary Squamous Cell Carcinoma

Papillary Squamous Cell Carcinoma

- Uncommon variant of SCCA
- Elderly age group
- Risk factors
  - Alcohol & Tobacco
  - Most do not arise from preexisting papillomas

Papillary Squamous Cell Carcinoma

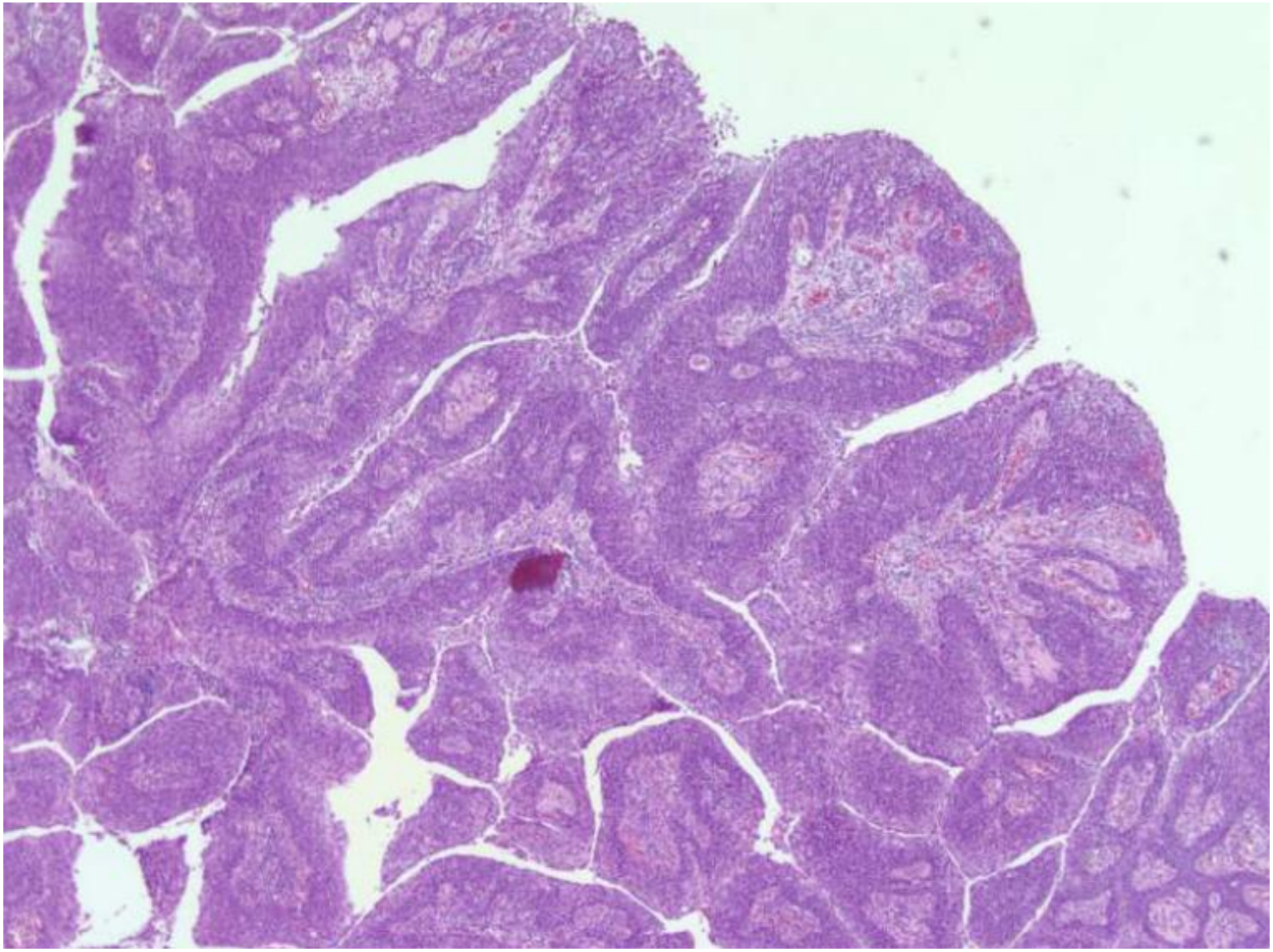
- **Gross appearance**
  - **Frond-like filiform papillae**
  - **Broad-based, cauliflower appearance**

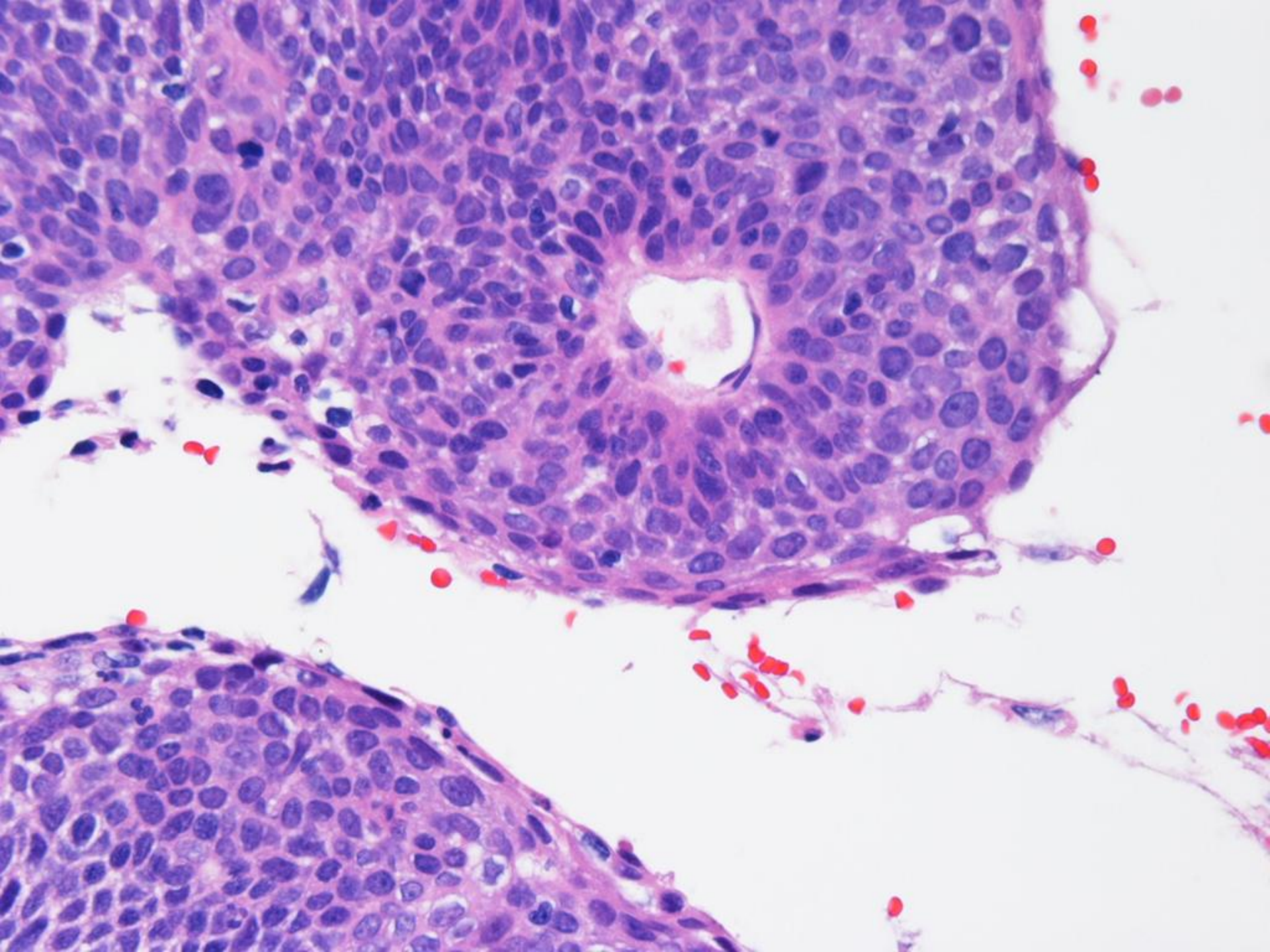
Papillary Squamous Cell Carcinoma

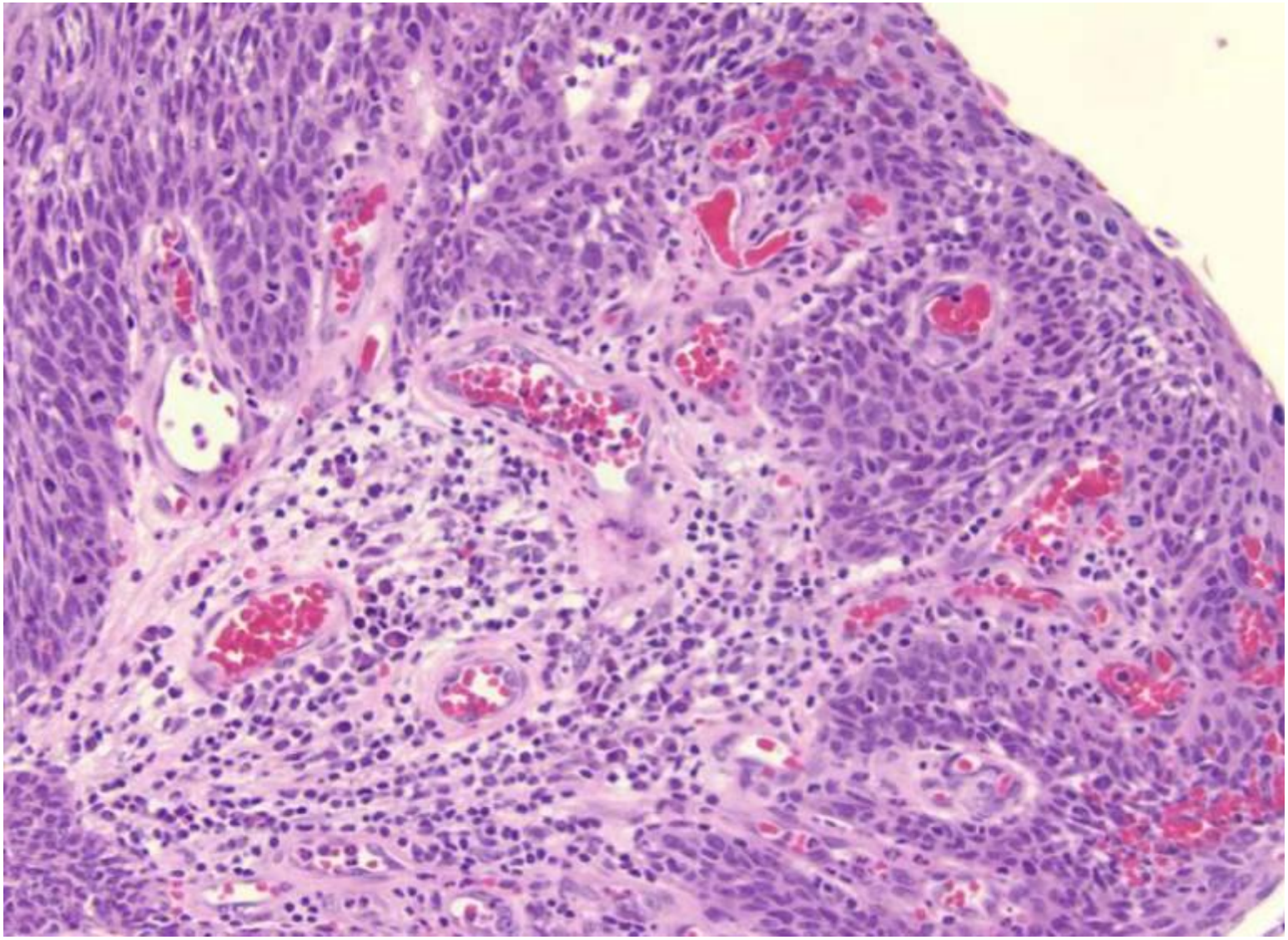
- Frond-like, finger-like projections
- True fibrovascular cores
- +/- keratinization

Malignant features

- Cytologic atypia
- Abnormal mitoses
- Poor maturation







Papillary Squamous Cell Carcinoma Pitfalls

- **Small or superficial biopsies**
- **Lack of invasive component**

Papillary Squamous Cell Carcinoma

- **May be difficult to diagnose (biopsy dependent)**
- **Same prognosis as conventional SCCA**

Spindle Cell Carcinoma

Spindle Cell Carcinoma

- **Nomenclature**
  - **“Pseudocarcinoma”**
  - **“Sarcomatoid carcinoma”**
  - **“Carcinosarcoma”**

Spindle Cell Carcinoma

- **Gross appearance**
  - **Rapidly growing**
  - **Polypoid**
  - **Superficial ulceration**

Spindle Cell Carcinoma

- **Location**
  - **Oral Cavity (tongue)**
  - **Larynx (glottis and hypopharynx)**
- **Clinical**
  - **Airway obstruction**

Spindle Cell Carcinoma Histology

Stromal Component

- Bland to highly atypical cytology
- Any growth pattern
- Heterologous elements may be present

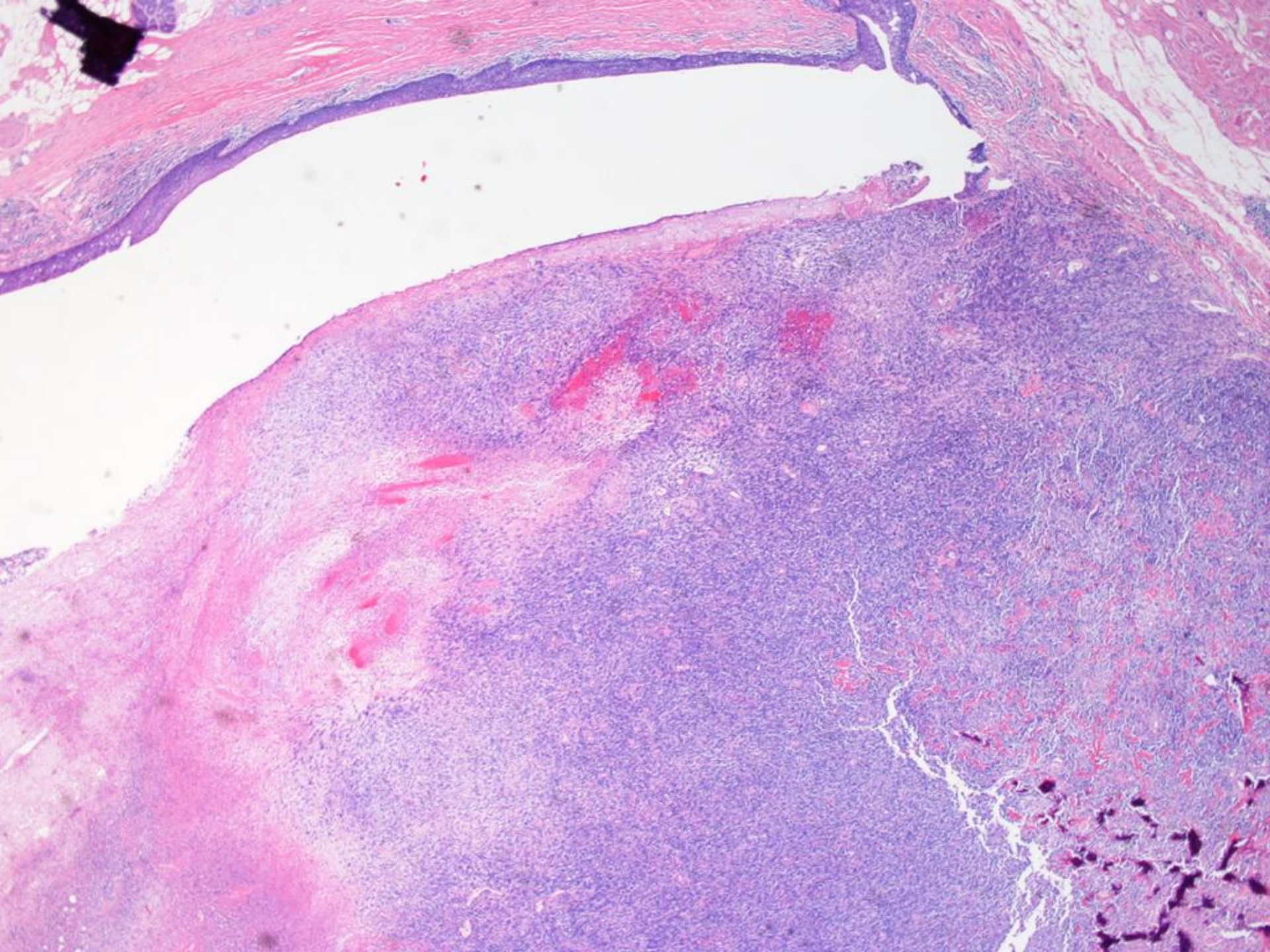
Squamous Component

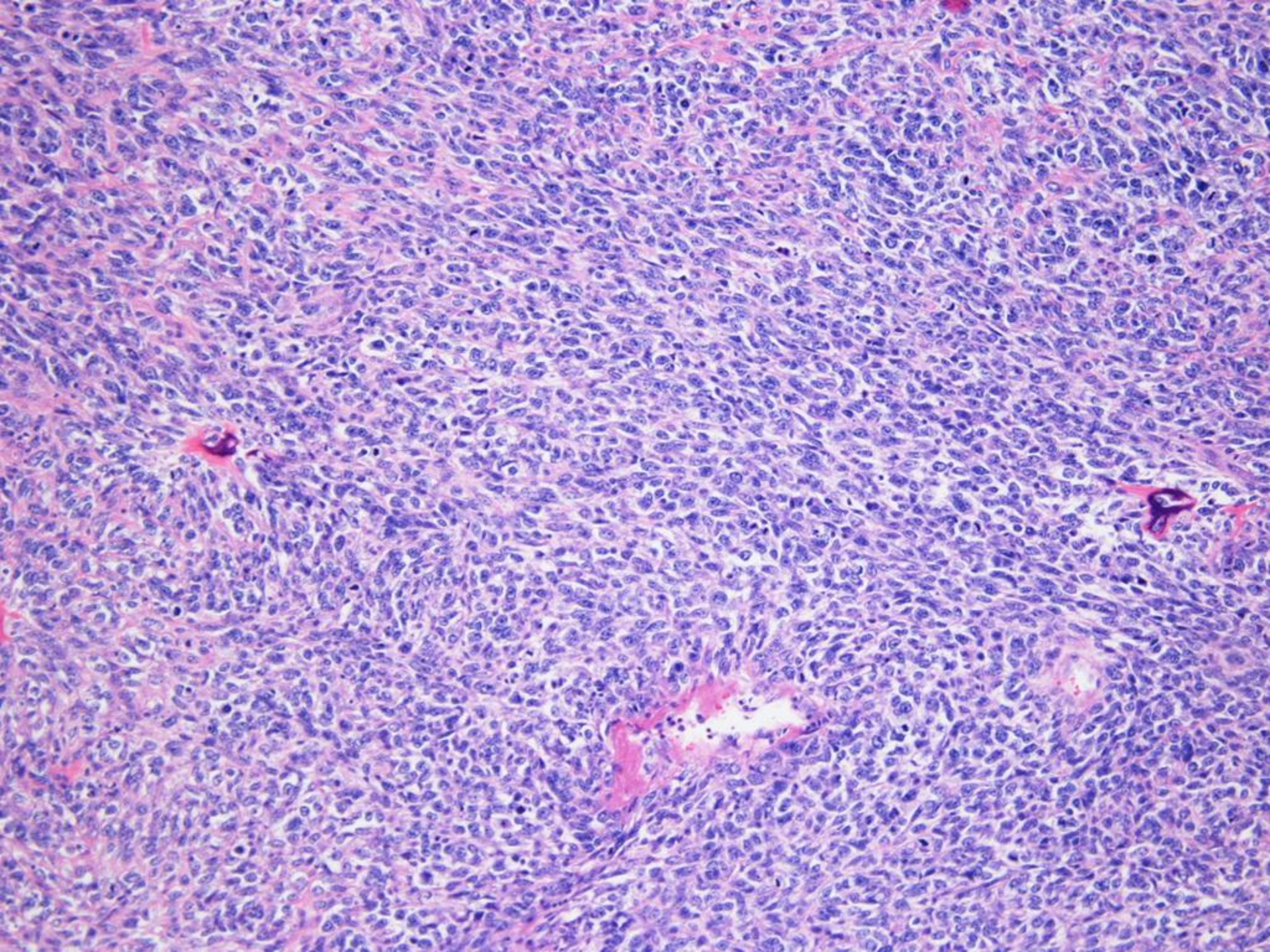
- Can be scant to absent
- May see in situ (dysplasia) or invasive

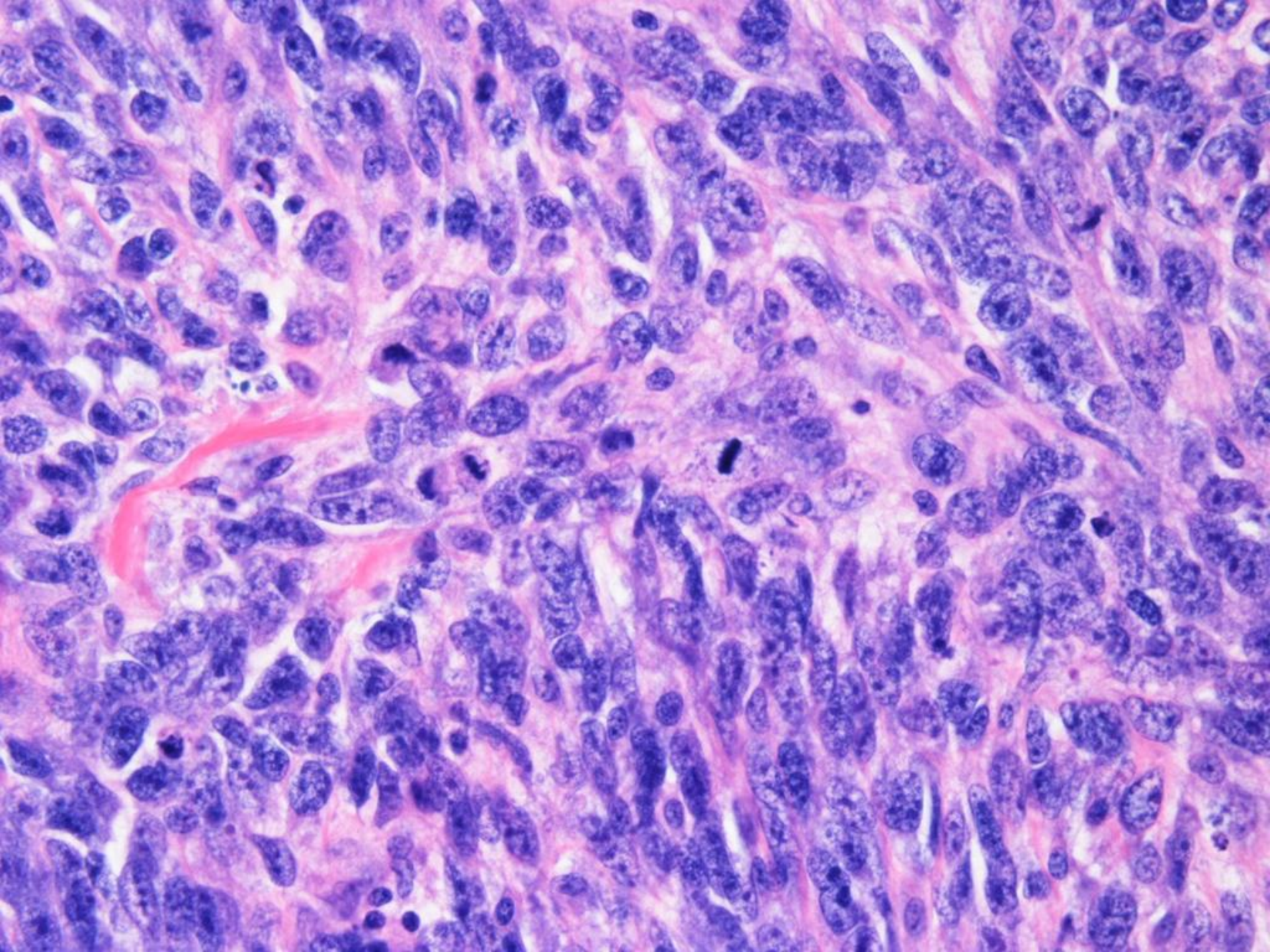
Spindle Cell Carcinoma Histology

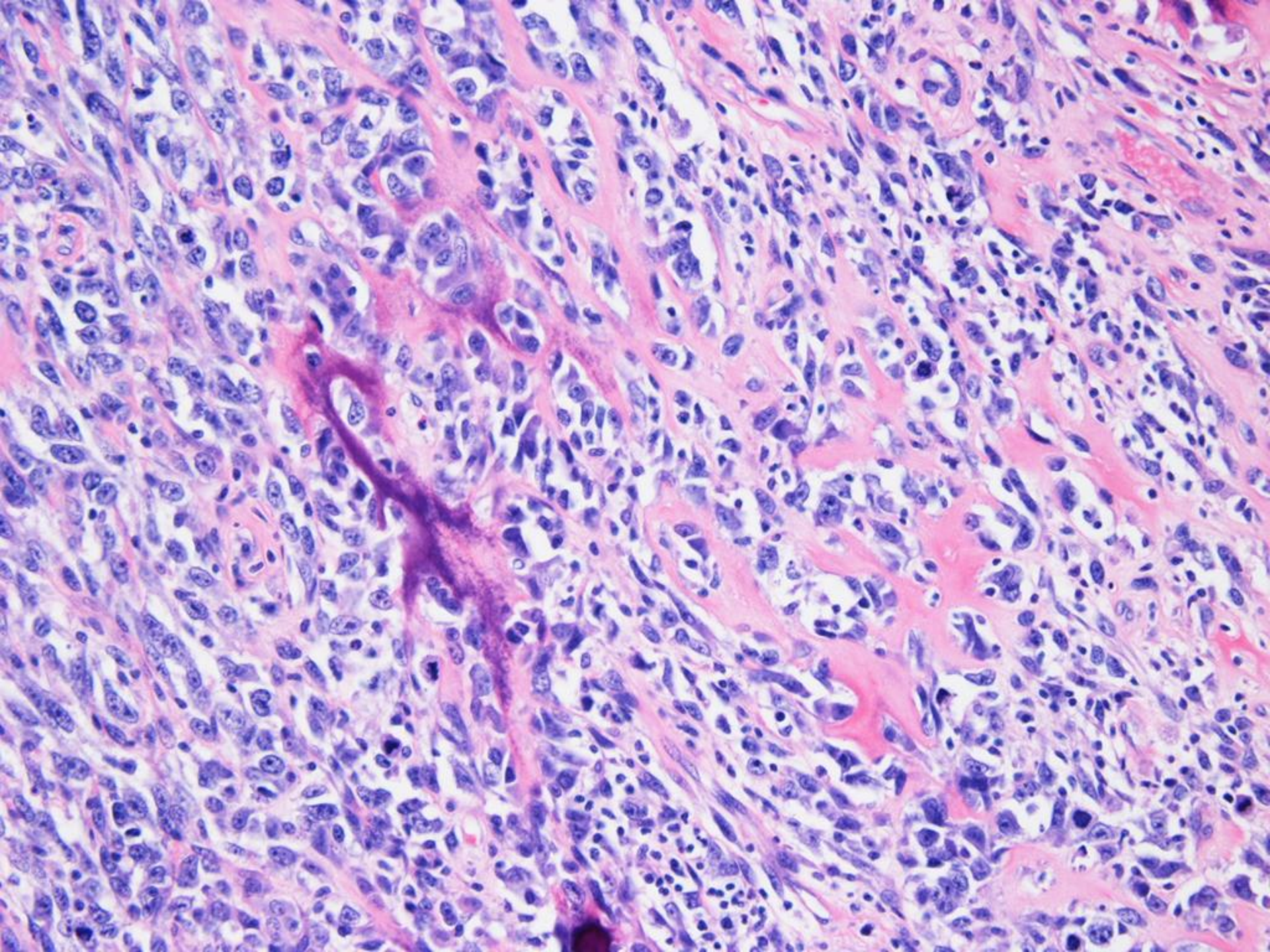
Hints

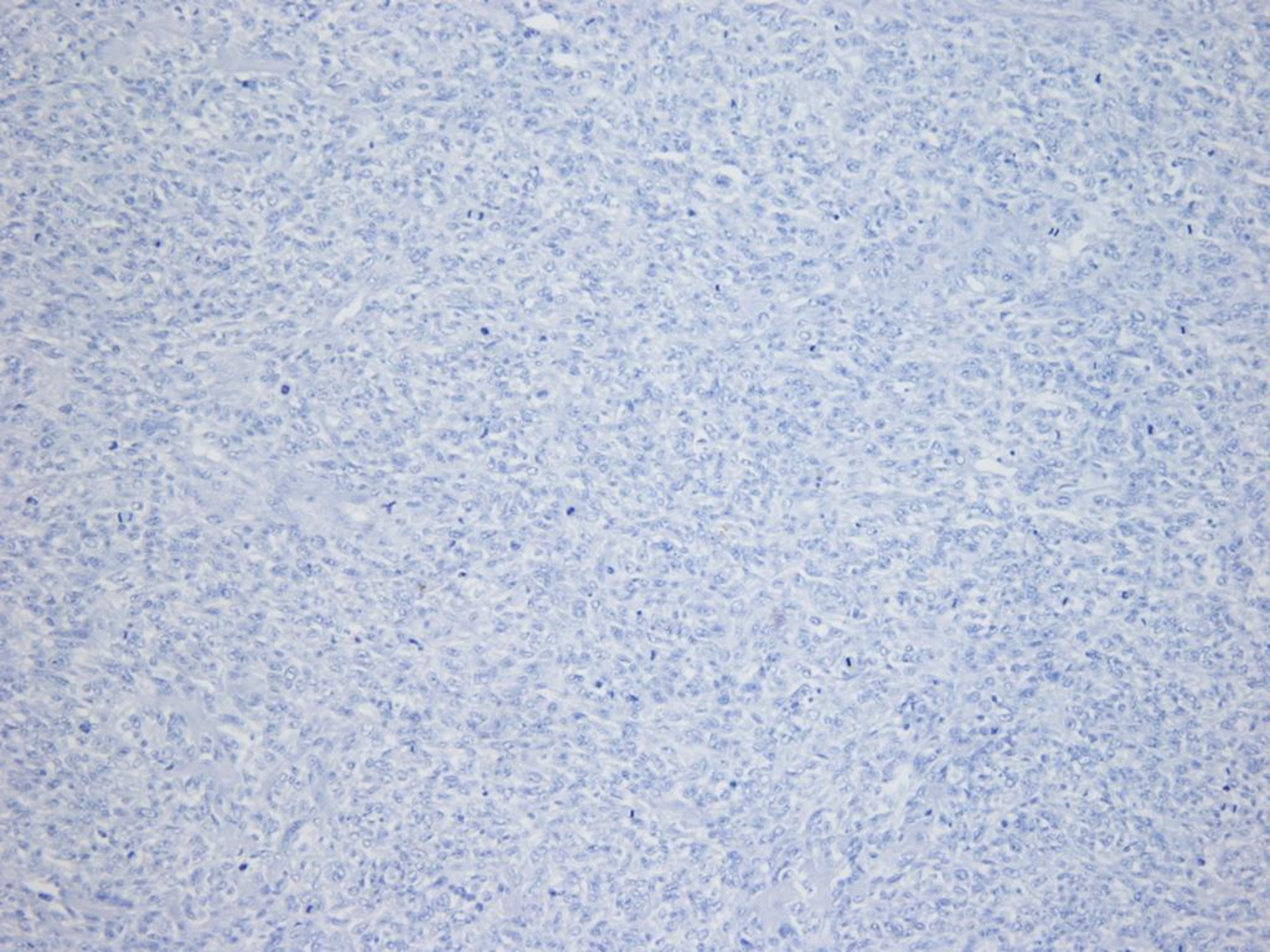
- **Location (true sarcomas are rare and tend to be deep seated masses)**
- **History**
- **Dysplastic overlying epithelium or associated conventional carcinoma**
- **Frankly malignant stromal component**
- **Immunohistochemistry ?**
    - **“Wondrously transformed and amazingly sarcomatoid”**
    - **May lose epithelial markers**

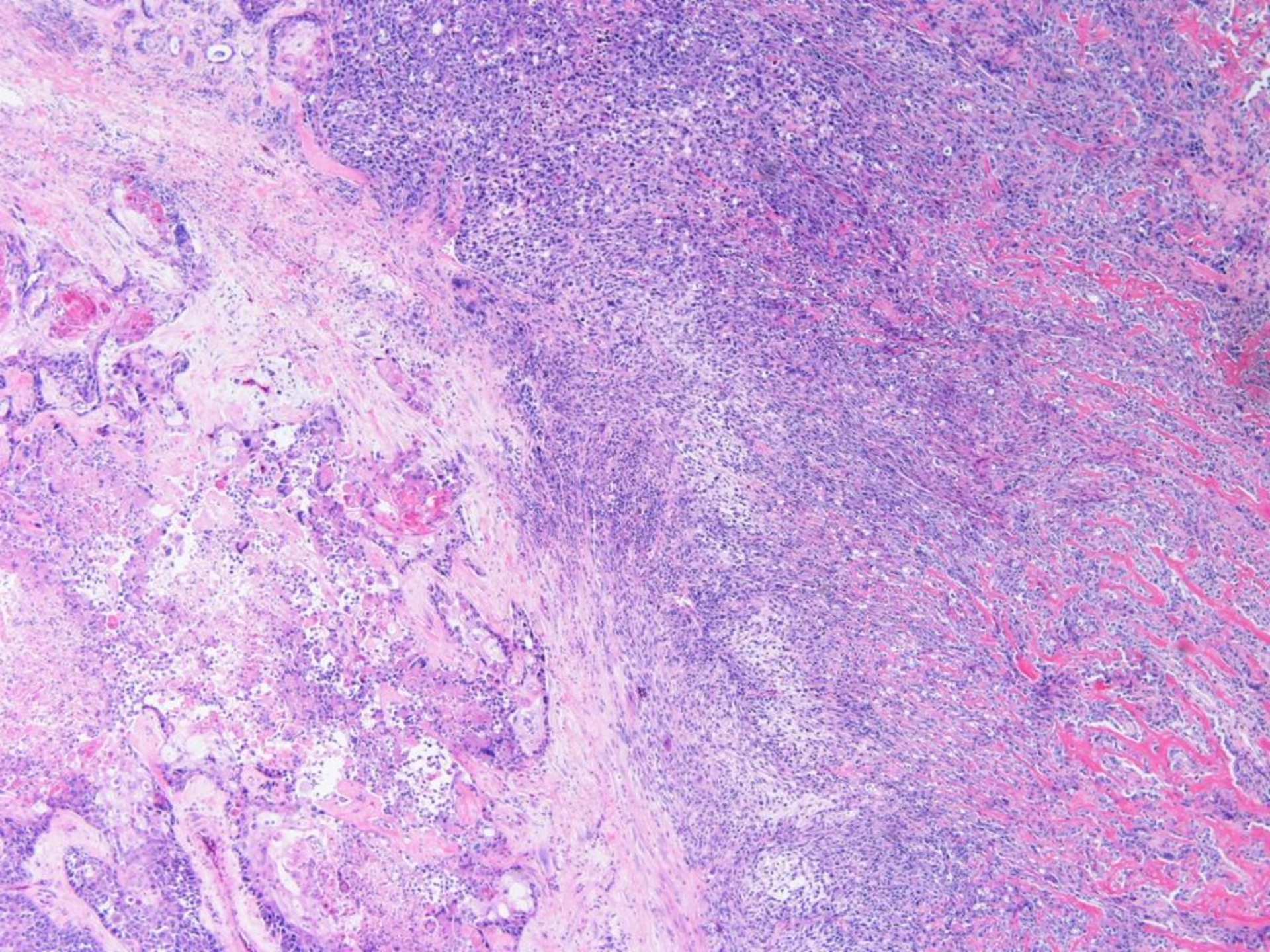


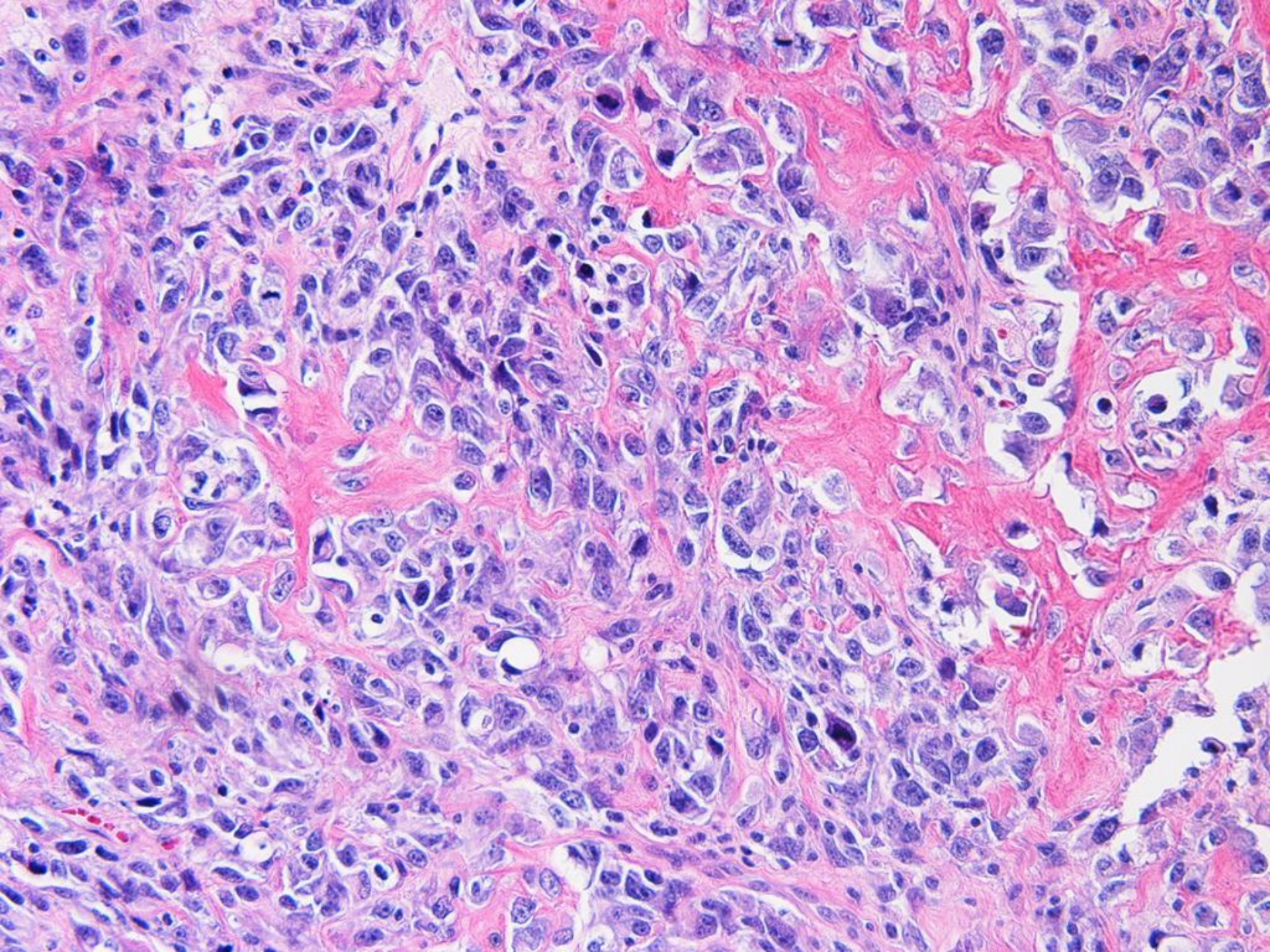


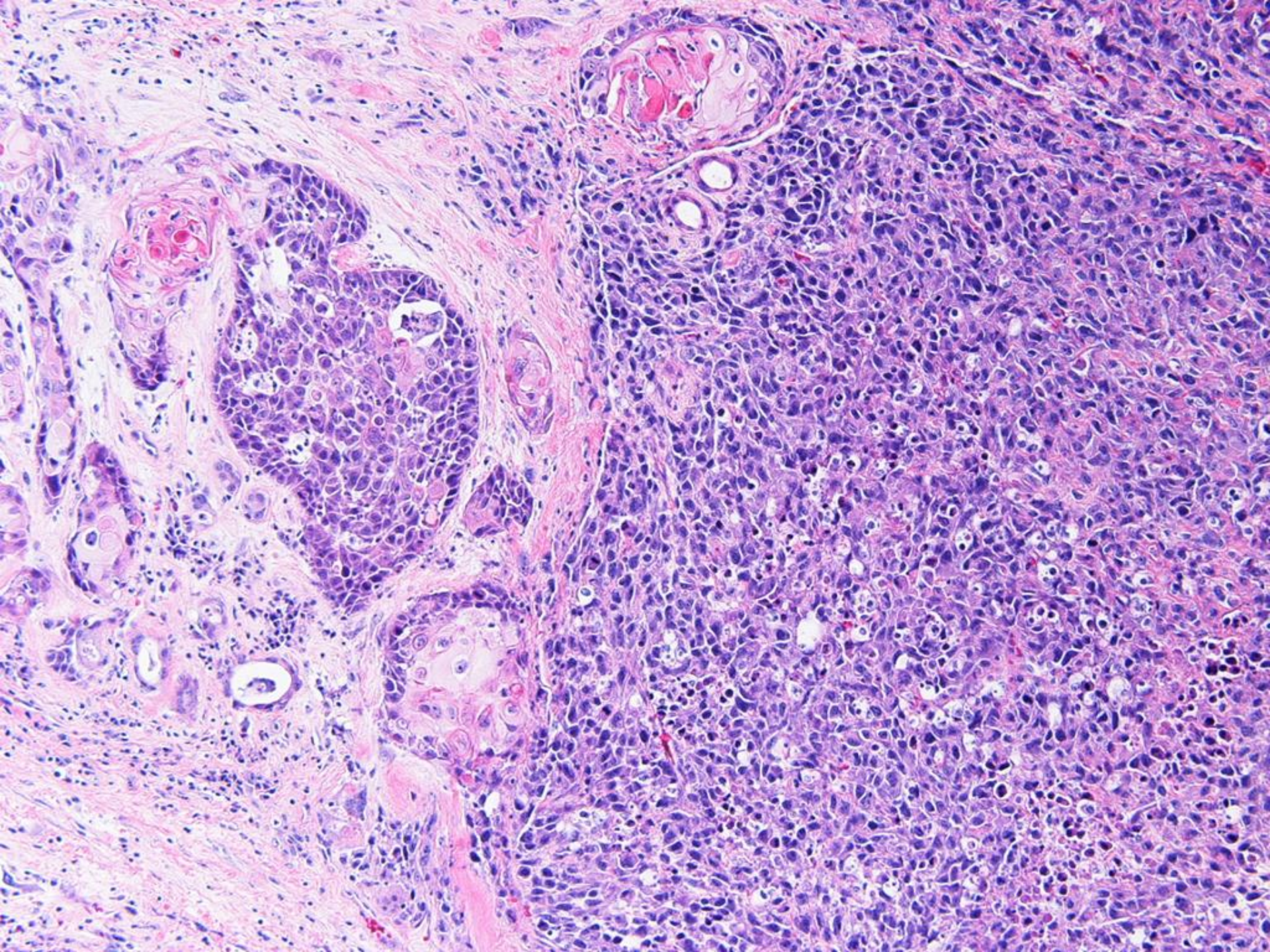












Update on Pathogenesis

Conventional (Non-HPV Associated)Squamous Cell Carcinoma

- Risk factors: Alcohol, Tobacco
- Older individuals, > age 60
- More common in males

Molecular Alterations in HNSCC (non-HPV)

- Concept of Field Effect

- Alteration of p53/RB pathways
  - P53 mutations in 60-80%
- CDKN2A frequently inactivated by mutation or methylation
- CCND1 amplified in >80% cases
- Overexpression of EGFR

HNSCC

- Incidence in decline beginning in early 1980's paralleling trends in smoking
- Recent increases in oropharyngeal cancers

Oropharyngeal Cancer

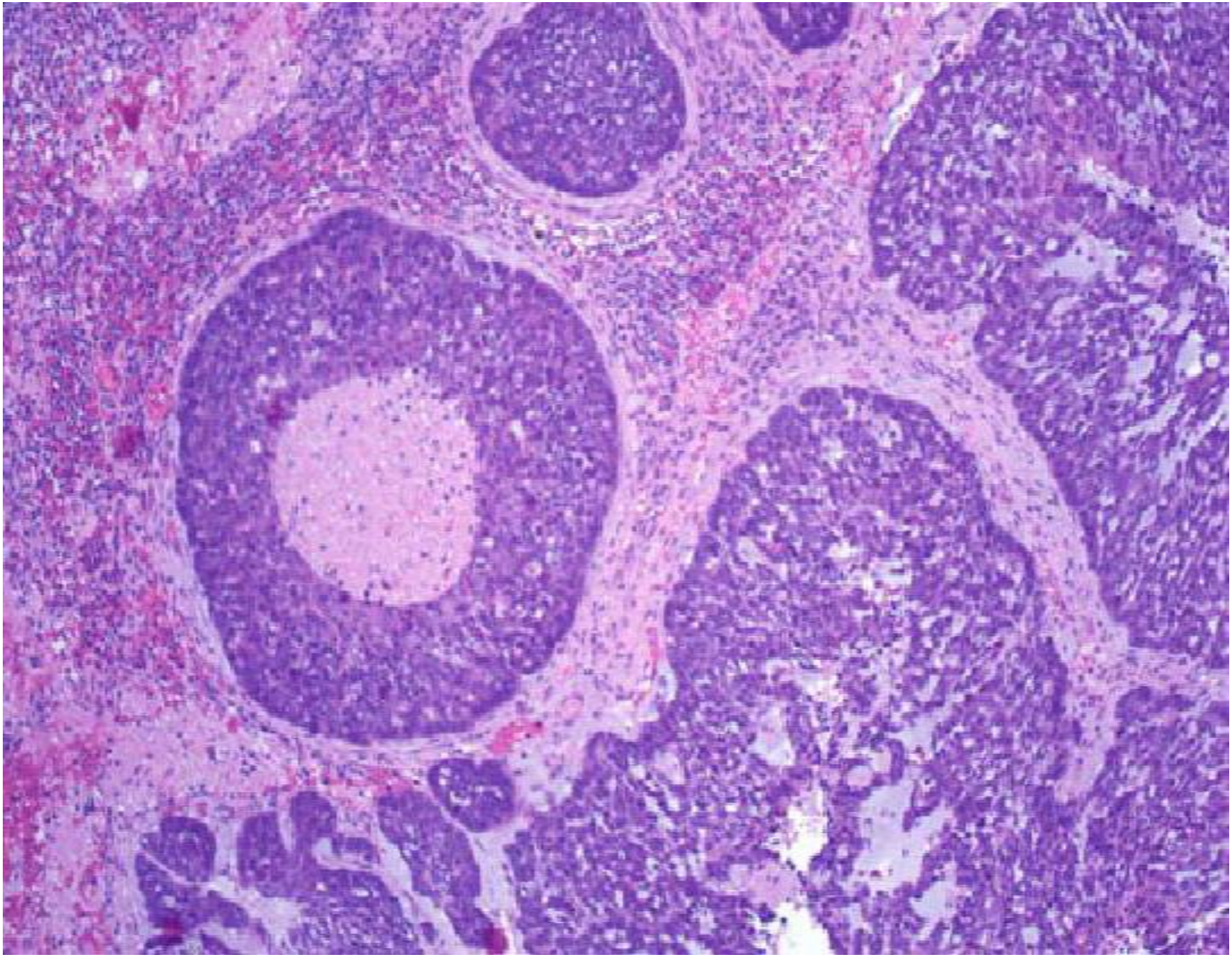
- Younger (often under age 45), no smoking history
- Risk factors: High number of sexual partners, history of oral-genital sex, marijuana use

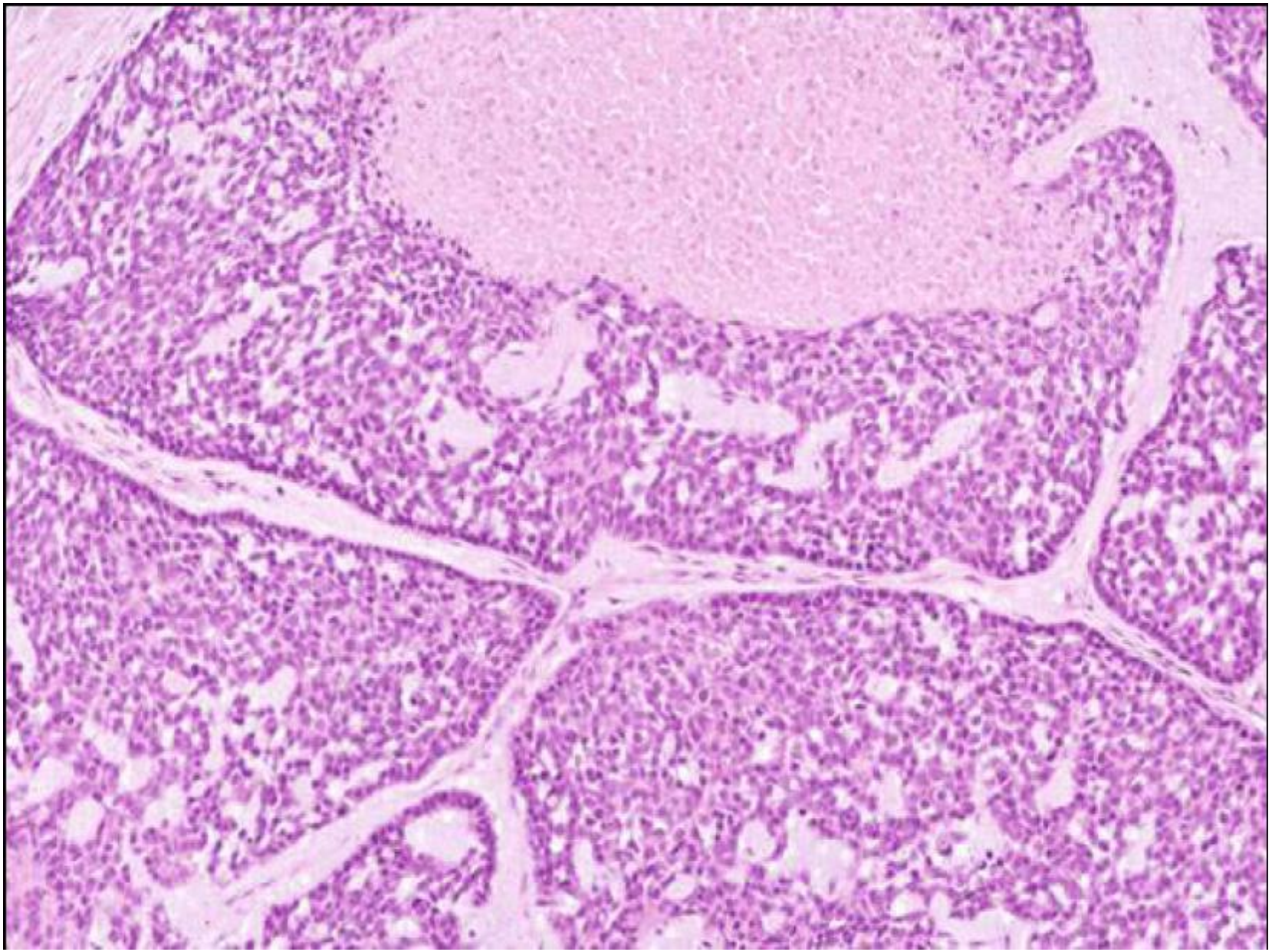
Oropharyngeal Cancer

- HPV identified in up to 70% of cases (most commonly type 16)

Features of HPV positive HNSC

- Arise from tonsillar crypts
- Non-keratinizing
- Permeated by infiltrating lymphocytes
- Exhibit lobular or basaloid growth (prognostic confusion)





HPV Associated Oropharyngeal Carcinoma

- HPV recognized as an independent prognostic indicator
- Patients with HPV associated carcinoma have better overall survival rates (82% vs 57% at 3 years, Ang et al, 2010)
- May contribute to recognized racial differences in survival

HPV Associated Oropharyngeal Carcinoma

- Molecular differences seen between HPV associated HNSCC and those with traditional risk factors
- P53 mutations rare in HPV associated cancers
- Viral oncoproteins E6 and E7 act to inactivate p53 and RB respectively
- Overexpression of p16

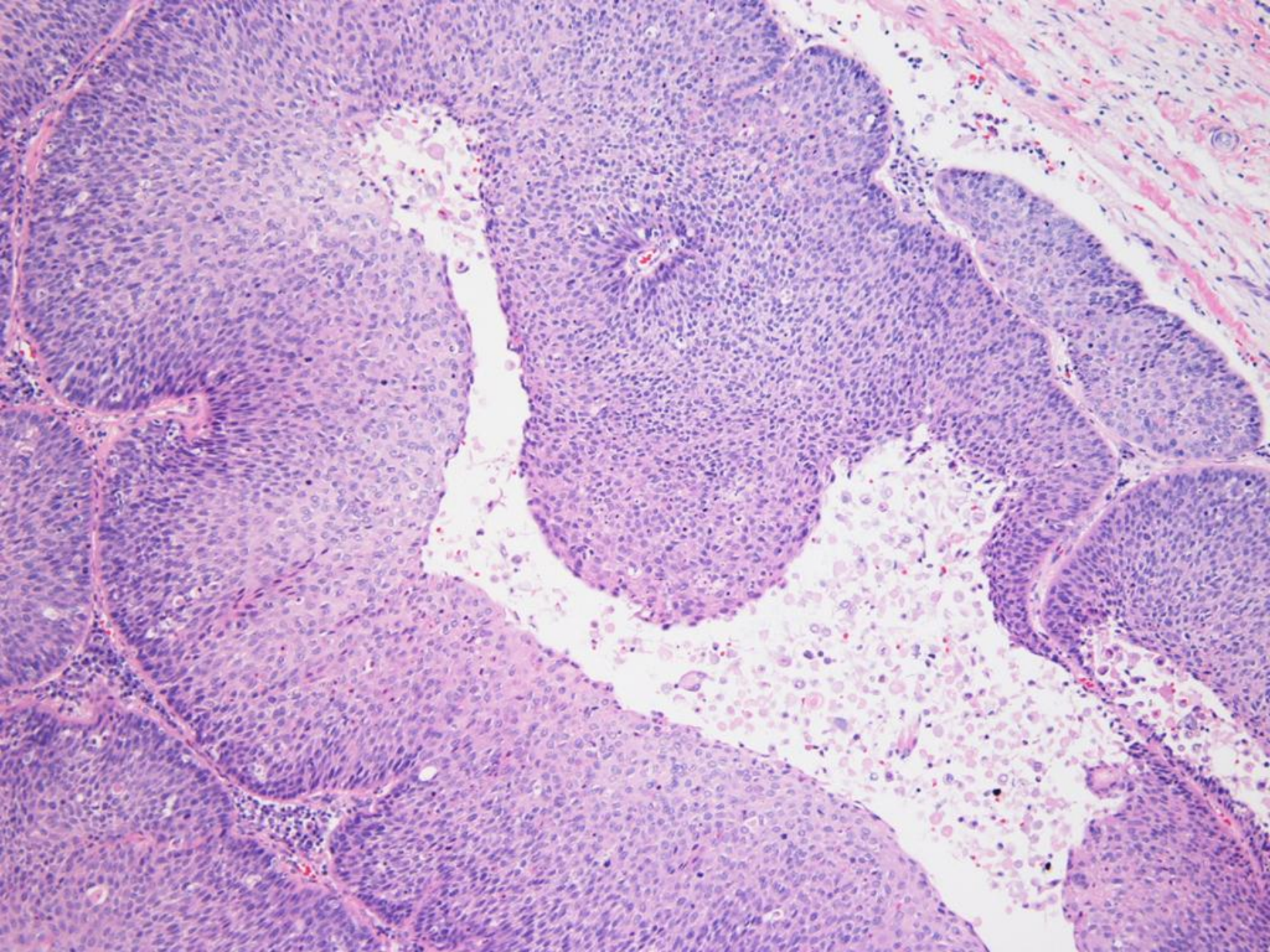
Reporting Suggestions

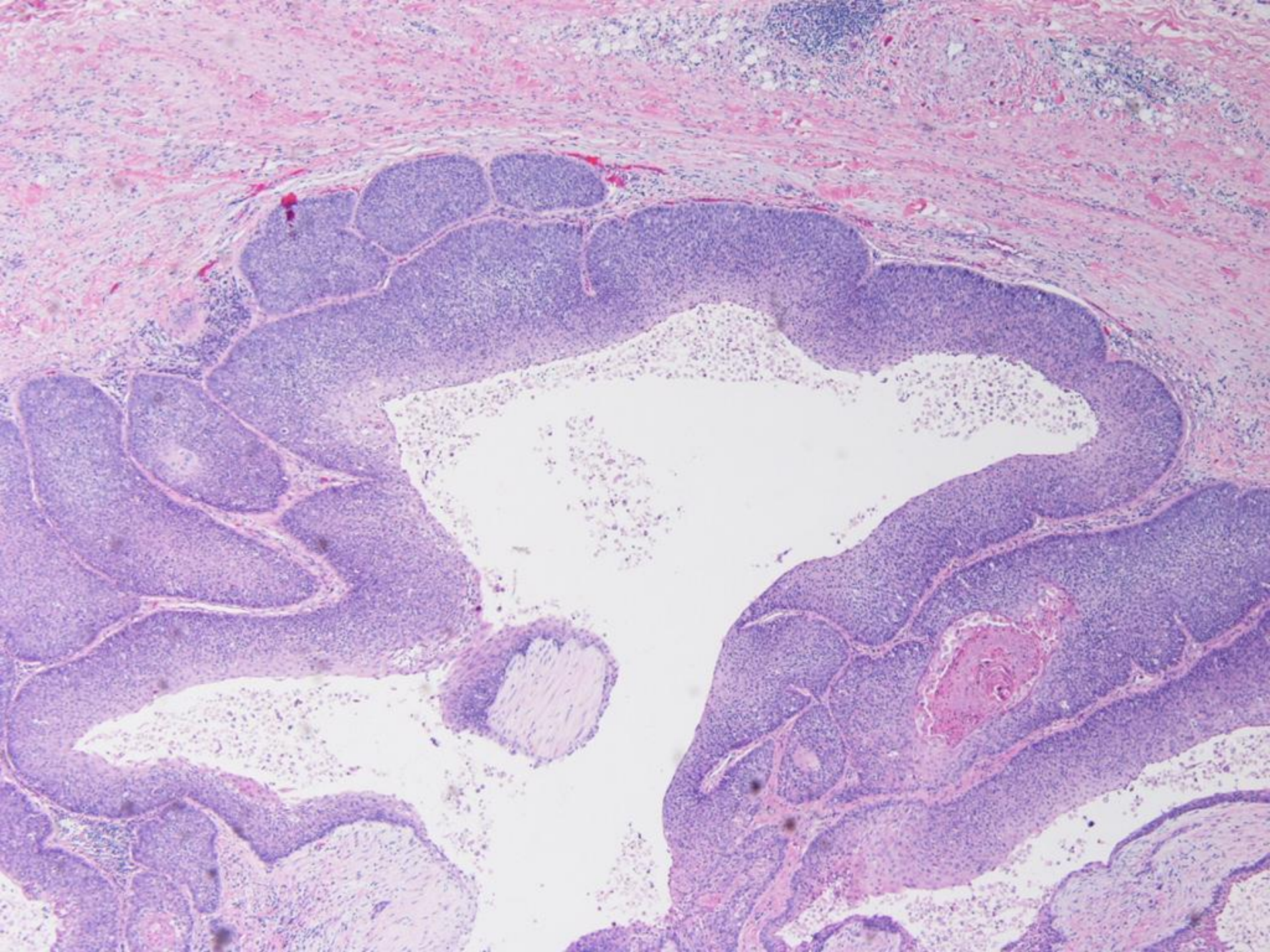
- Classify as non-keratinizing squamous cell carcinoma
- Suspend use of “poorly differentiated” and “basaloid” for oropharyngeal carcinomas
- Routinely report HPV status of all oropharyngeal HNSCC

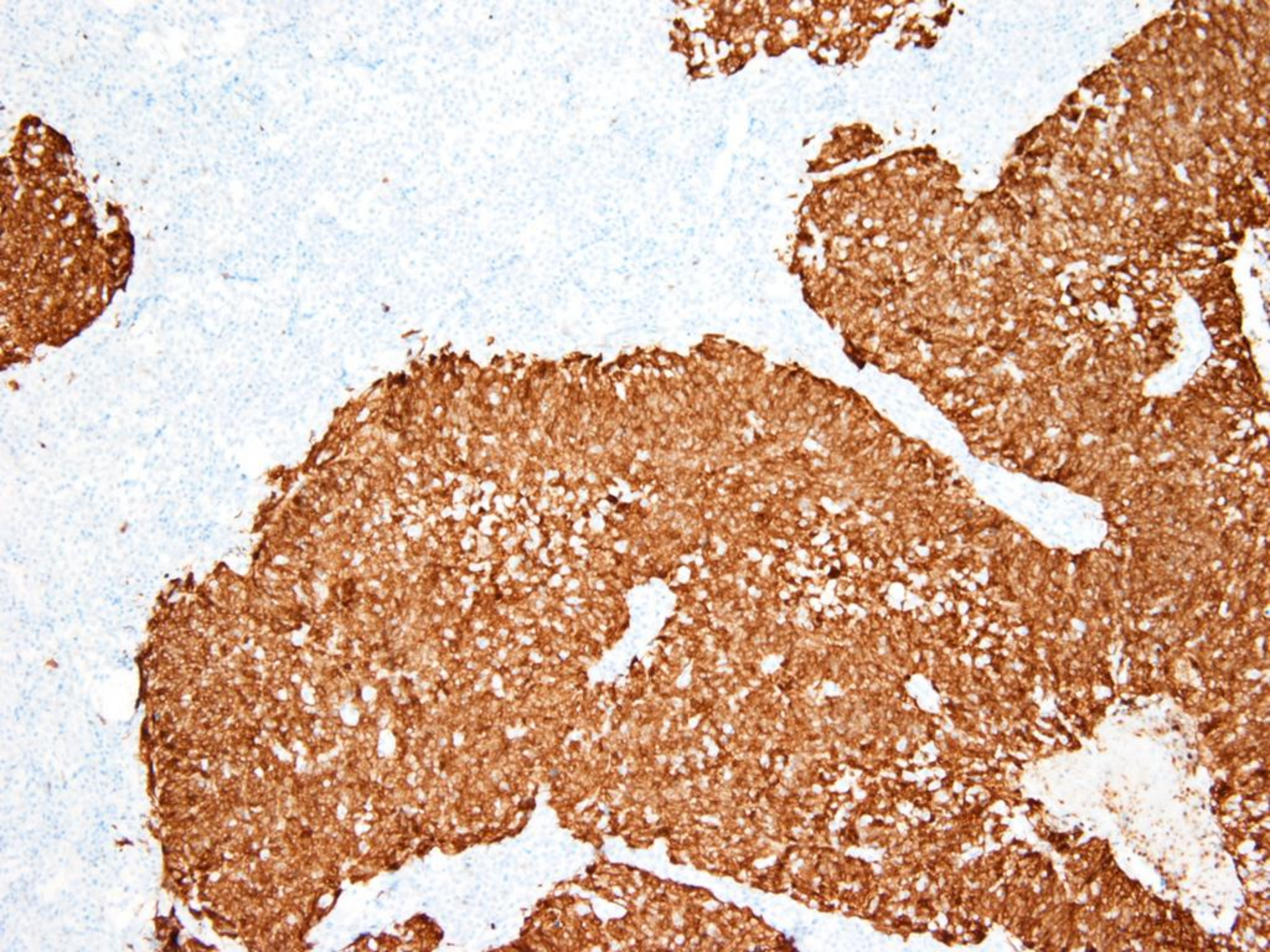
Westra (2009)

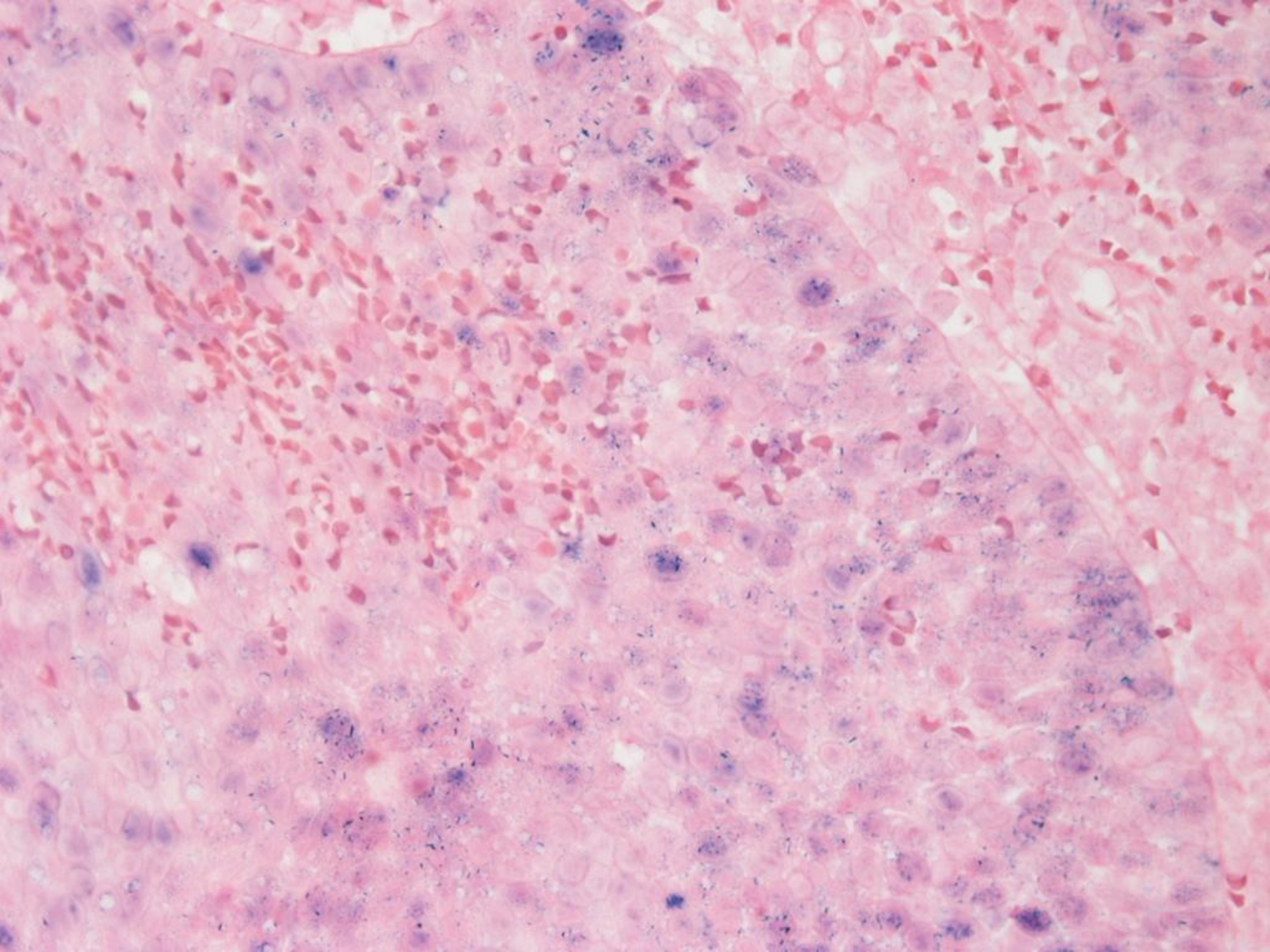
HPV Testing

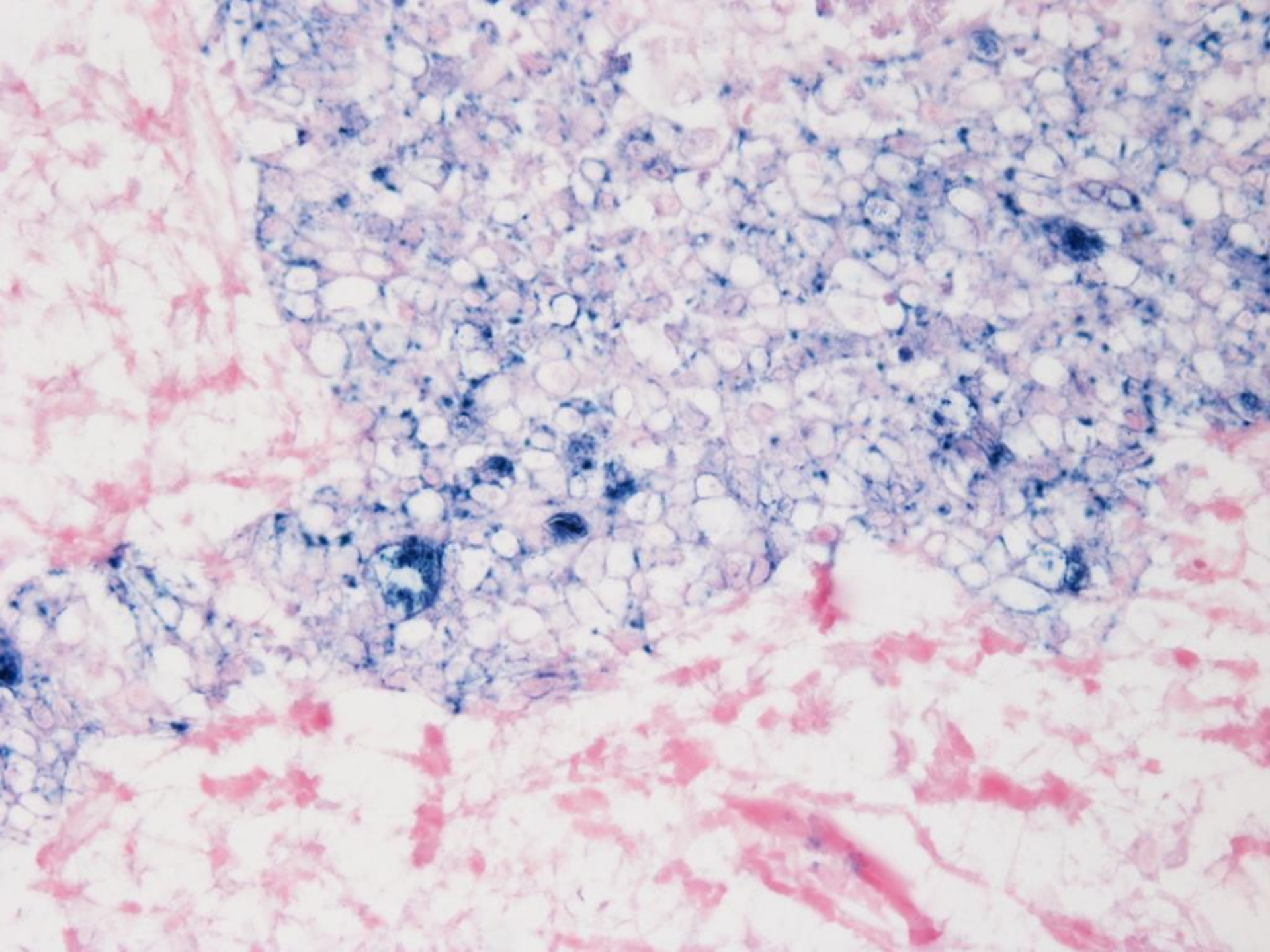
- PCR for HPV 16 DNA
  - May be too sensitive and classify cases as HPV associated without integration of viral DNA
- RT-PCR for E6 and E7 transcripts
  - Detects only productive infection
  - Not reliable from formalin fixed, paraffin embedded tissue
- In Situ Hybridization
  - Probes commercially available
  - Technically difficult with background artifact and subjective interpretation
- p16 immunohistochemistry
  - Easily performed in almost all laboratories
  - Cutoffs for calling positive not standardized

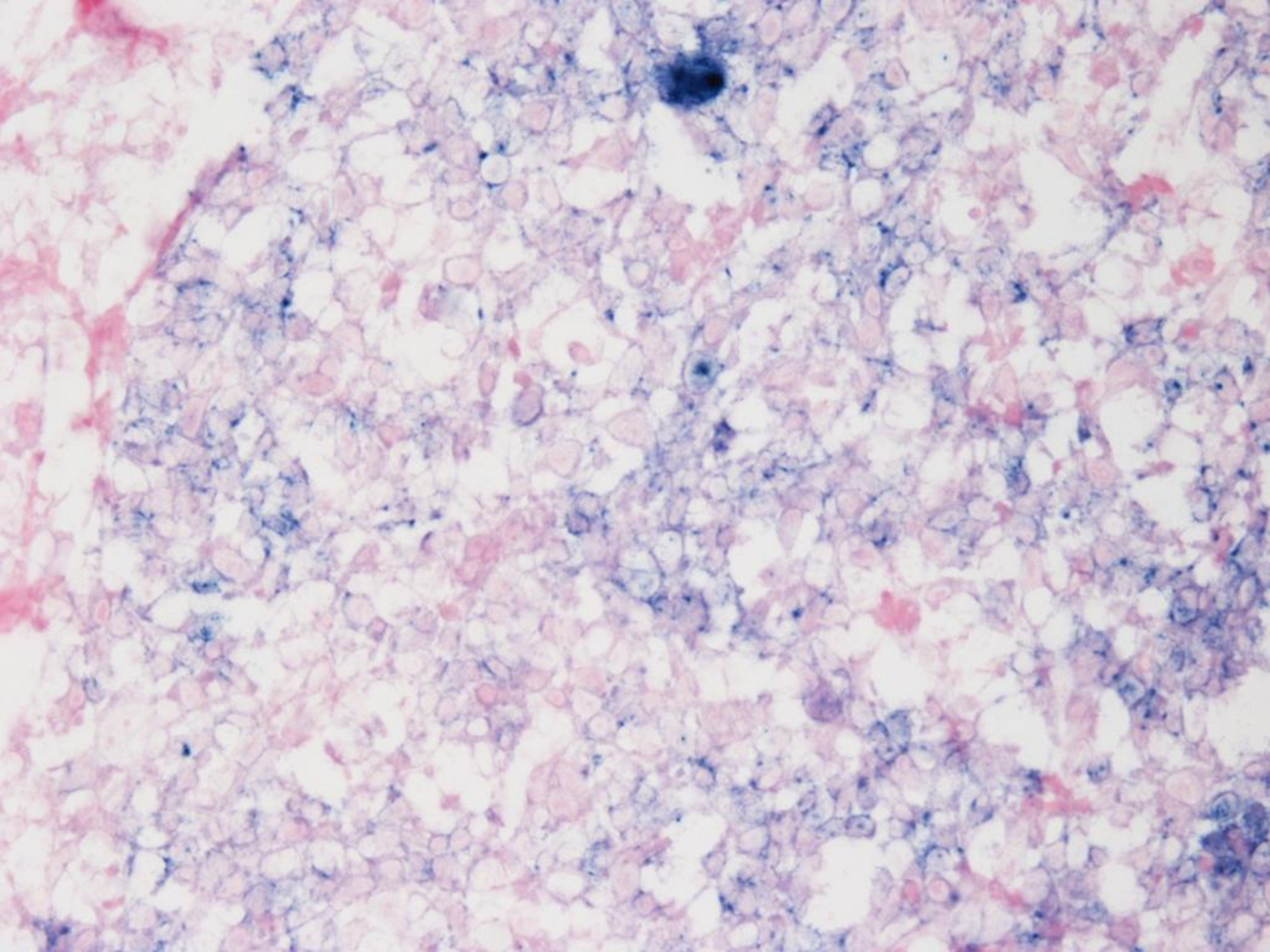












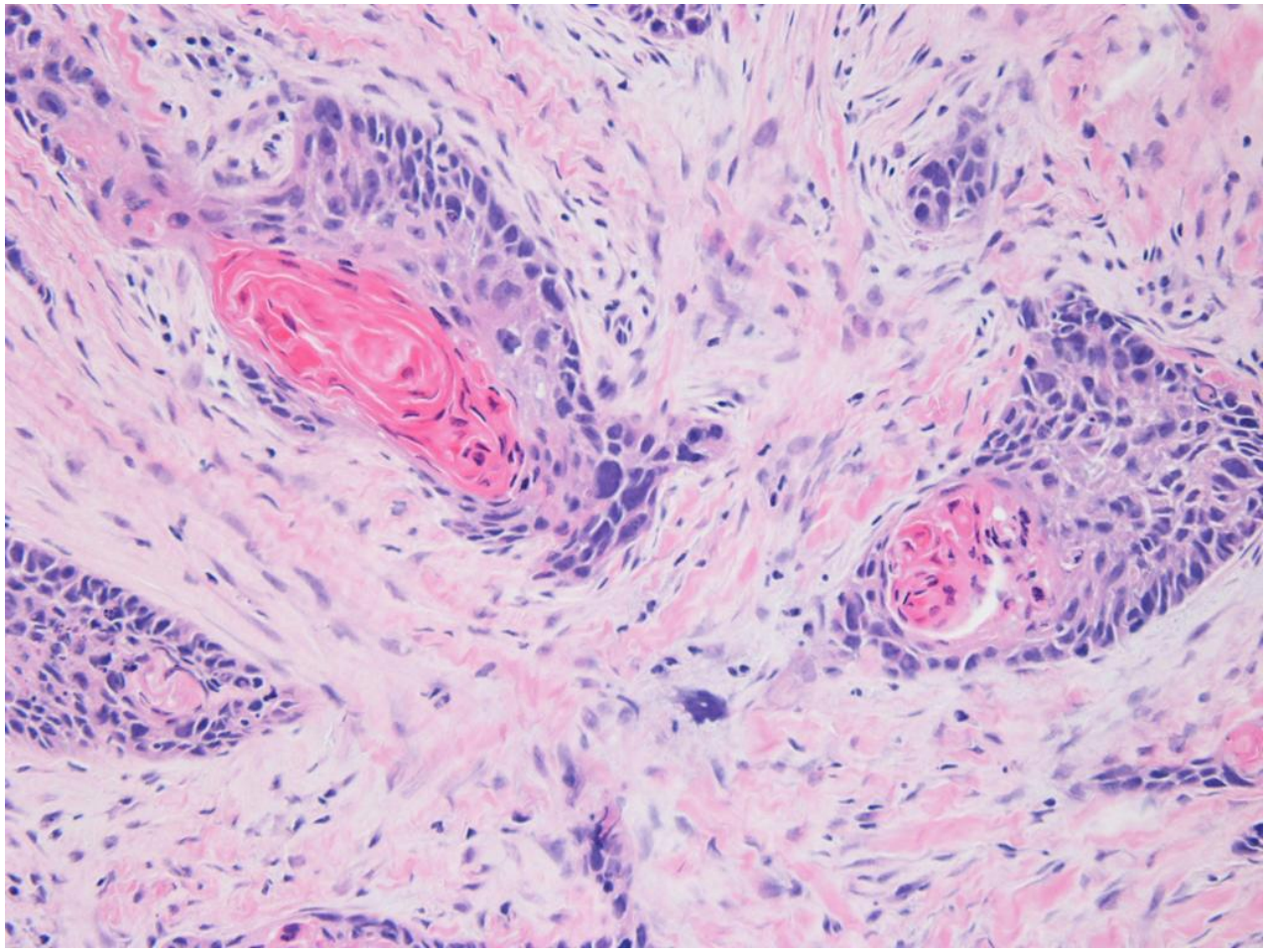
HPV Testing Strategies

- p16 alone (May be sufficient for risk stratification)
- p16 + ISH
- p16 + PCR
- p16 + ISH + PCR

- Although determining HPV status is recommended for all newly diagnosed oropharyngeal carcinomas, methods of testing have not been standardized

Conclusions

- HNSCC is a common cause of morbitity and mortality worldwide.
- HPV associated carcinomas represent a distinct form of HNSCC with unique molecular features and improved prognosis
- Identification of HPV associated carcinomas is recommended, although testing methods have not been standardized



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