Head and Neck Pathology Update

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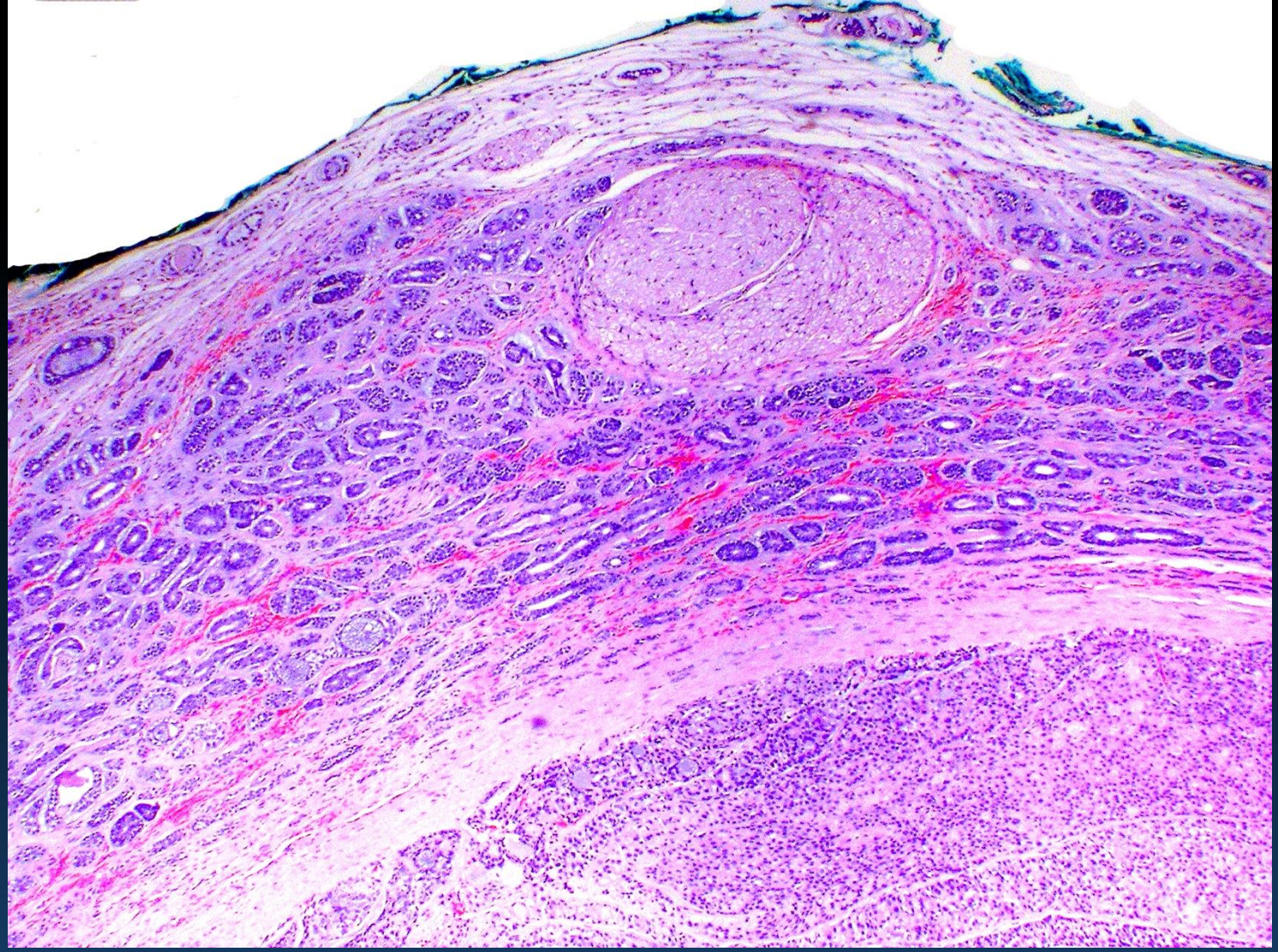
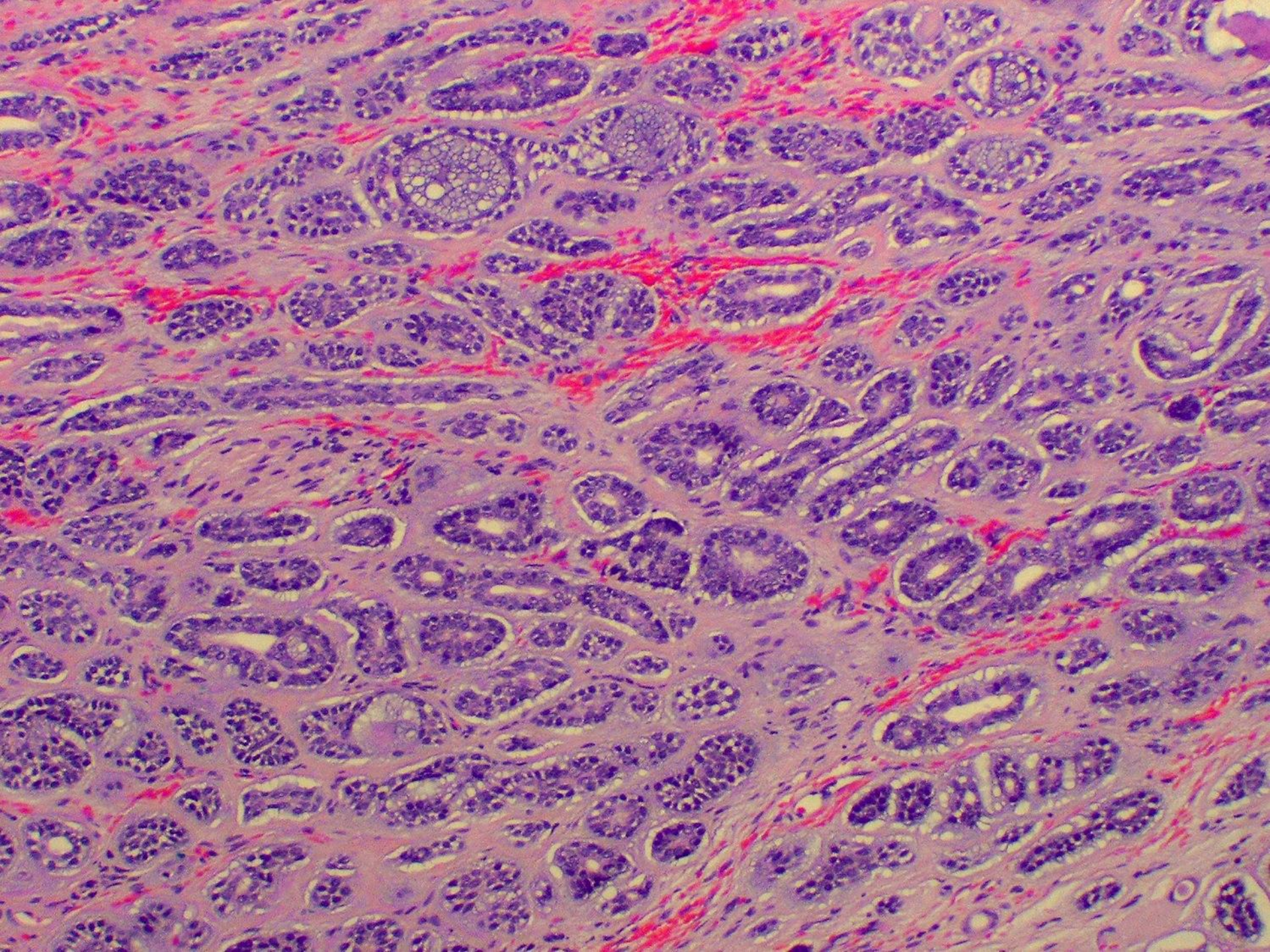
Overview

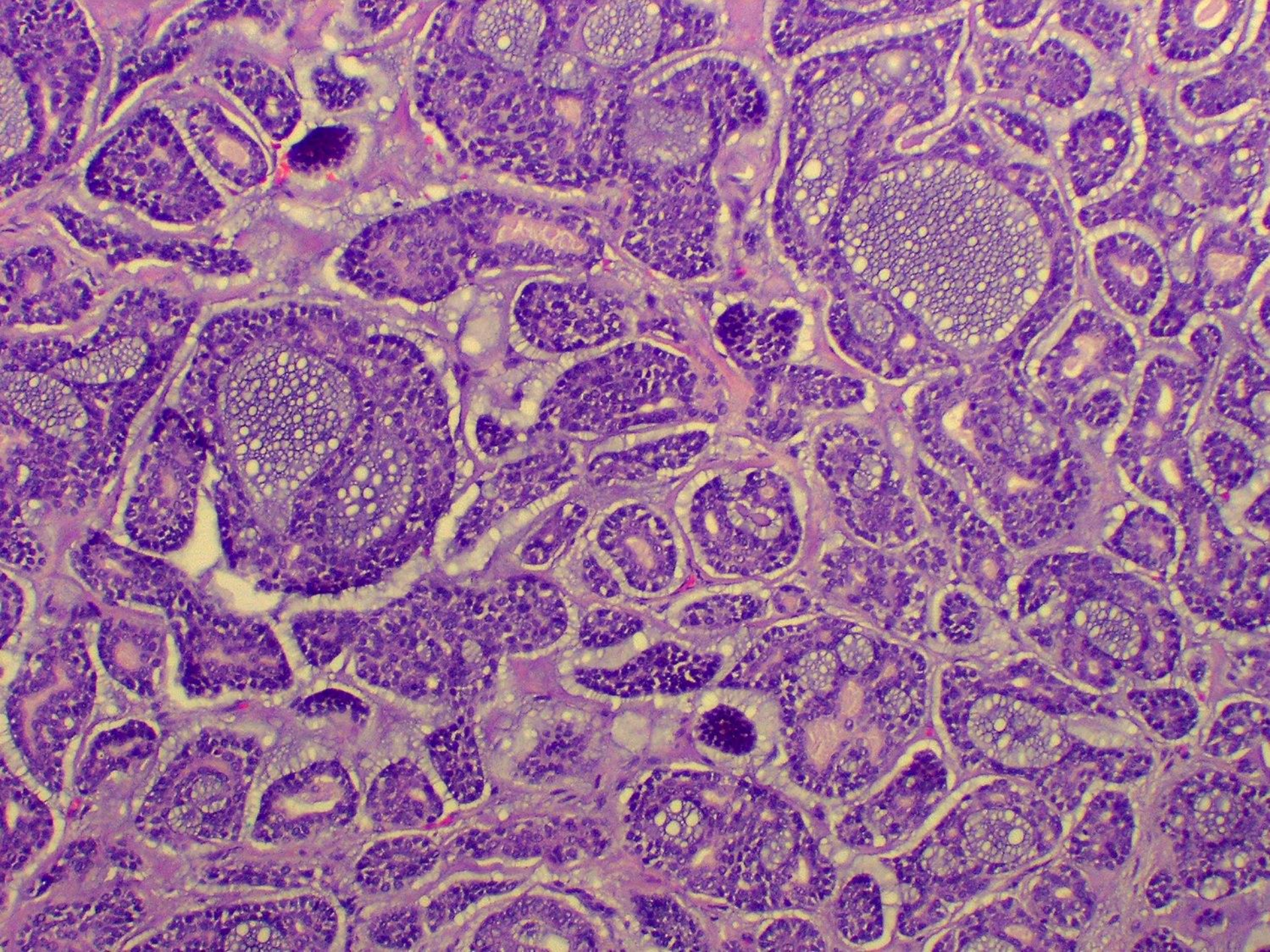
- Select salivary gland tumors
- Some sinonasal confounders along the way
- Increasing role of ancillary techniques in diagnosis
  - Immunohistochemistry
  - FISH, Cytogenetics
  - Mutational analysis, NGS

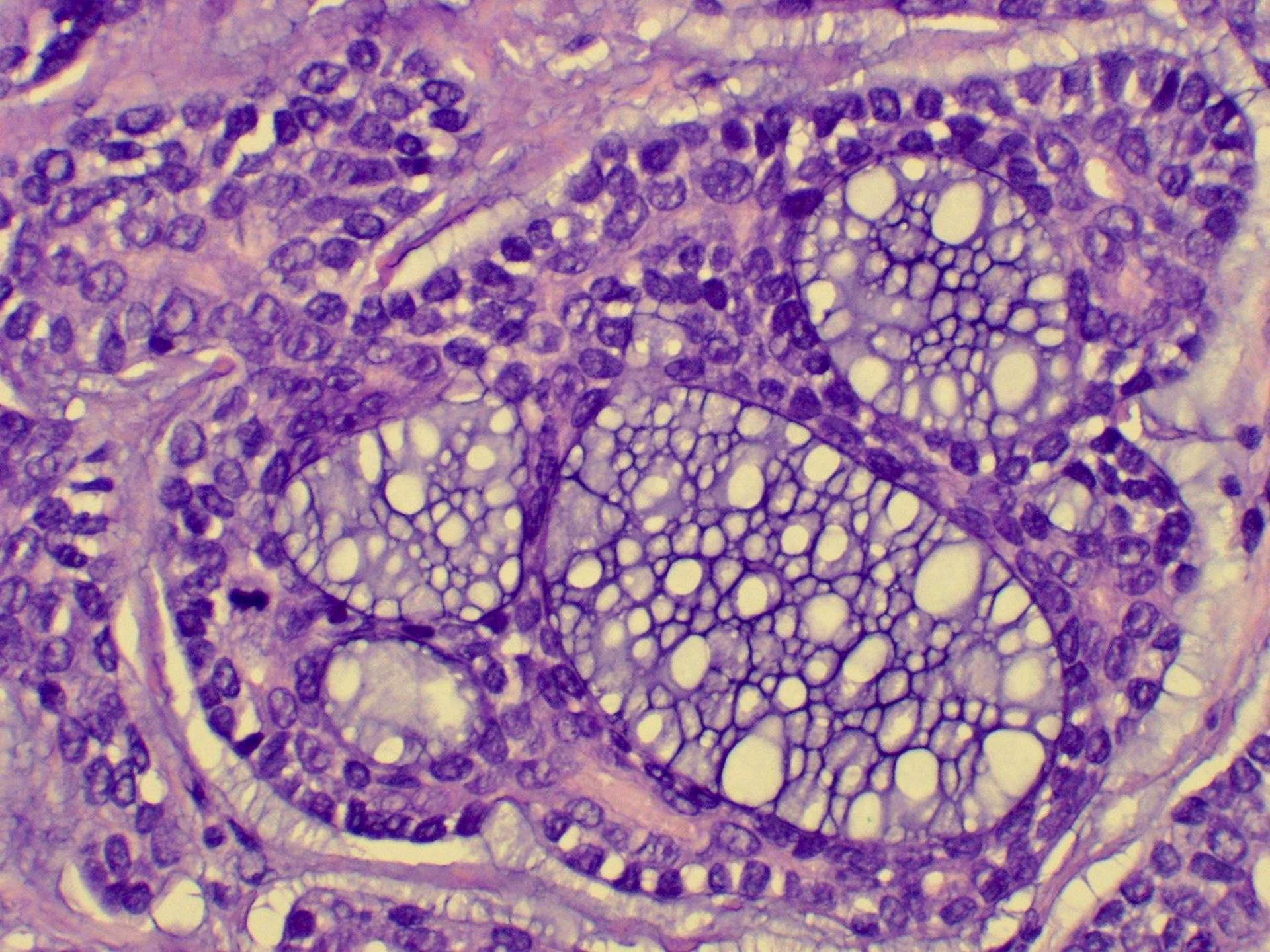


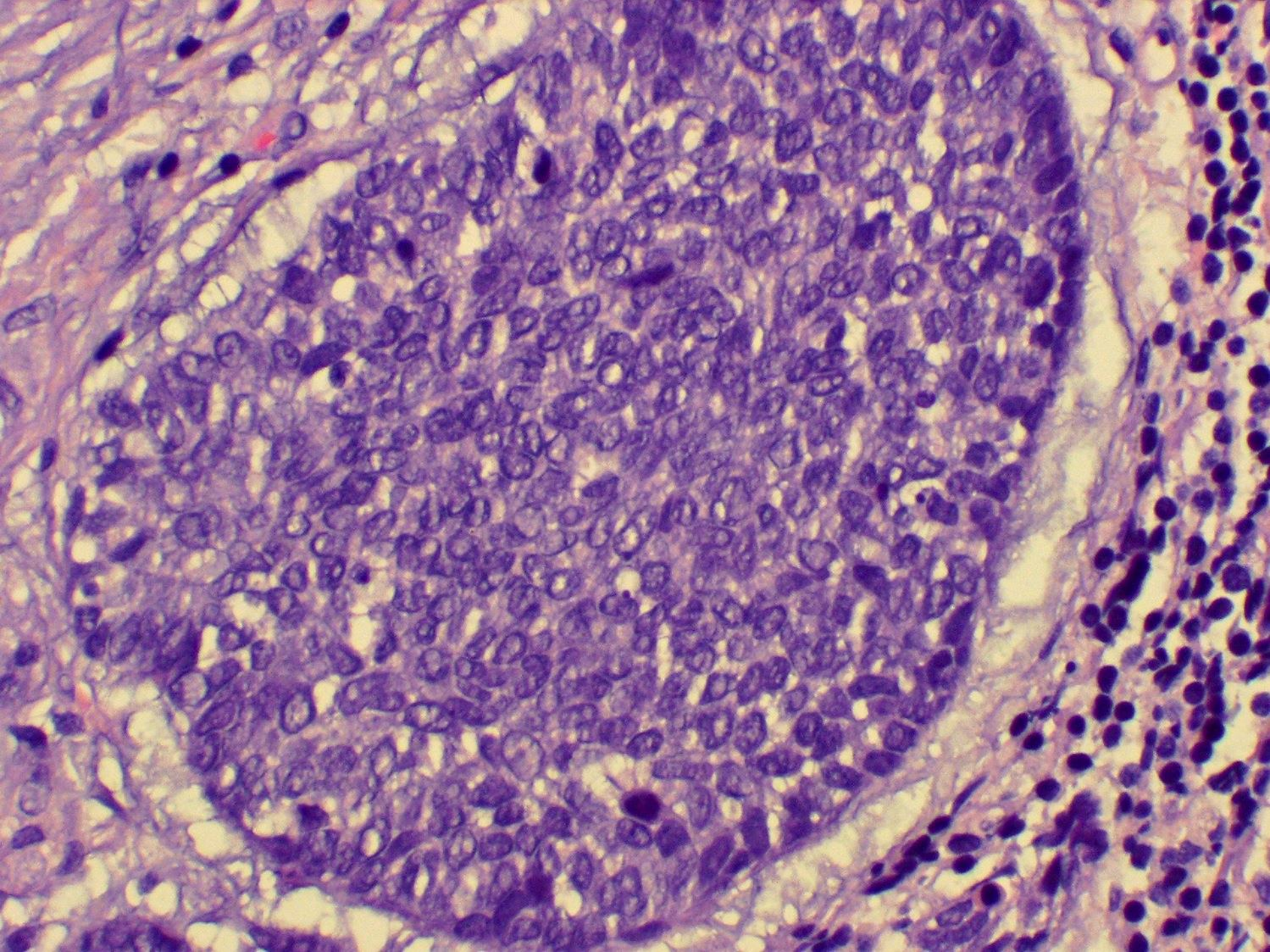
Case History

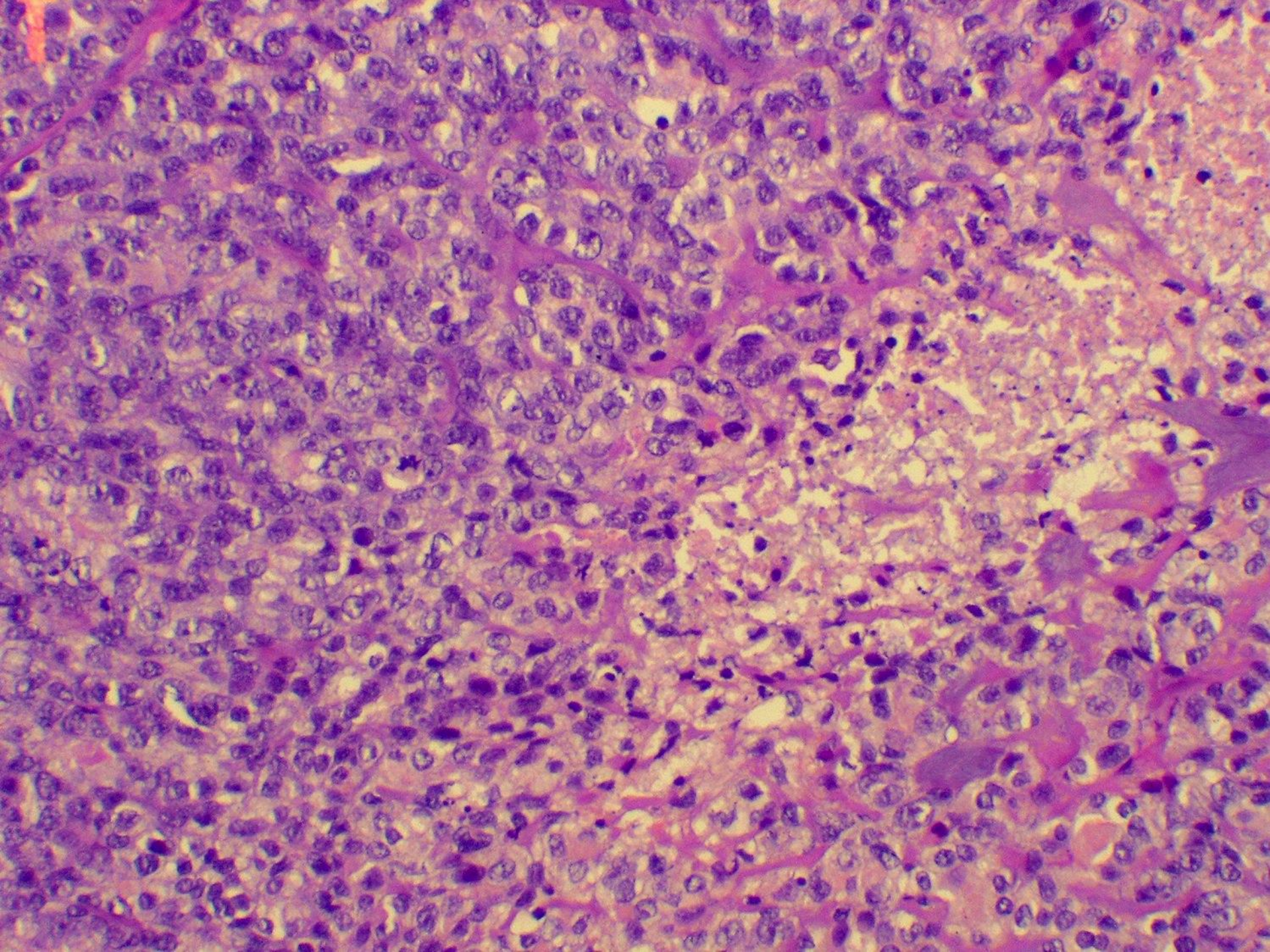
43 year old male with a tongue mass

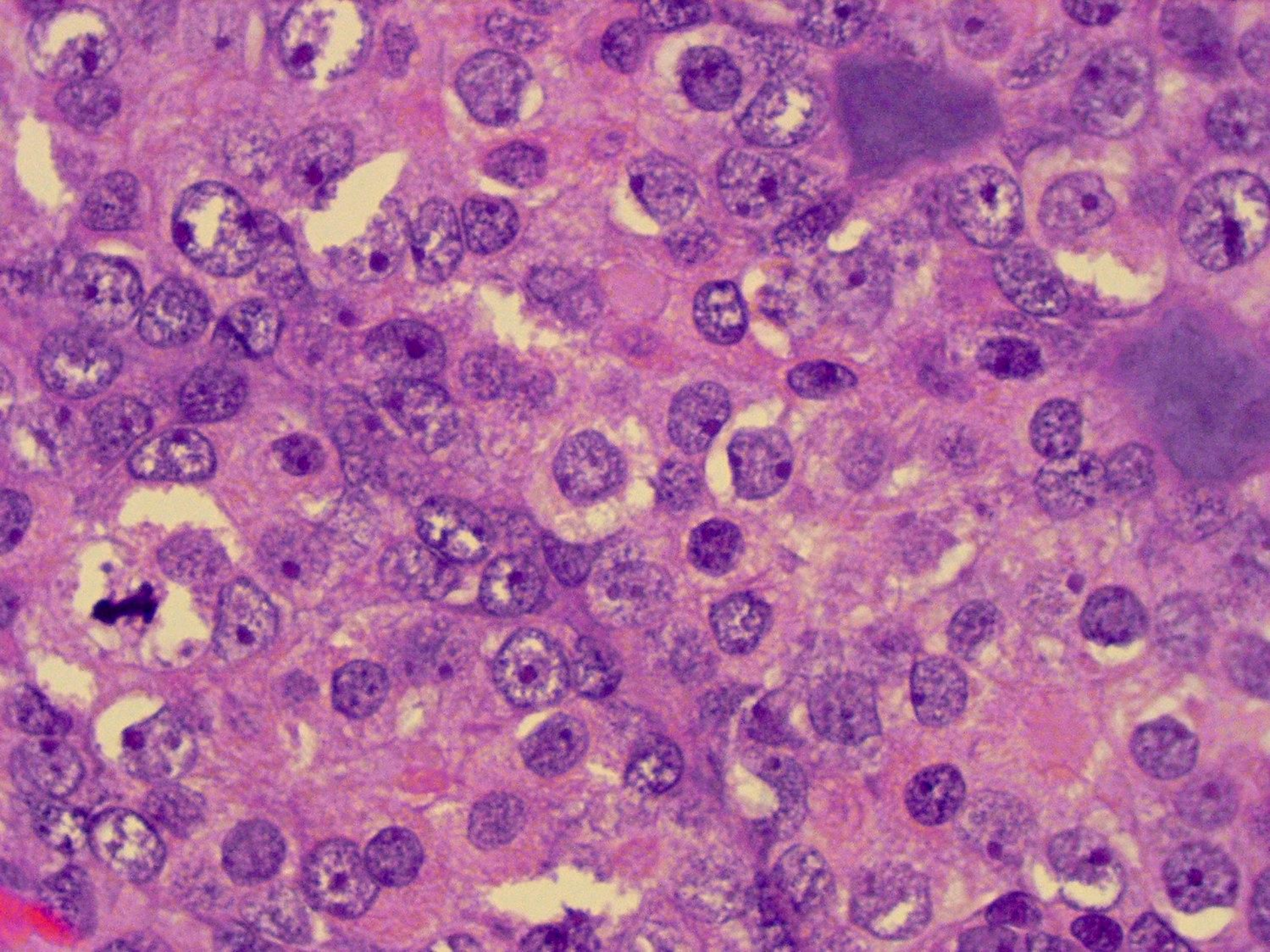










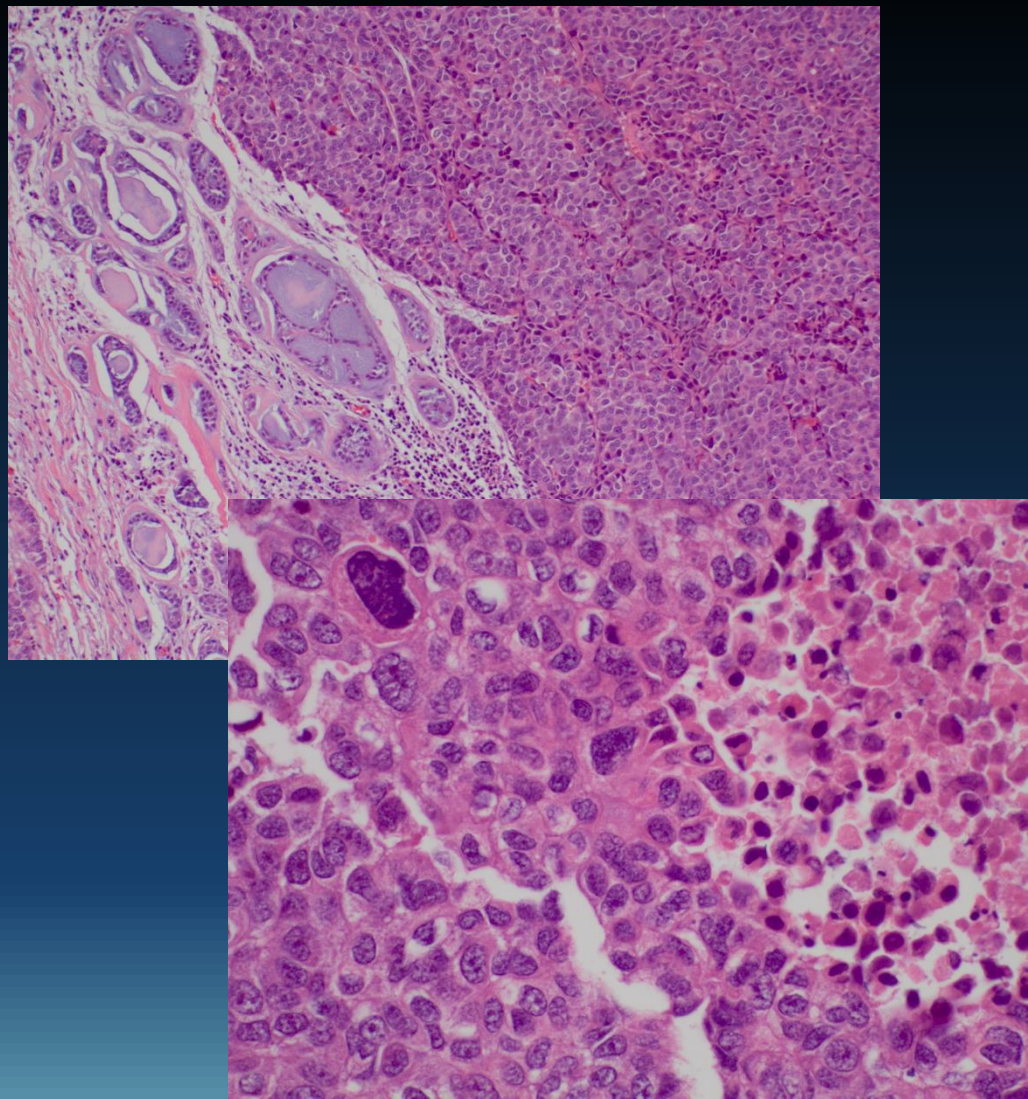


Diagnosis

- Adenoid cystic carcinoma with focal solid growth and high grade transformation (dedifferentiation)

High-grade Transformation in Salivary Gland Tumors

- Abrupt transformation of a low-grade carcinoma to a high-grade component
- First described in acinic cell ca (1988)
- Rare cases reported with other types
  - P(LG)A, epithelial-myoepithelial ca, MEC, and AdCC
- Aggressive course

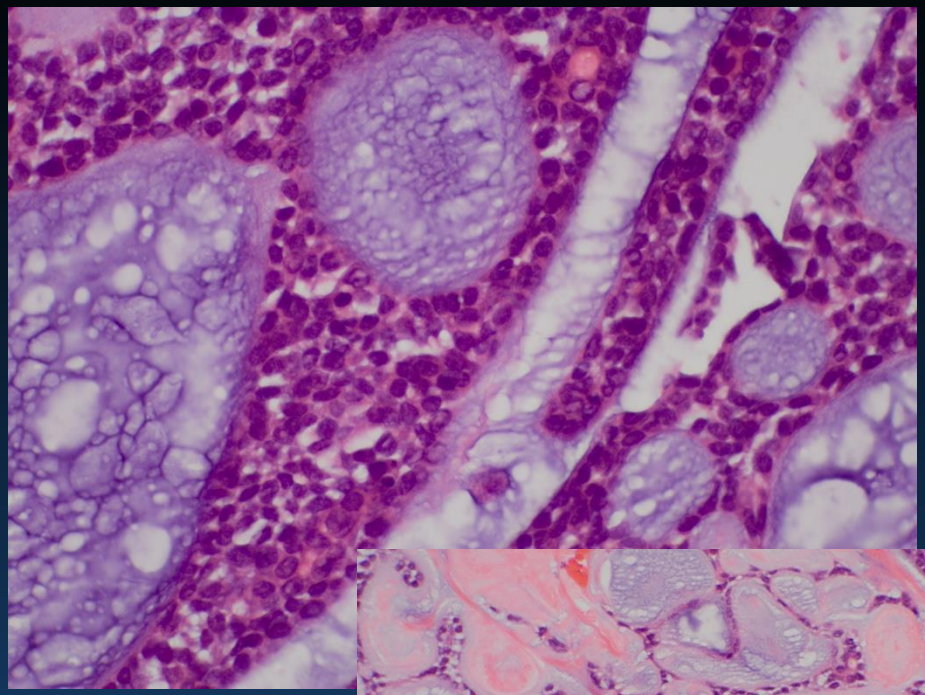


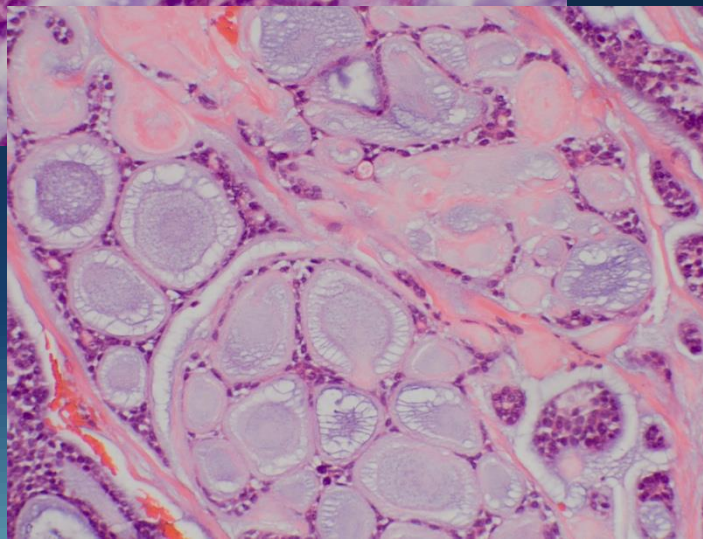
Adenoid Cystic Carcinoma
Clinical

- 10% of salivary gland tumors
- 30% of minor salivary gland tumors
- Slow but relentless disease progression
  - 89% 5-yr survival
  - 50-70% 10-yr survival
- Local and hematogenous spread
  - Mets to lung, bone, liver, brain

Adenoid Cystic Carcinoma
Pathology

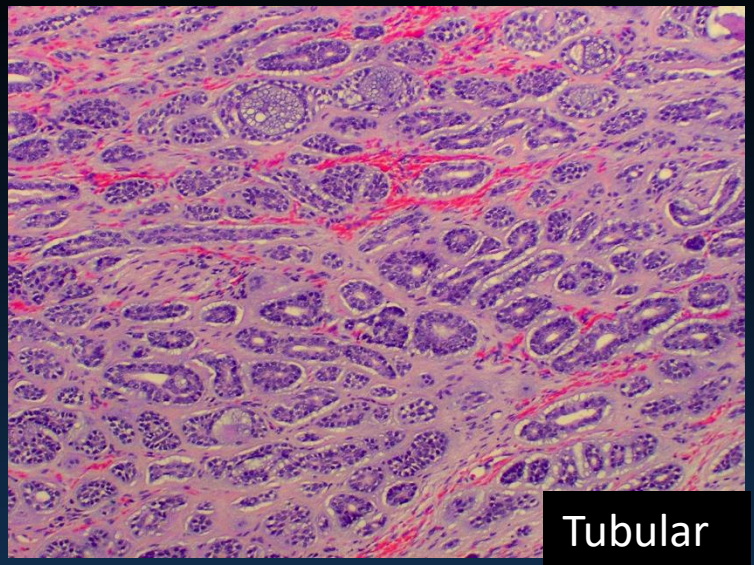
- Myoepithelial cells
  - Hyperchromatic, angulated nuclei
  - Molding
  - Clear cytoplasm
- Ductal type epithelial cells
- Hyalinized/mucoid/myxoid mucopolysaccharide filled spaces



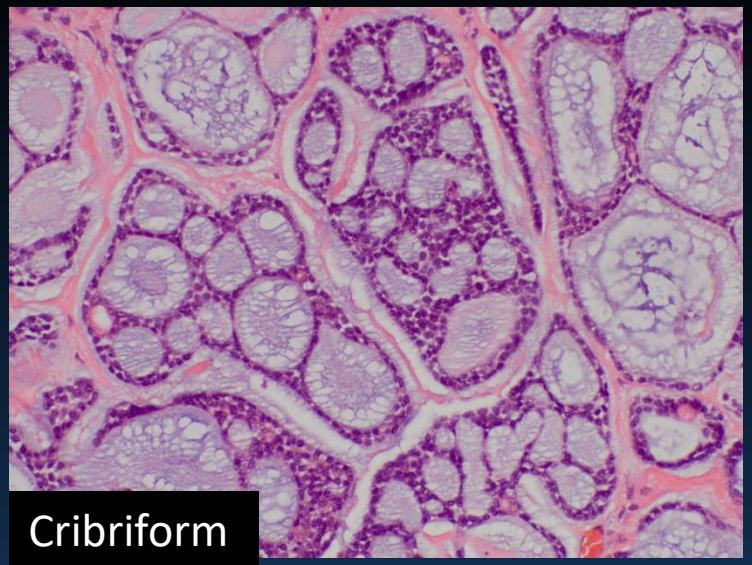


Adenoid Cystic Carcinoma

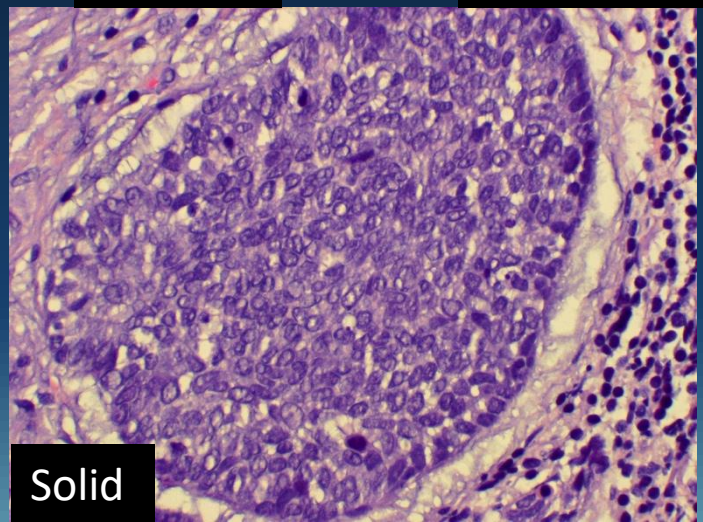
Growth Patterns



Tubular



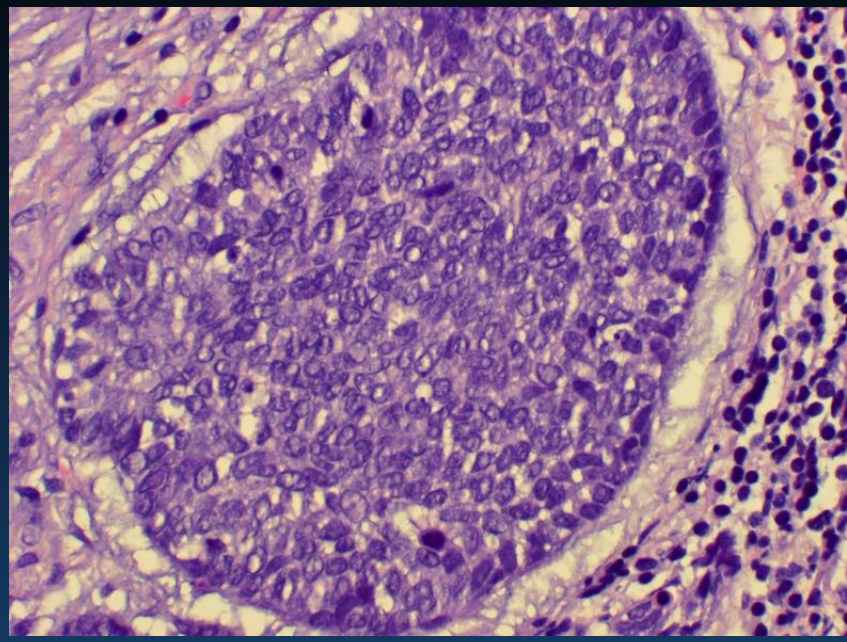
Cribriform



Solid

Adenoid Cystic Carcinoma
Growth Pattern and Prognosis

- Solid pattern
  - Aggressive course
    - 39% 15 year survival without solid
    - 5% 15 year survival with >30% solid
  - Mitoses, necrosis
  - Retains basaloid morphology with rounded nests and myoepithelial phenotype



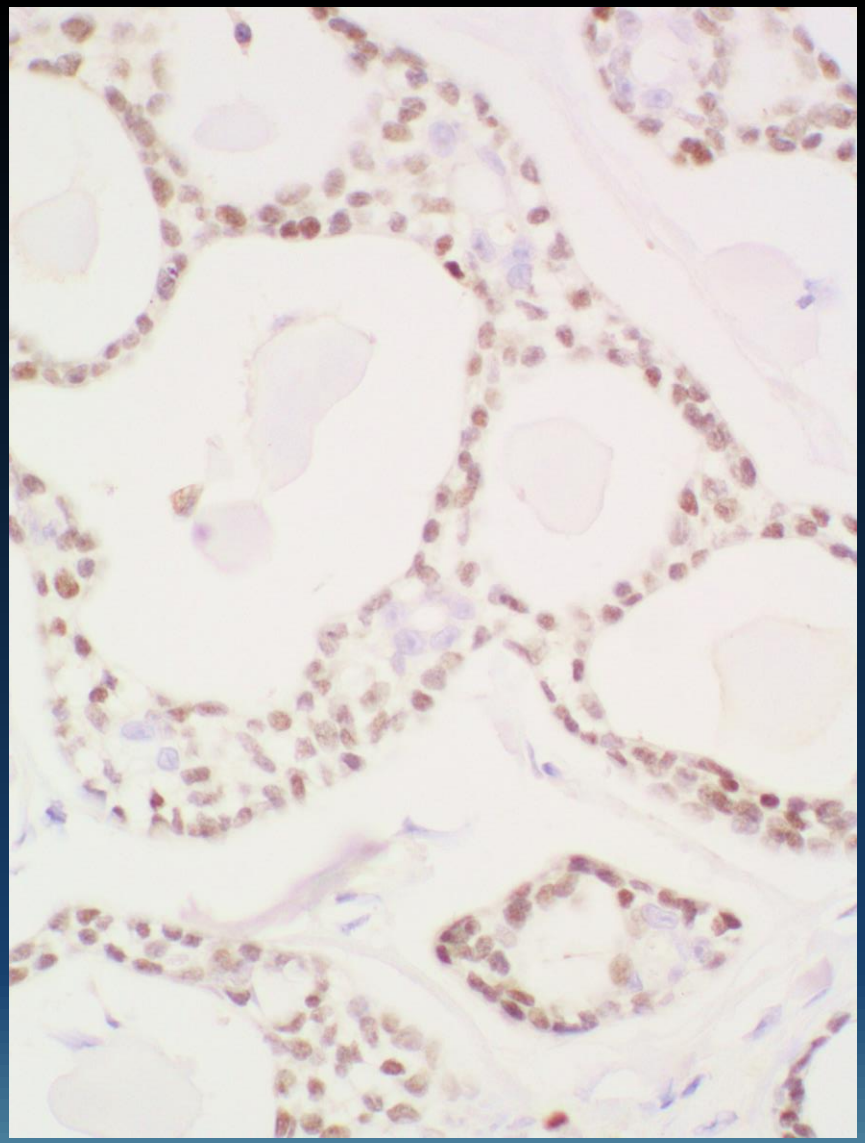
Adenoid Cystic Carcinoma
Cytogenetics

- t(6:9) *MYB* oncogene-*NFIB* transcription factor
  - Rarely t(8:9) *MYBL1/NFIB*
- >80% of AdCC

Persson et al PNAS (2009) and Persson et al Genes, Chromosomes, and Cancer (2012)

MYB Immunohistochemistry

- 82% AdCC (+)
- 14% non-AdCC tumors tested (+)
  - 4 of 5 basaloid SCCs
- All non-AdCC tumors were translocation (-)

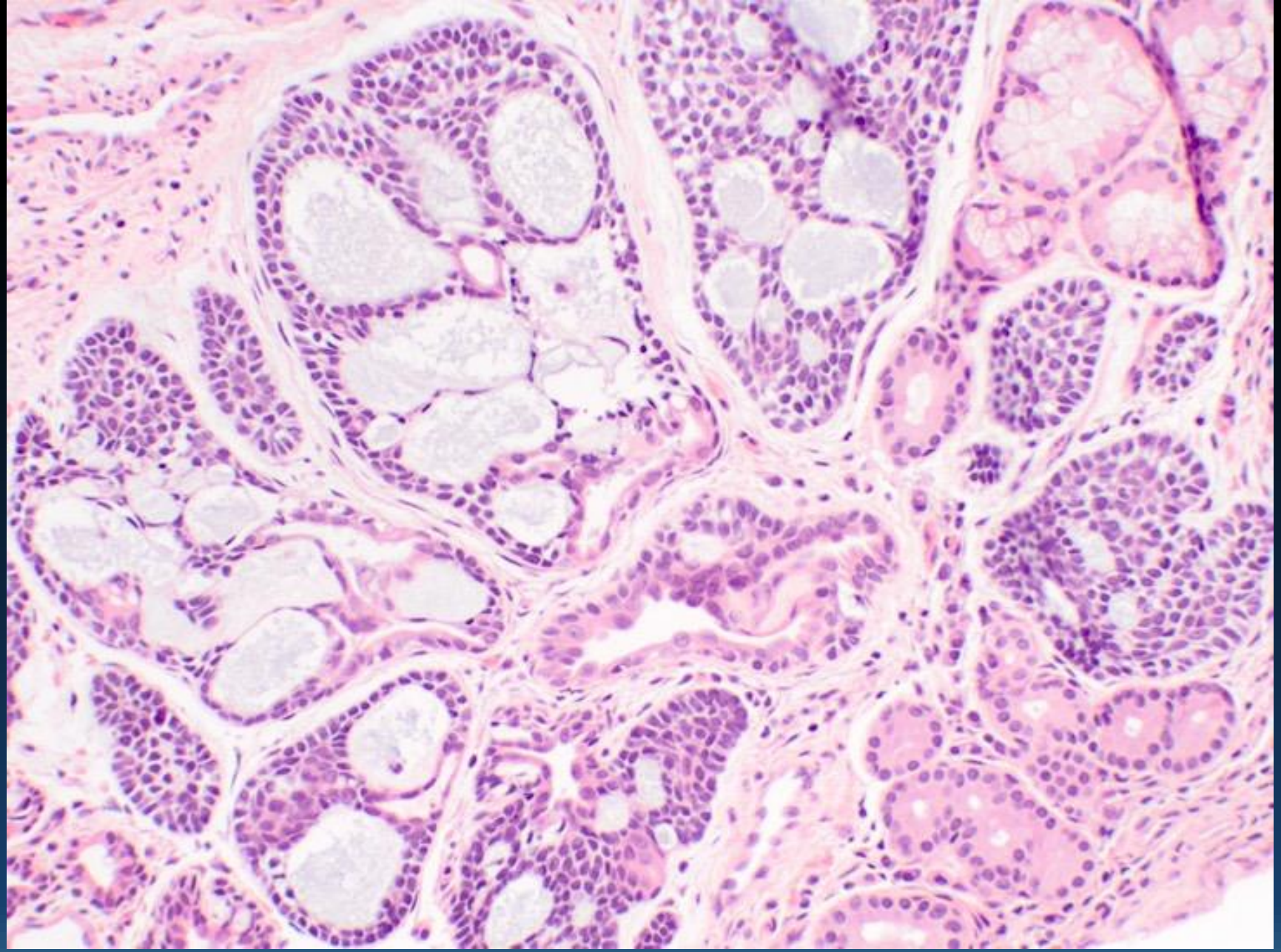


Brill et al Modern Pathol (2011)

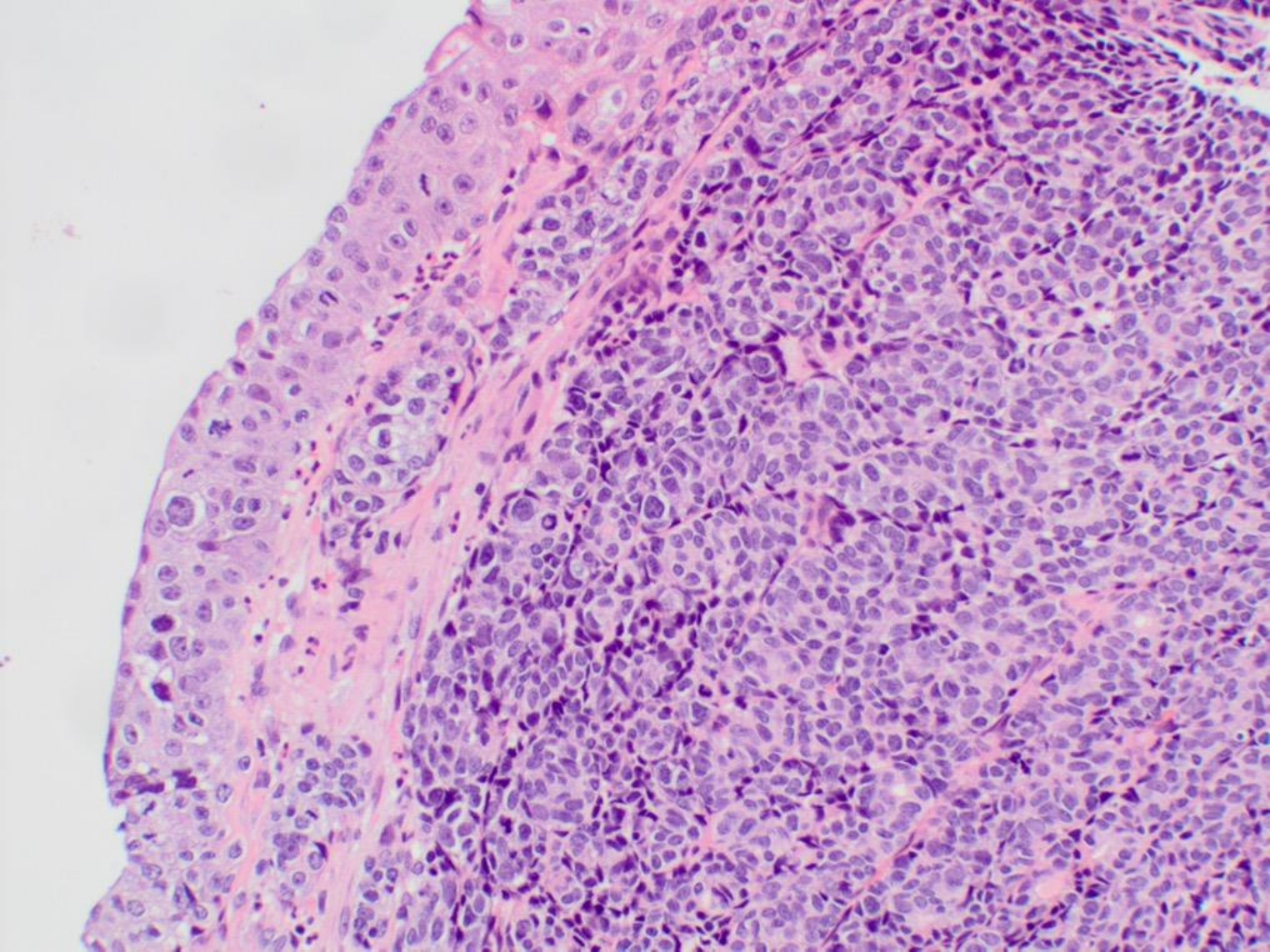
Adenoid Cystic Carcinoma
Differential Diagnosis

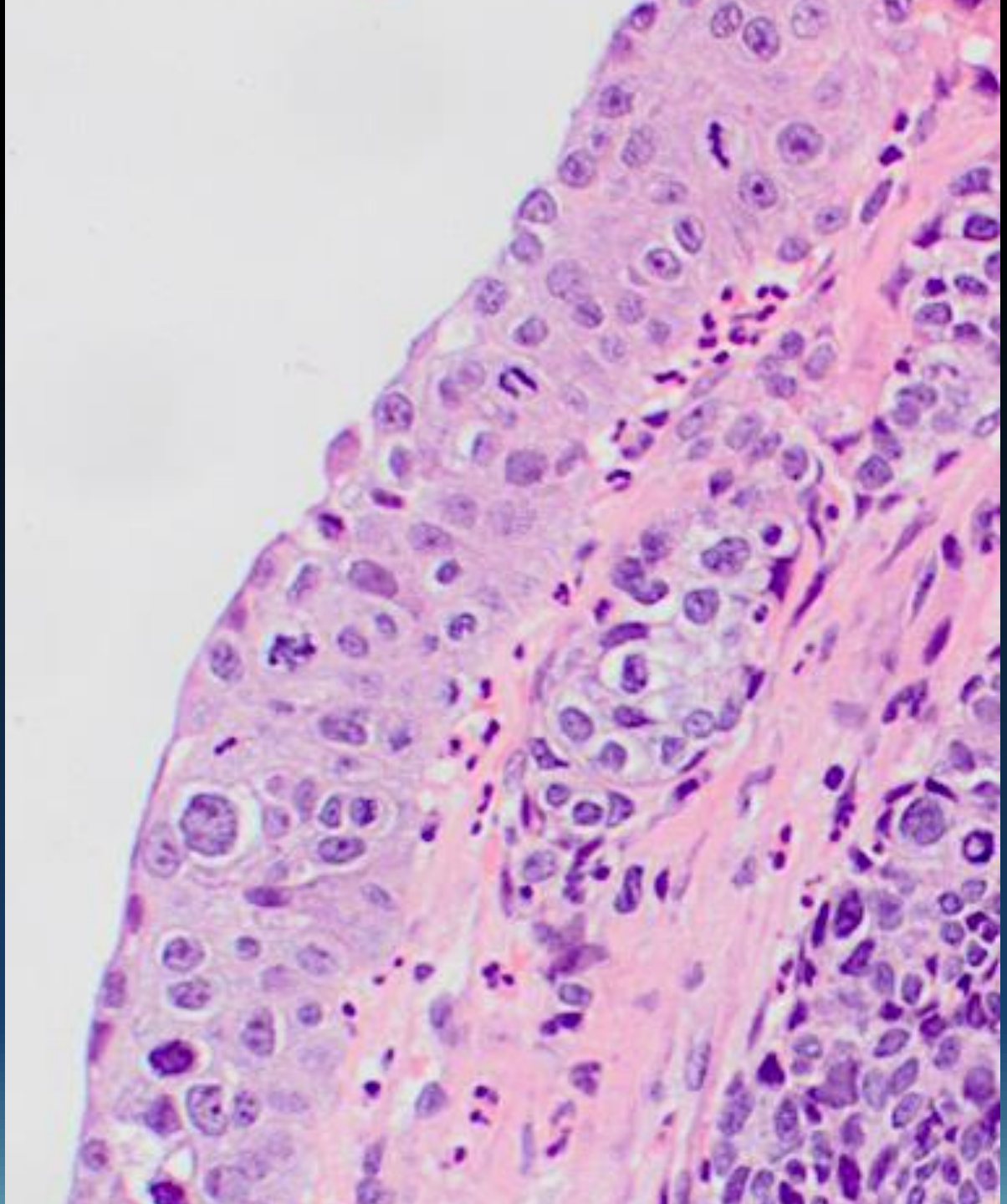
- Solid: Other basaloid neoplasms
  - Basal cell adenoma/adenocarcinoma
  - SCC with basaloid features
  - High-grade neuroendocrine carcinoma

Other Basaloid Head and Neck Tumors



45 year old female with a sinonasal tract mass





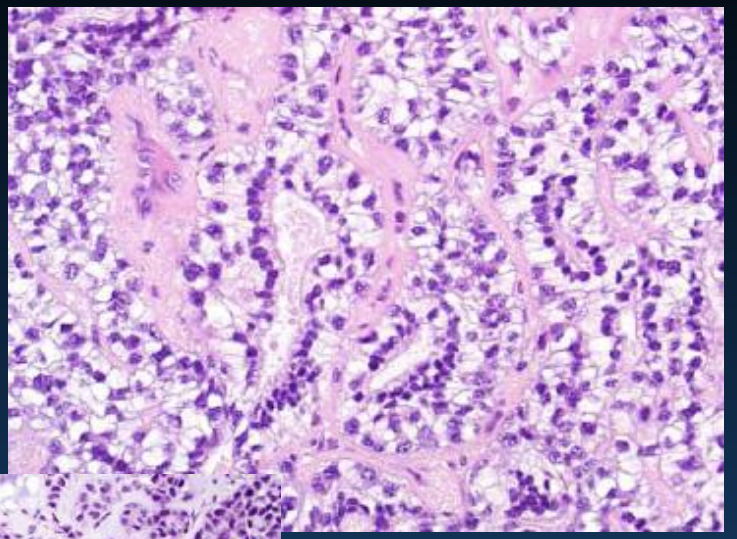
HPV-related Multiphenotypic Sinonasal Carcinoma

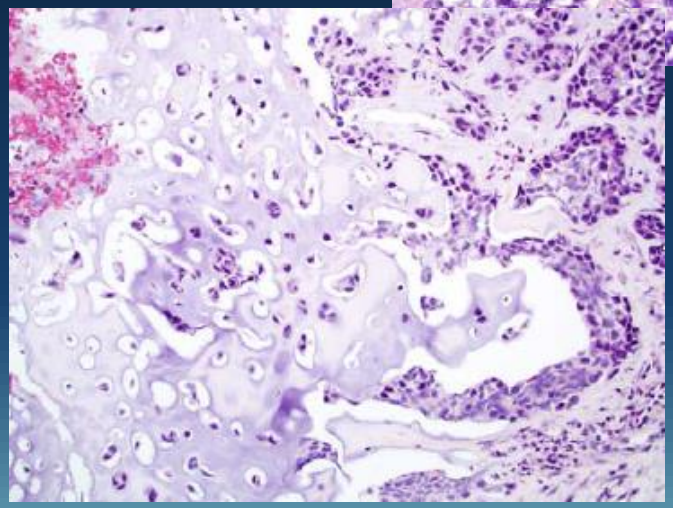
An Expanded Series of 49 Cases of the Tumor Formerly Known as HPV-related Carcinoma With Adenoid Cystic Carcinoma-like Features

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

Am J Surg Pathol (2017)

- Coexisting surface squamous dysplasia
- Adenoid cystic-like features
  - Other salivary gland morphology
  - Squamous
  - Sarcomatoid
- Most HPV type 33
- *MYB* negative
- Indolent clinical course



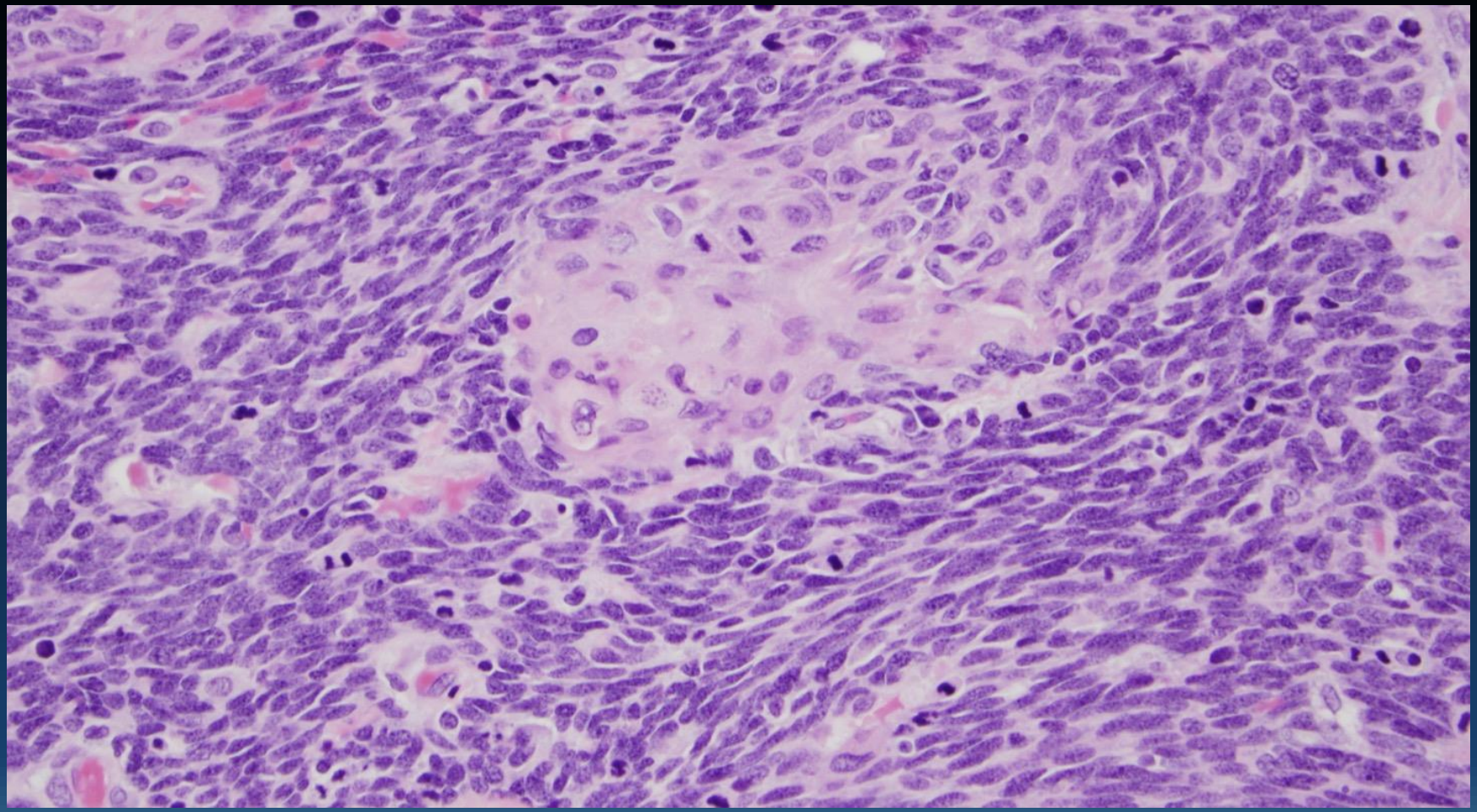


HR-HPV in Head and Neck Cancer at Various Sites

- Oropharynx: 80-90%
- Sinonasal Cavity: 20-25%
- Oral Cavity: 3-6%
- Larynx: <5%

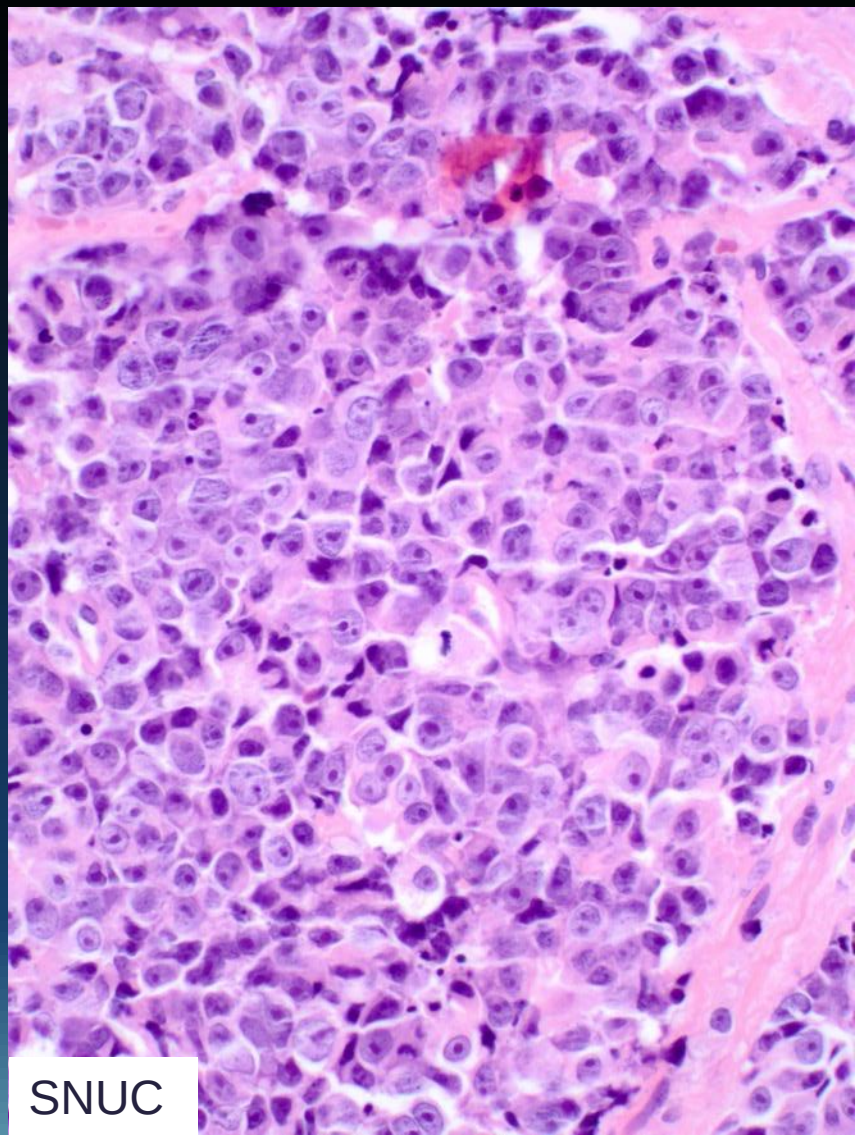
- Heterogeneous tumors
- Prognostic significance unclear outside oropharynx

Oropharyngeal HPV-related SCC



Sinonasal Undifferentiated Carcinoma

- 3-5% of all sinonasal carcinomas
- Broad age range; average 50-60
- Sinuses with local extension
- IHC
  - Variable p63 (but p40) negative
  - NSE, but only rare chromo/synapto
  - P16+, but HPV-
- 5-year survival 35%

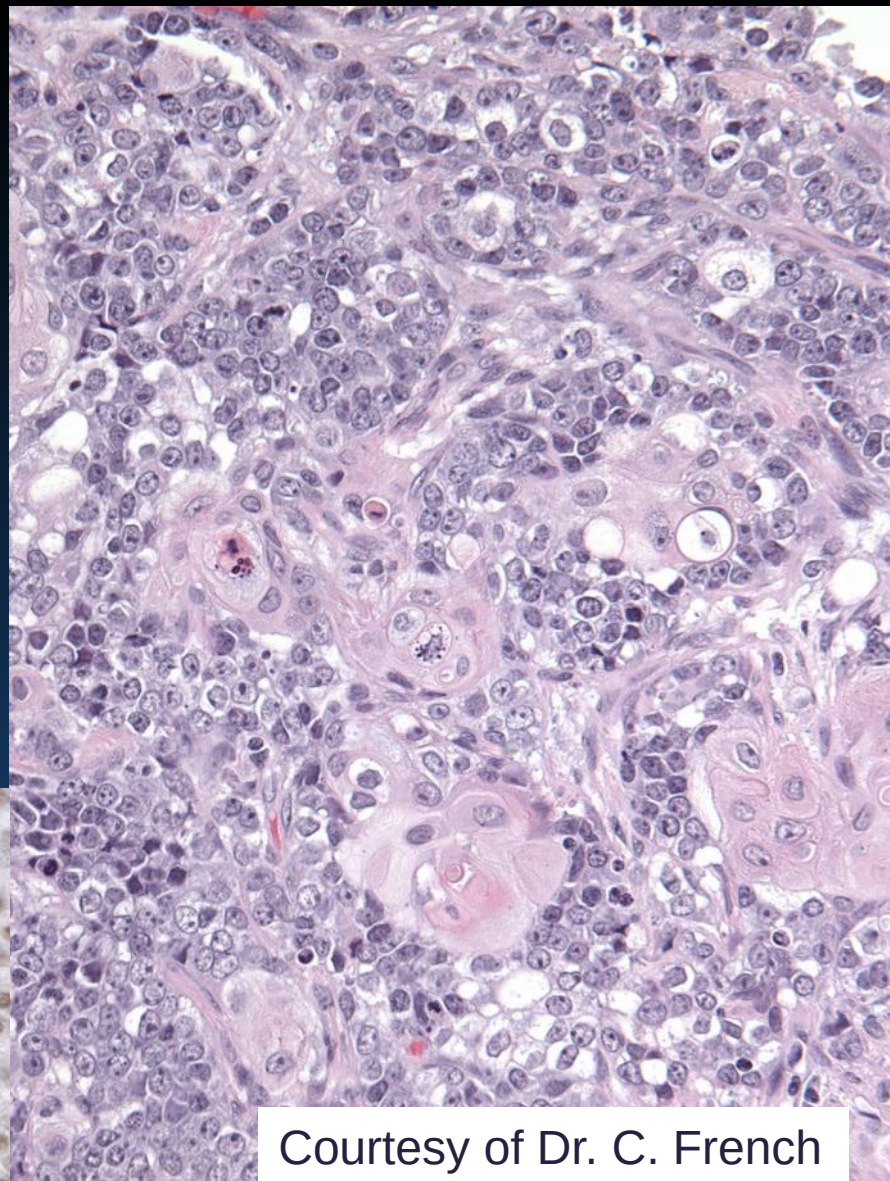


Sinonasal Undifferentiated Carcinoma
Differential Diagnosis

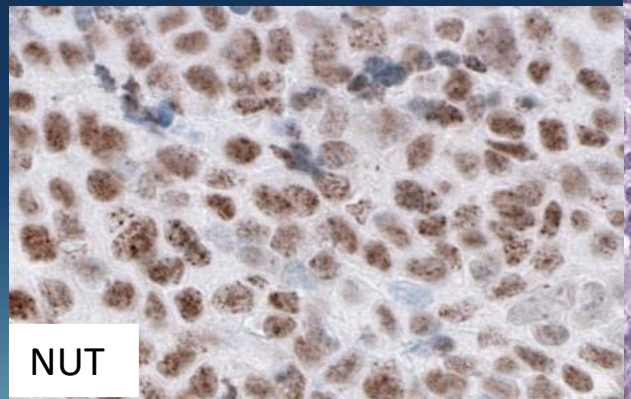
- HPV-related multiphenotypic sinonasal carcinoma
- Nasopharyngeal carcinoma
- Solid AdCC
- NUT carcinoma
- SMARCB1 (INI1) deficient carcinoma
- Neuroendocrine carcinoma
- Basaloid squamous cell carcinoma
- Olfactory neuroblastoma
- Rhabdomyosarcoma
- Melanoma
- Lymphoma

NUT Carcinoma

- Areas of abrupt keratinization
- Very aggressive
- Rearrangement of *NUT* (15q14)
- P63/P40 positive
- NUT IHC
- Trials using HDACi and BET inhibitors



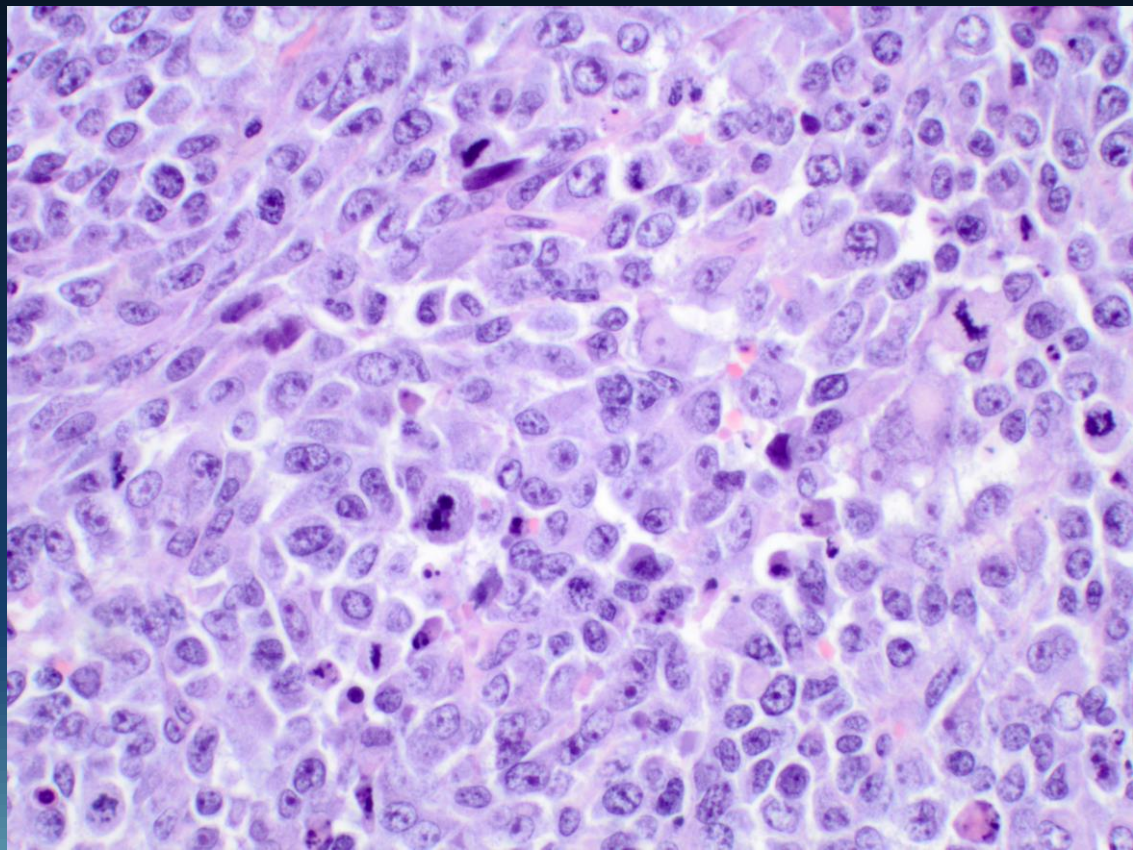
Courtesy of Dr. C. French



NUT

SMARCB1 (INI1) Deficient Carcinoma

- Rhabdoid morphology
- May be synapto, p63/p40, p16 +
- Lacks squamous differentiation

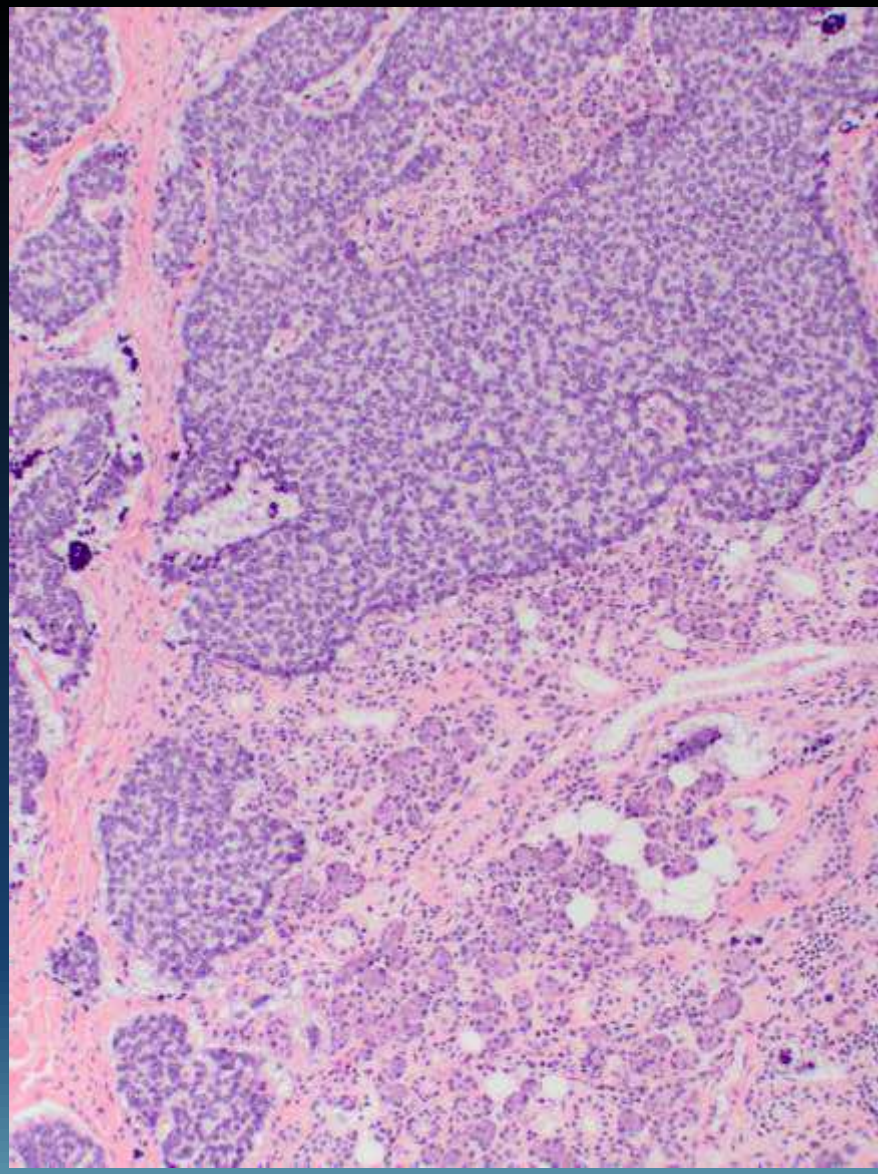


Bishop et al *Am J Surg Pathol* (2014)

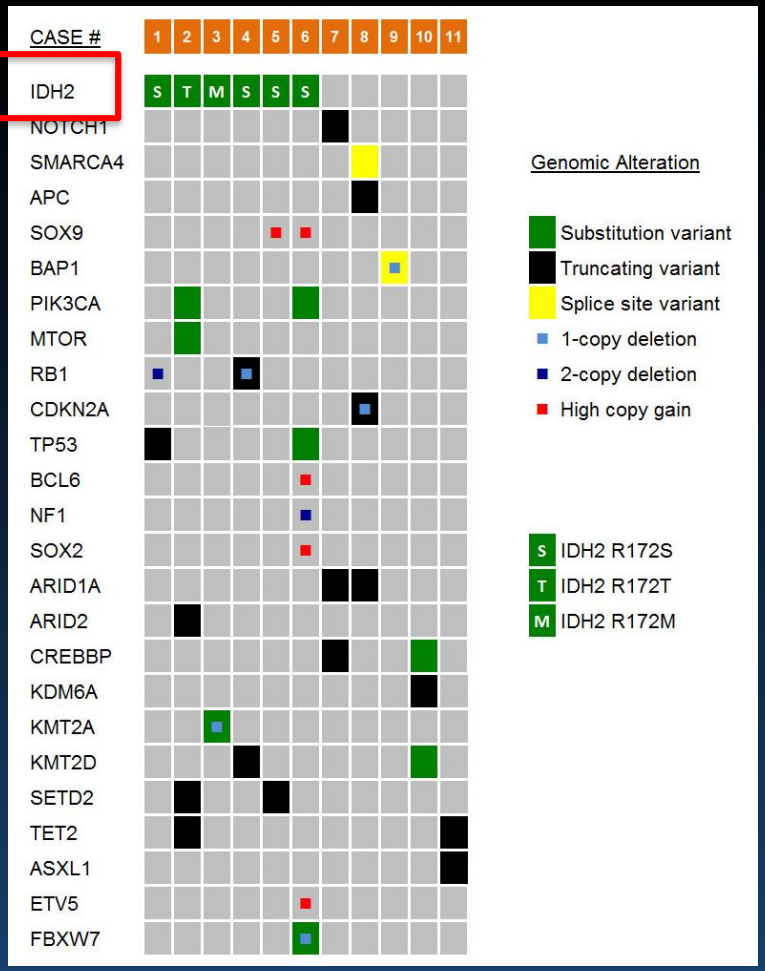
Adamantinoma-like Ewing family tumor

- EWSR1-FLI1 rearrangement
- p40, keratin, CD99 +
- Can be synapto, S100, p16+
- May have focal squamous differentiation

Bishop et al *Am J Surg Pathol* (2015)



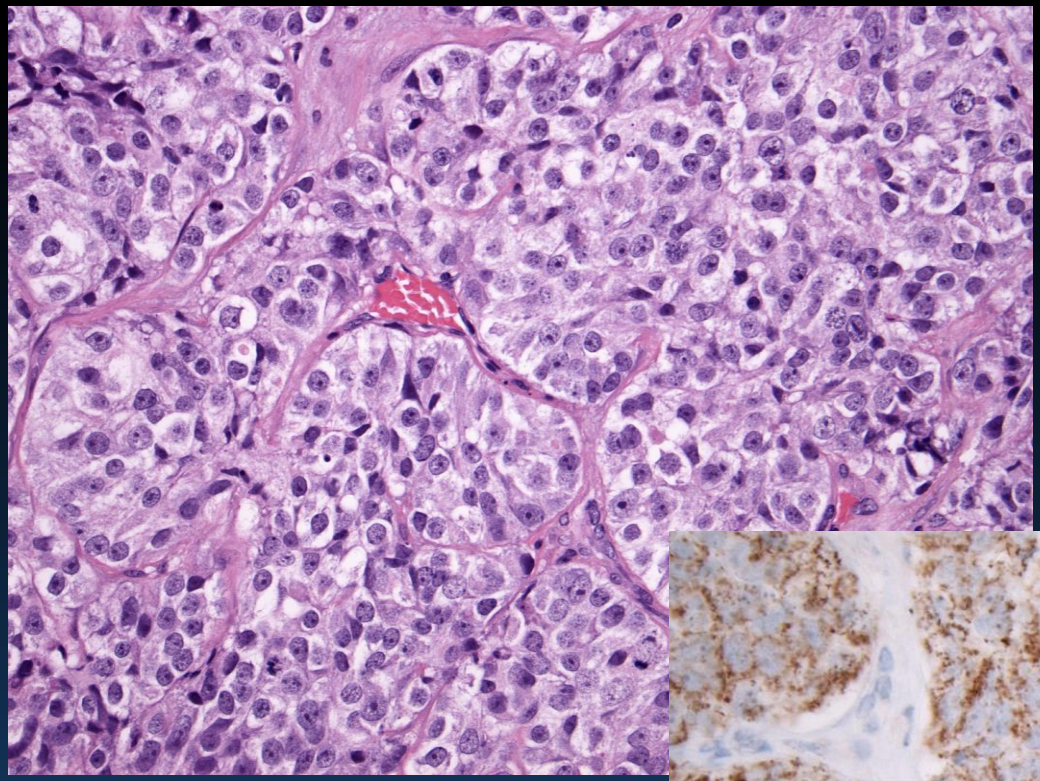
Sinonasal Undifferentiated Carcinoma



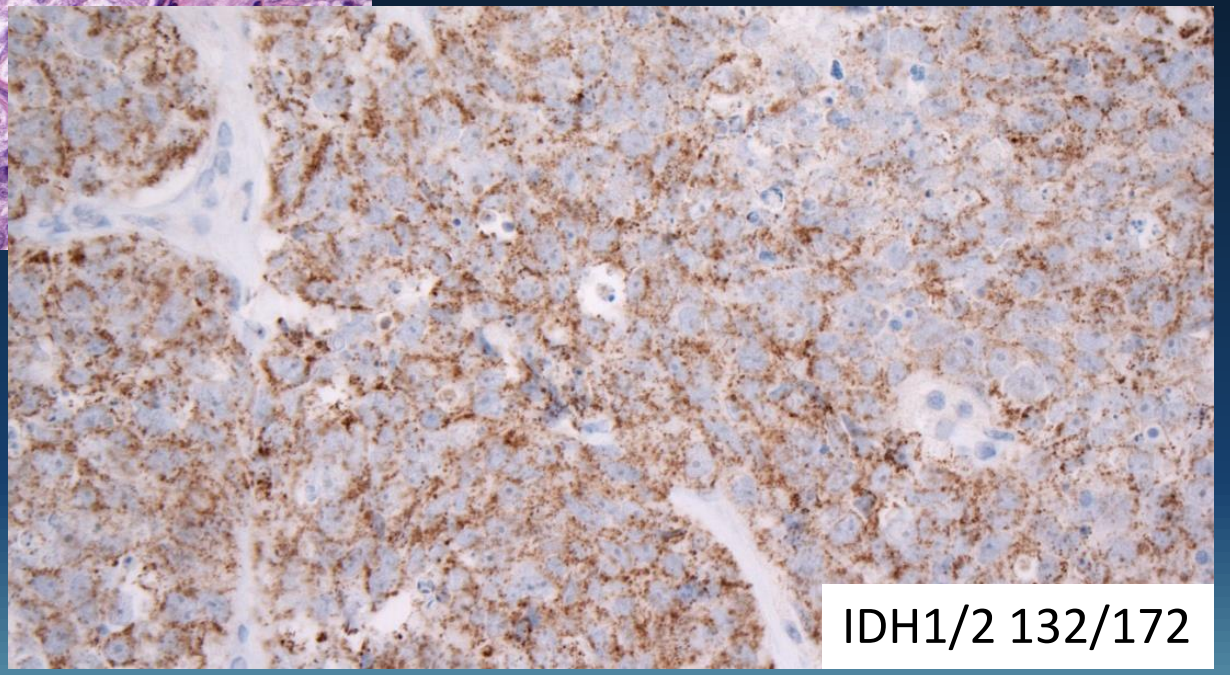
- *IDH2* mutations at the known hotspot R172 identified in 6/11 (55%) SNUCs

Jo et al *Mod Pathol* (2017)

Sinonasal Undifferentiated Carcinoma



- Mutant IDH1/2 staining in 26/53(49%) SNUCs
- Potentially targetable with IDH inhibitors
- Specific for SNUC



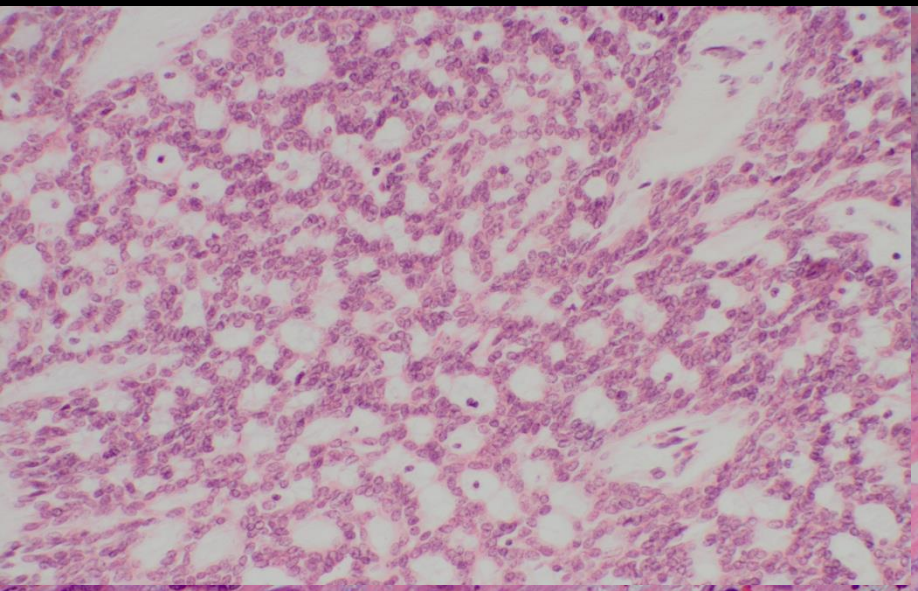
IDH1/2 132/172

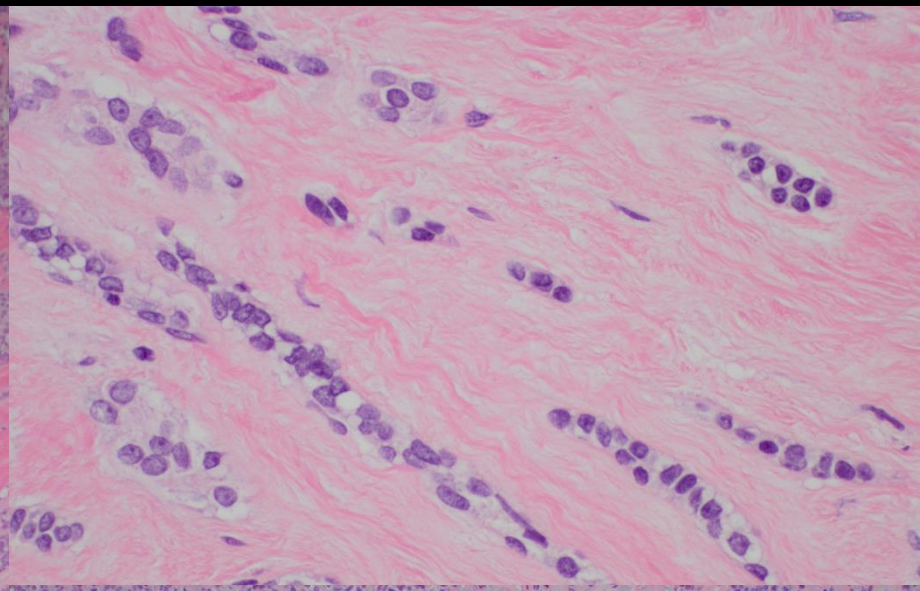
Jo et al *Mod Pathol* (2017)
Mito et al *Am J Surg Pathol* (2018)

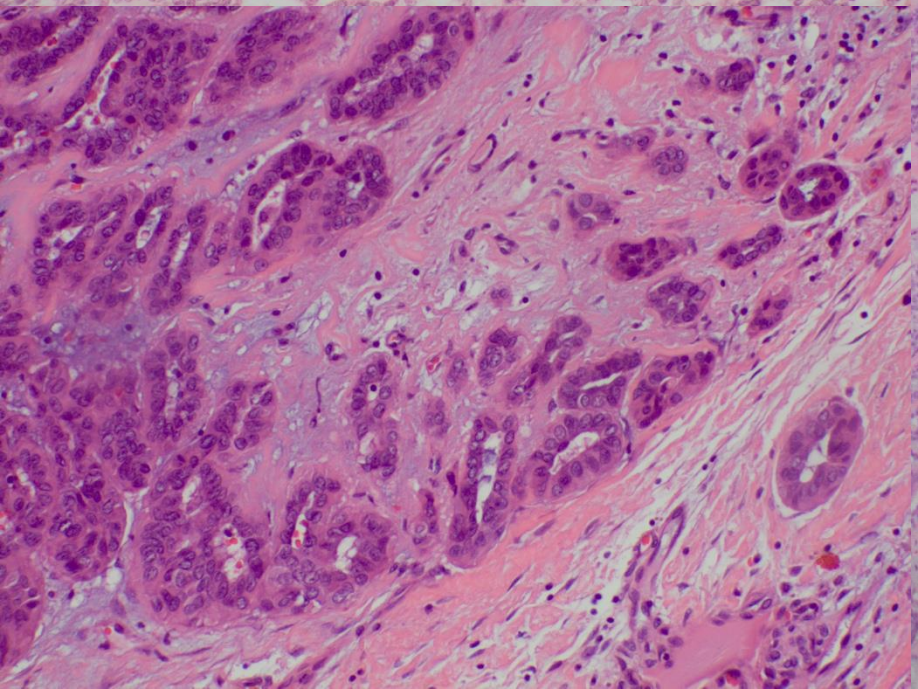
Adenoid Cystic Carcinoma
Differential Diagnosis

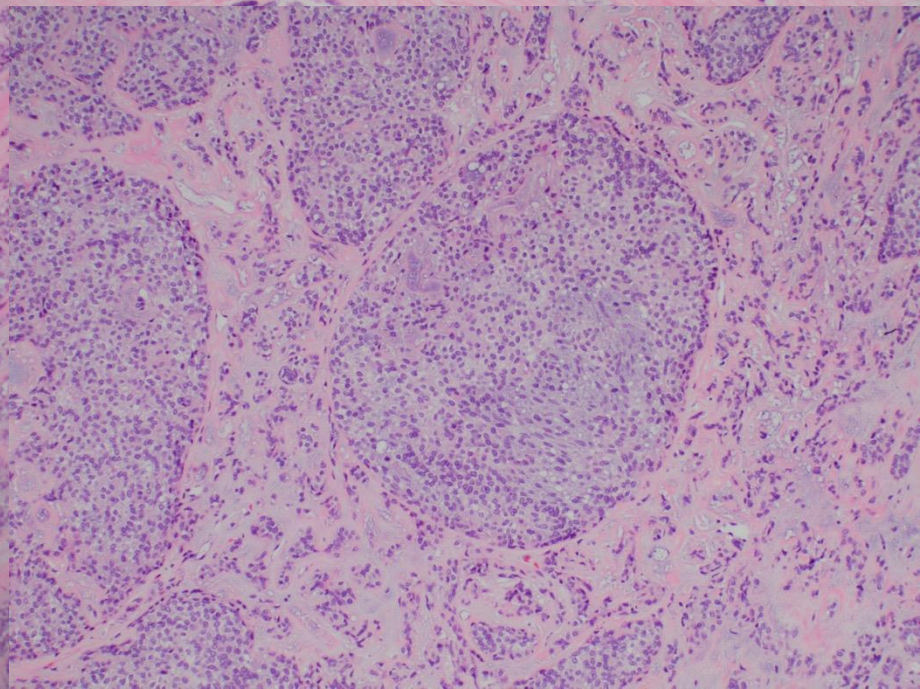
- Tubular/Cribriform
  - **Polymorphous adenocarcinoma**
  - Other biphasic tumors
    - Basal cell adenoma/adenocarcinoma
    - **Pleomorphic adenoma**
    - Epithelial-myoepithelial carcinoma

P(LG)A Architecture



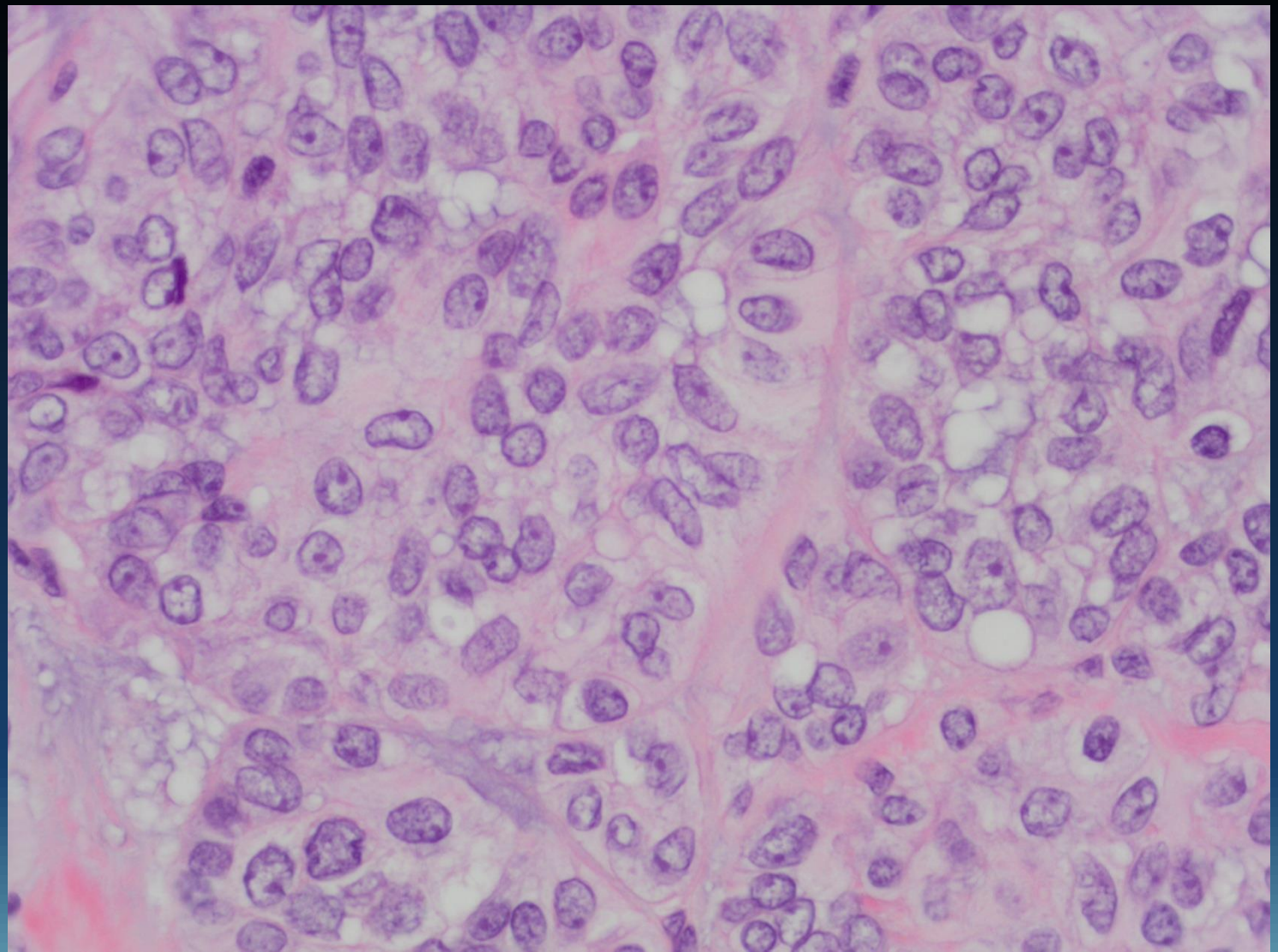




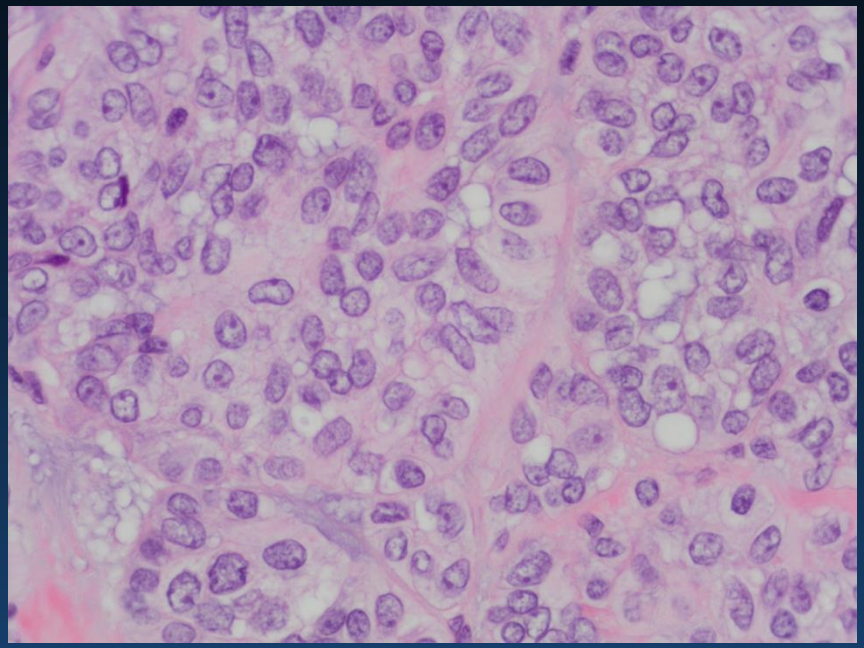


Polymorphous Adenocarcinoma

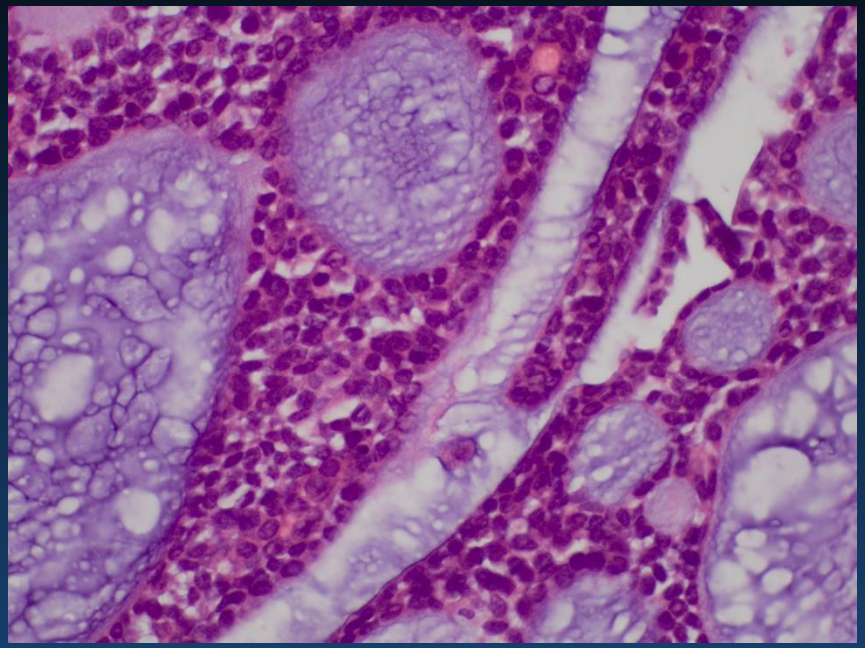
Cytology



Polymorphous Adenocarcinoma



Adenoid Cystic Carcinoma



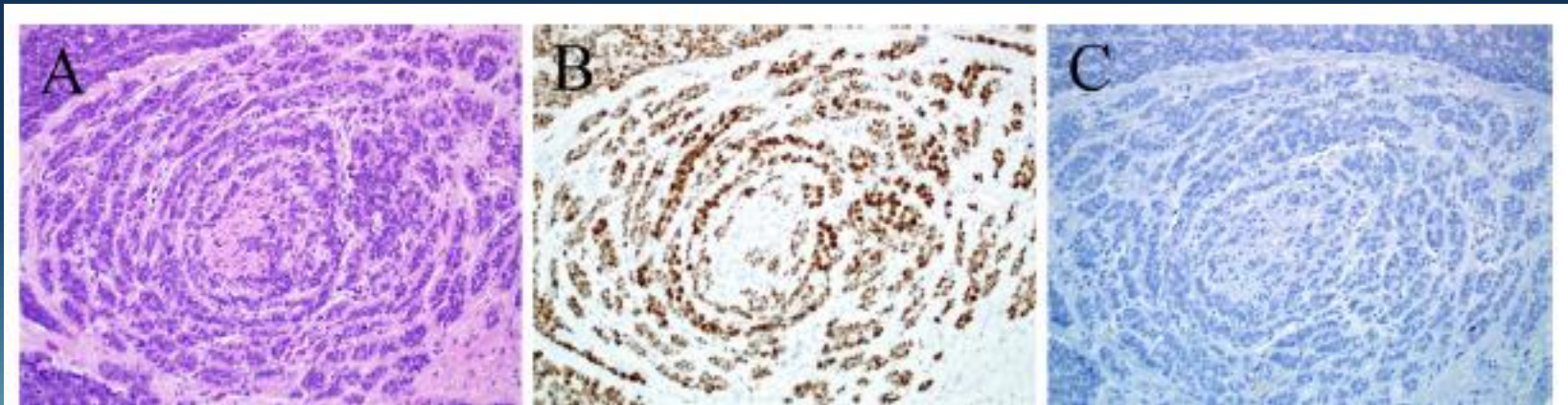
Polymorphous Adenocarcinoma
Clinical

- 2nd most common intraoral salivary gland malignancy (60% palate)
- 2:1 F:M
- Most 50-70 years
- Recurrence 19%
- Regional spread 9-15%
- Death uncommon

Polymorphous Adenocarcinoma
Pathology

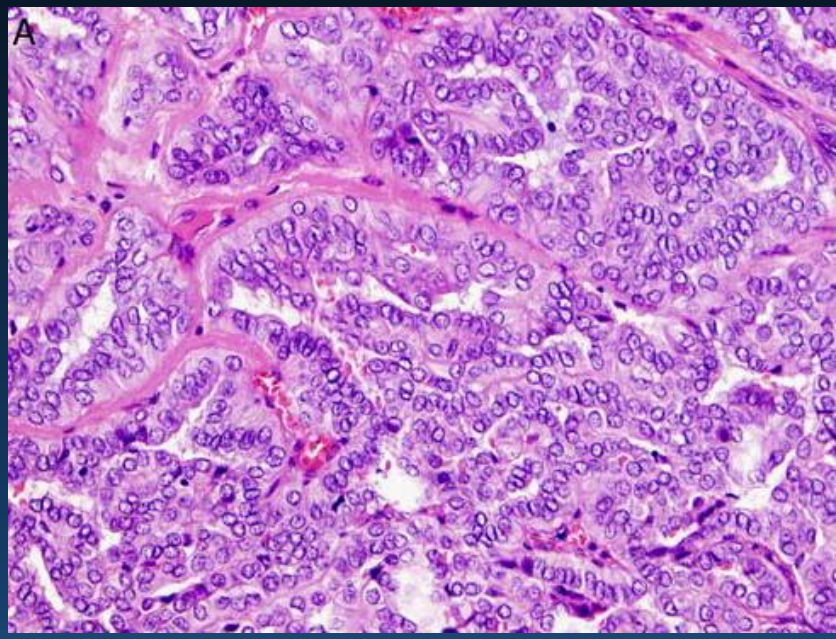
- Architecturally diverse
  - Solid, trabecular, papillary, ductal
- Cytologically uniform
  - Dominant population of bland cells with vesicular nuclei
- Perineural invasion common
- P63+/P40-
- CK7, S100, mammaglobin+

Rooper et al *Head Neck Pathol* (2015)



Polymorphous Adenocarcinoma
Genetics

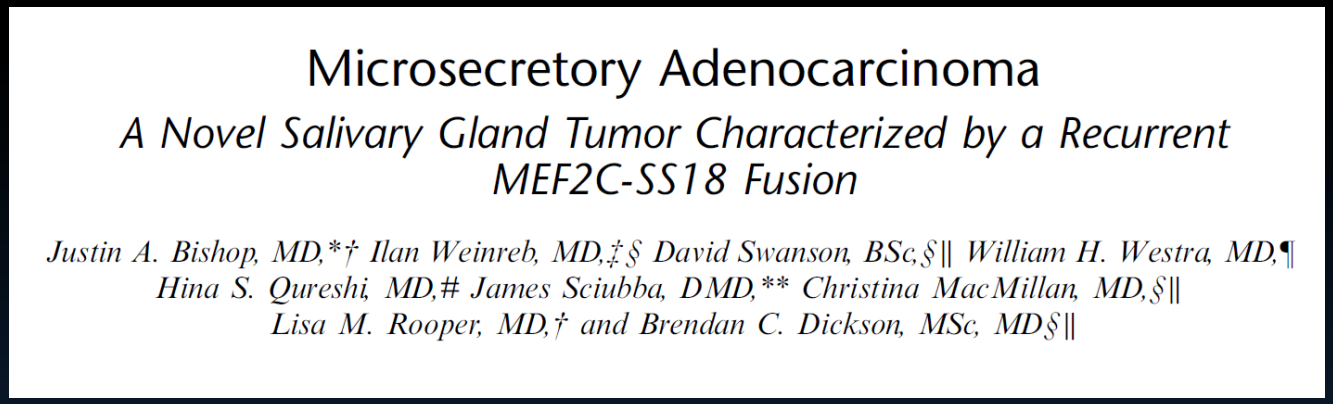
- *PRKD* gene family rearrangements and point mutations
- Cribriform adenocarcinoma of minor salivary gland
  - *PRKD* gene rearrangements
  - Cribriform
  - Papillary carcinoma-like nuclear features
  - Tongue
  - Nodal metastasis
  - Emerging entity
- Significant overlap



Skalova et al *Am J Surg Pathol* (2011)

Weinreb et al *Nature Genetics* (2014)
Weinreb et al *Genes Chromosomes and Cancer* (2014)

Microsecretory carcinoma



Microsecretory Adenocarcinoma

A Novel Salivary Gland Tumor Characterized by a Recurrent MEF2C-SS18 Fusion

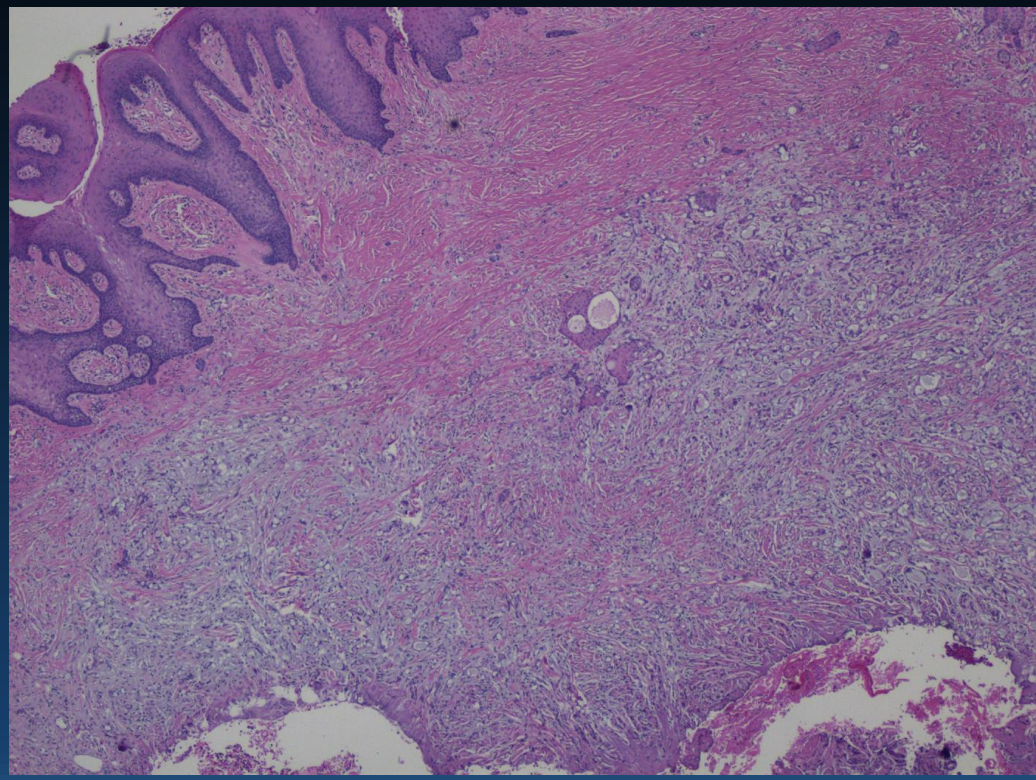
Justin A. Bishop, MD,† Ilan Weinreb, MD,‡§ David Swanson, BSc,§‖ William H. Westra, MD,¶ Hina S. Qureshi, MD,# James Sciubba, DMD,** Christina MacMillan, MD,§‖ Lisa M. Rooper, MD,† and Brendan C. Dickson, MSc, MD§‖*

Bishop et al *Am J Surg Pathol* (2019)

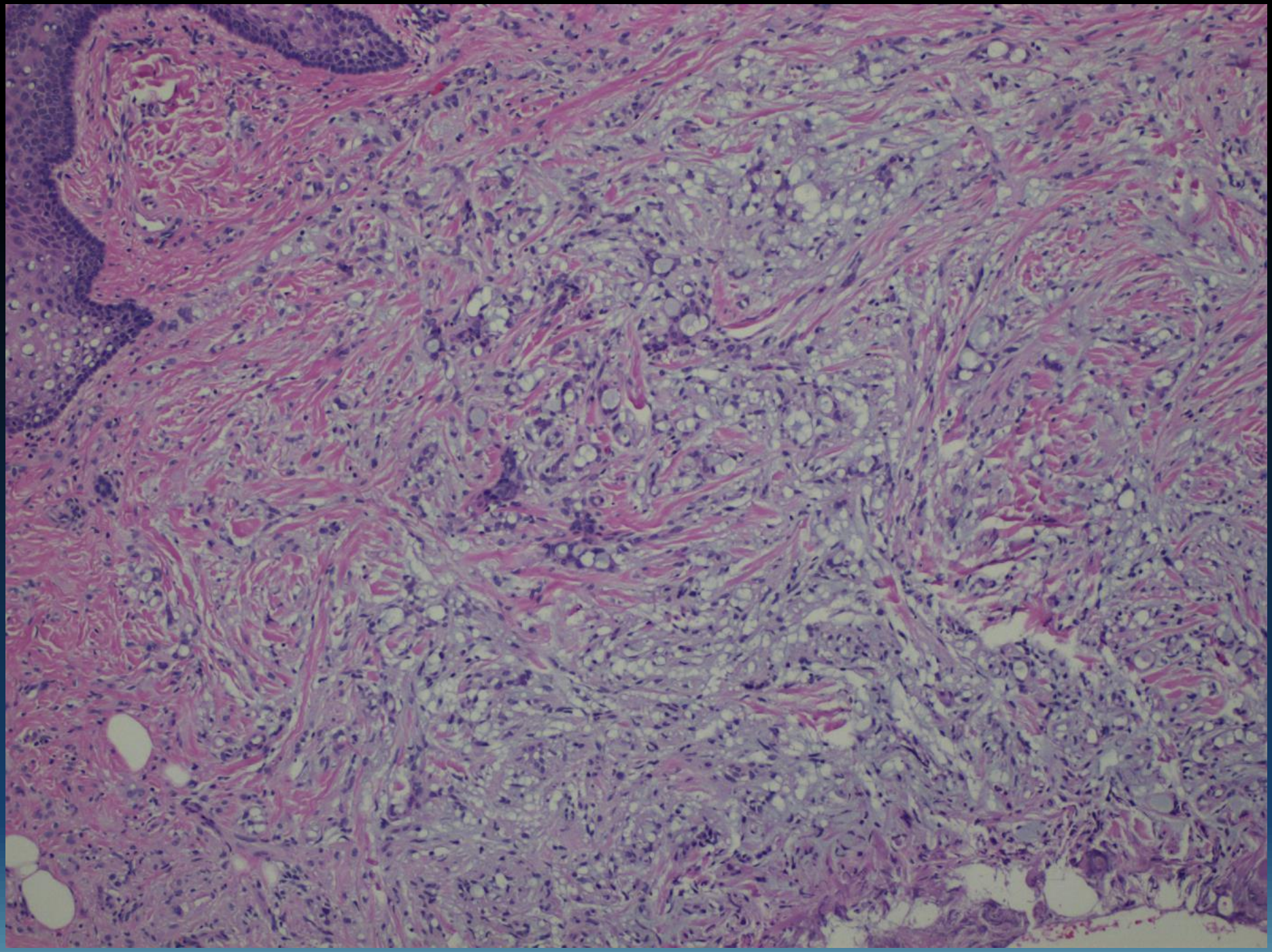
- Low-grade tumor from a group of adenocarcinoma, NOS cases
- Mostly oral cavity
- 5 cases
- All harbor novel MEF2C-SS18 translocation identified by RNA-Seq
- S100, p63+
- p40, SMA, calponin, mammaglobin-

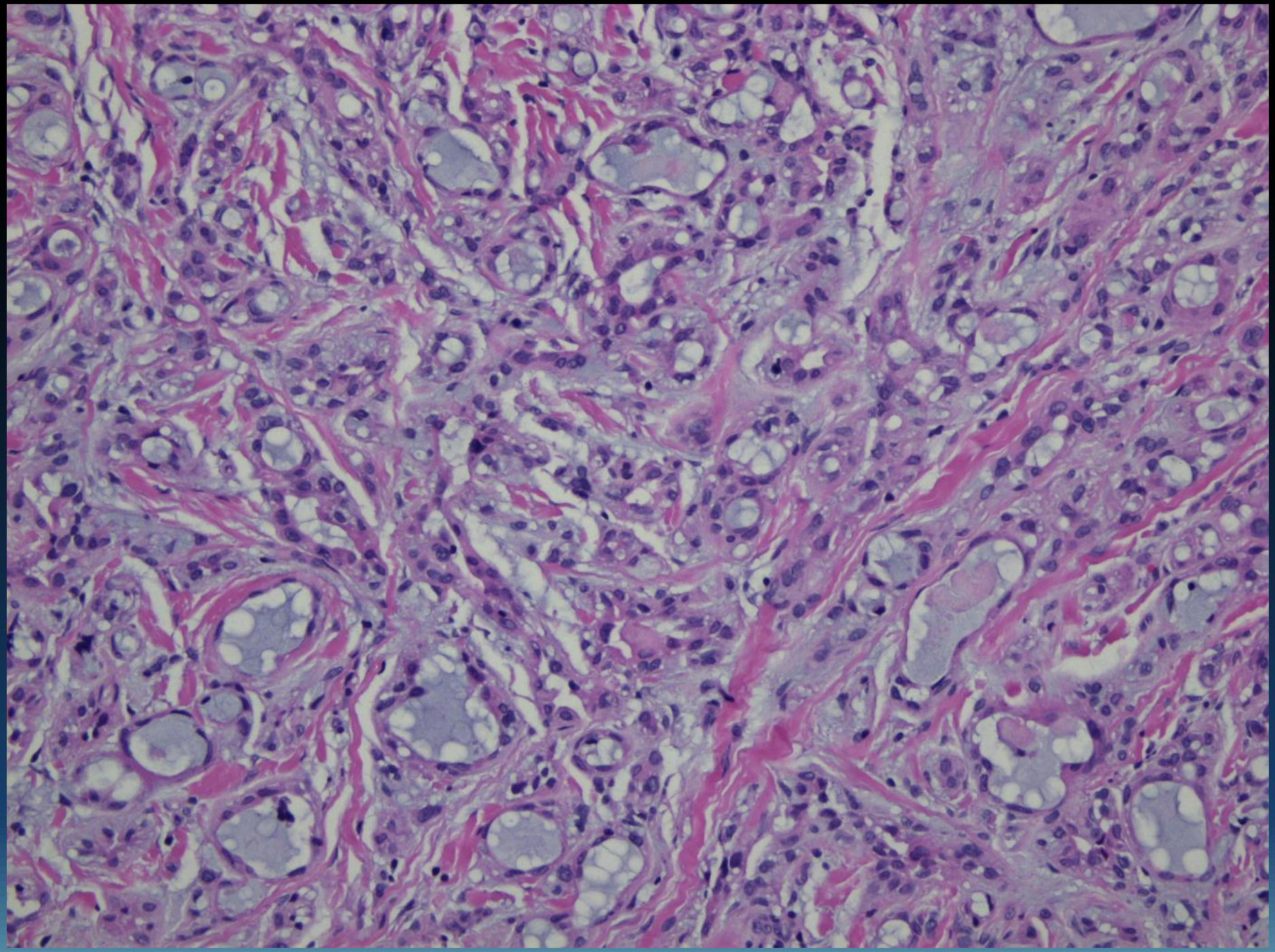
Microsecretory carcinoma

- Intercalated duct-like cells
- Eosinophilic to clear cytoplasm
- Small, uniform oval nuclei
- Infiltrative microcyts and cords
- Intraluminal secretions
- Cellular fibromyxoid stroma

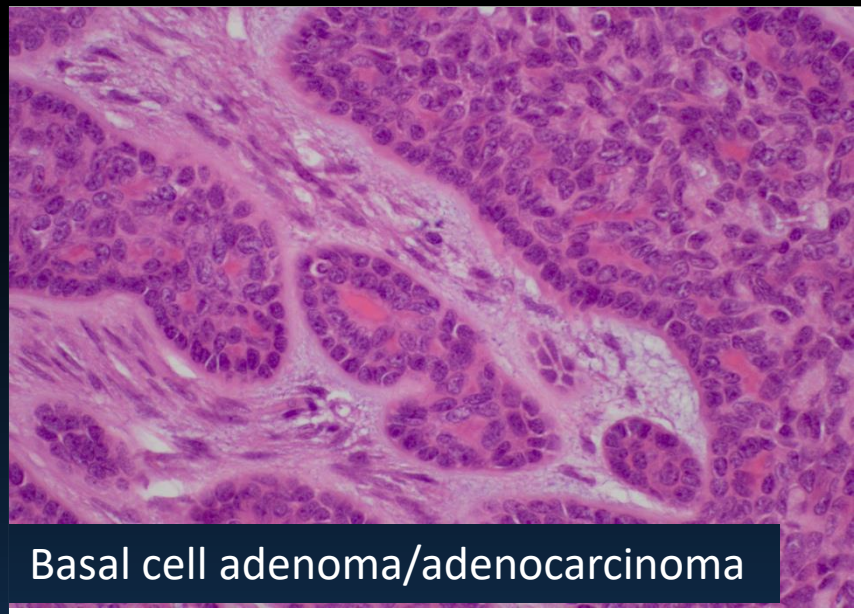


Bishop et al *Am J Surg Pathol* (2019)

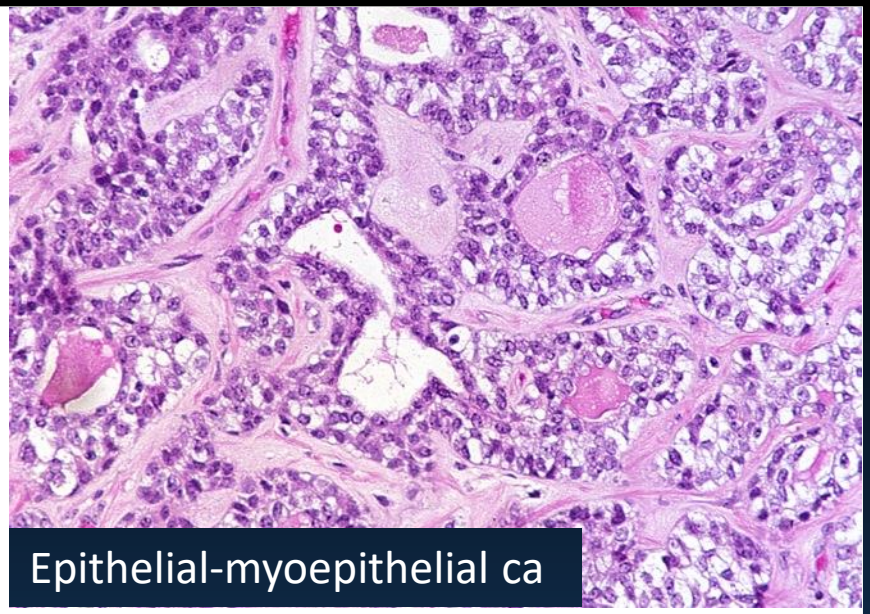




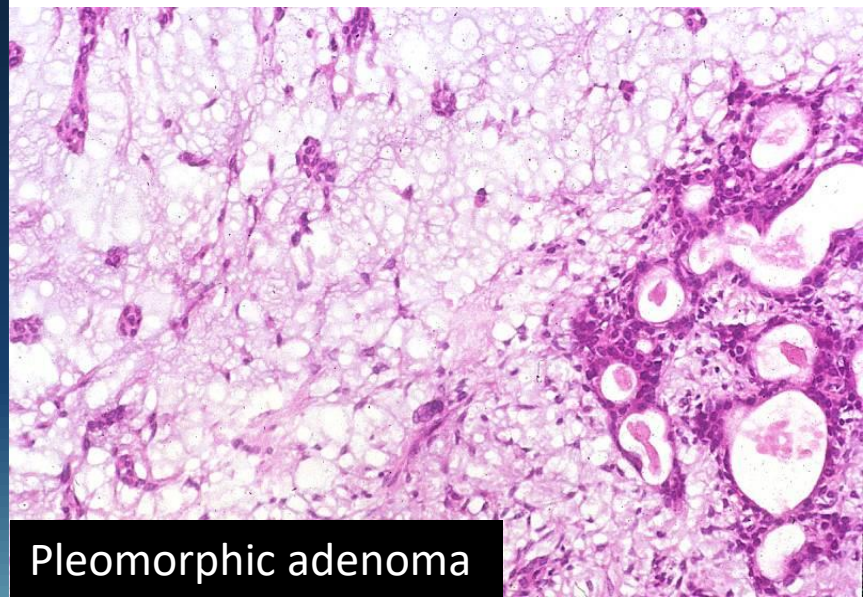
Biphasic Tumors: Architectural Relationships



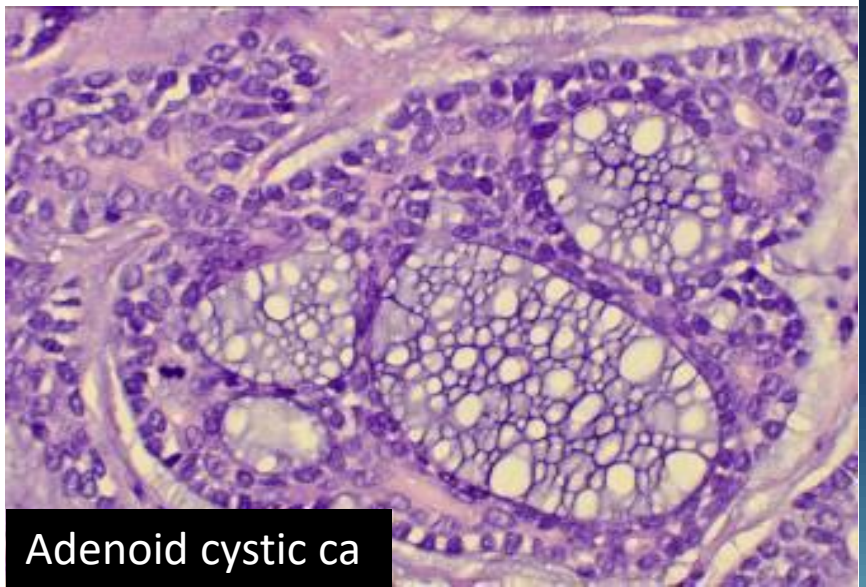
Basal cell adenoma/adenocarcinoma



Epithelial-myoepithelial ca

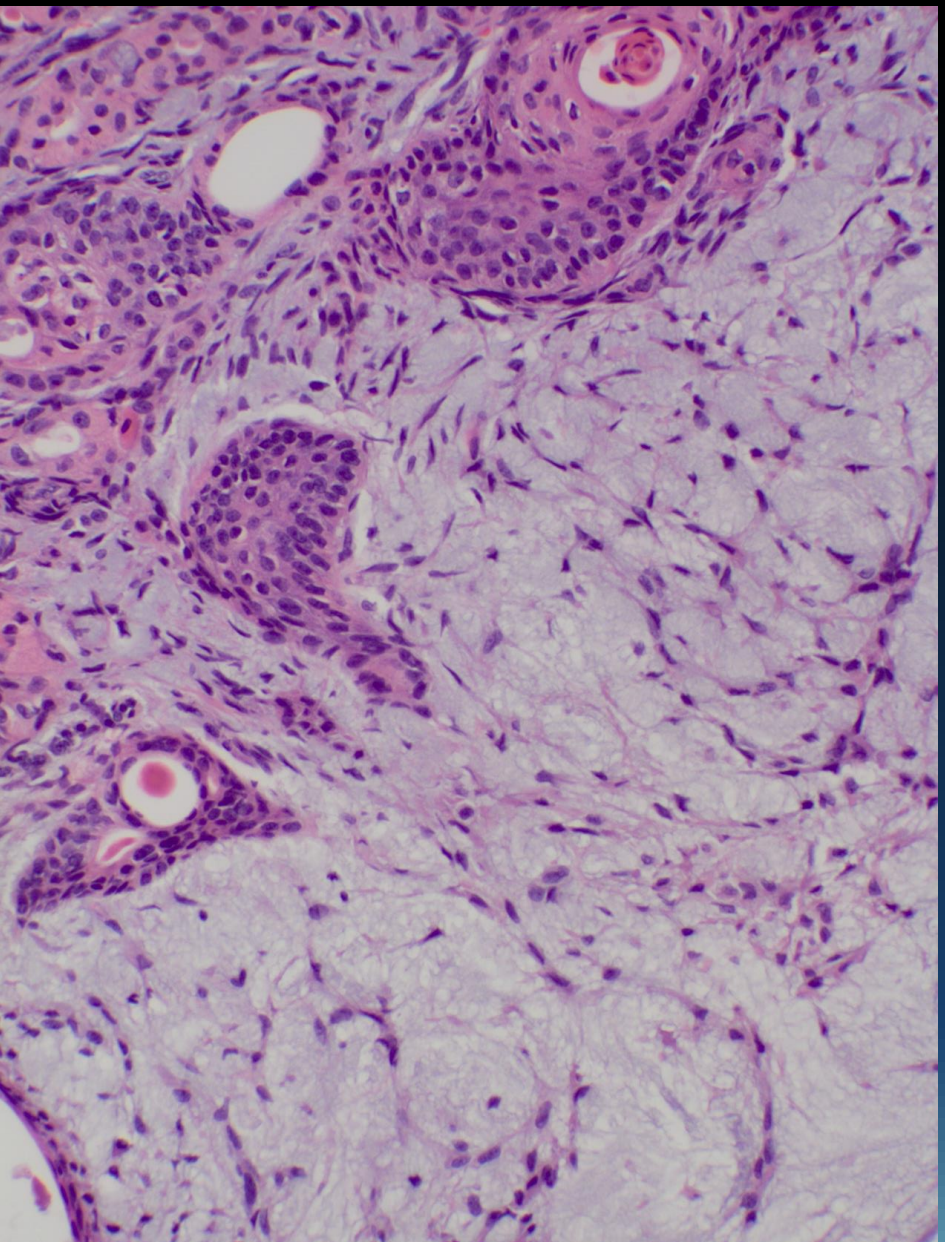


Pleomorphic adenoma



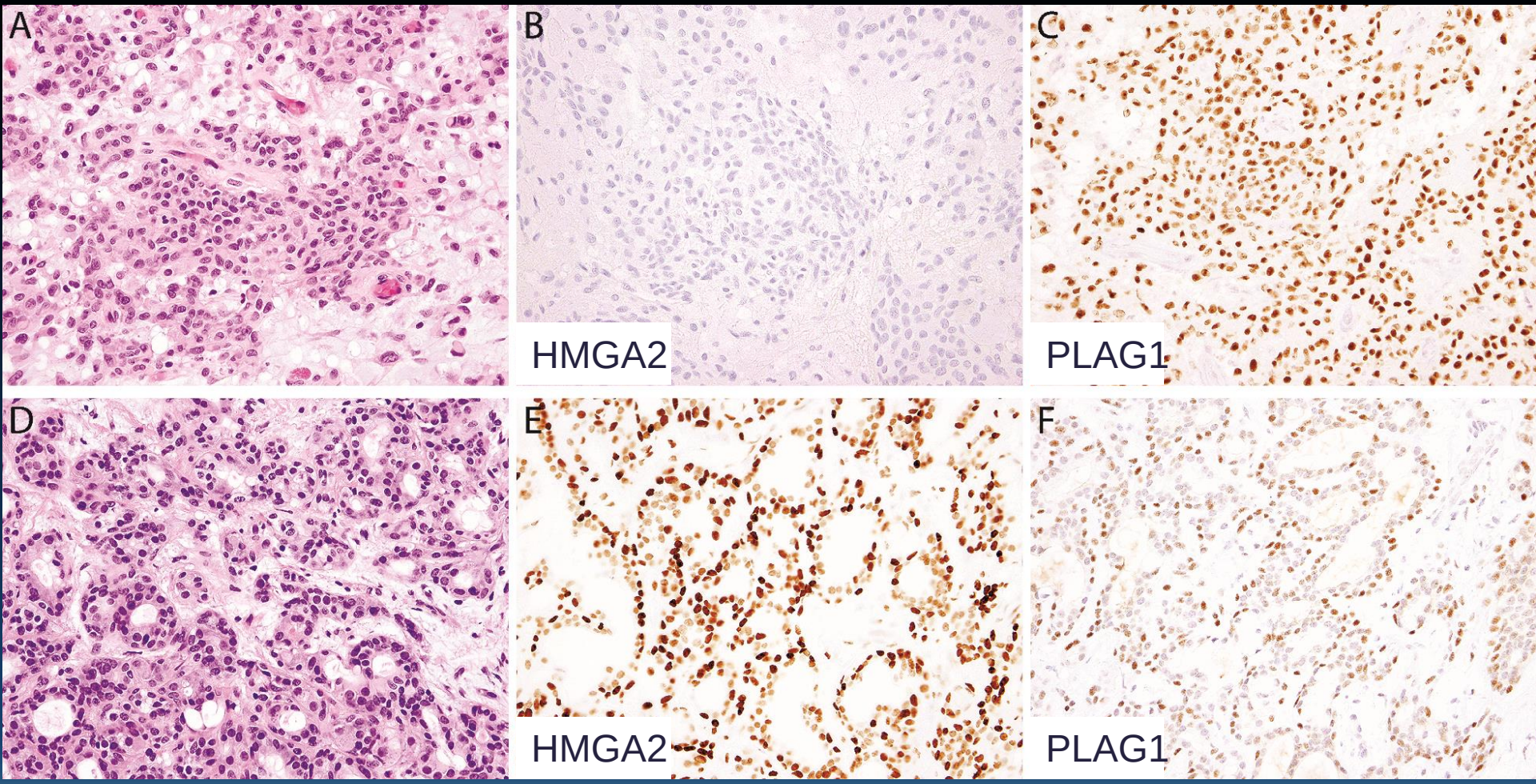
Adenoid cystic ca

Pleomorphic Adenoma



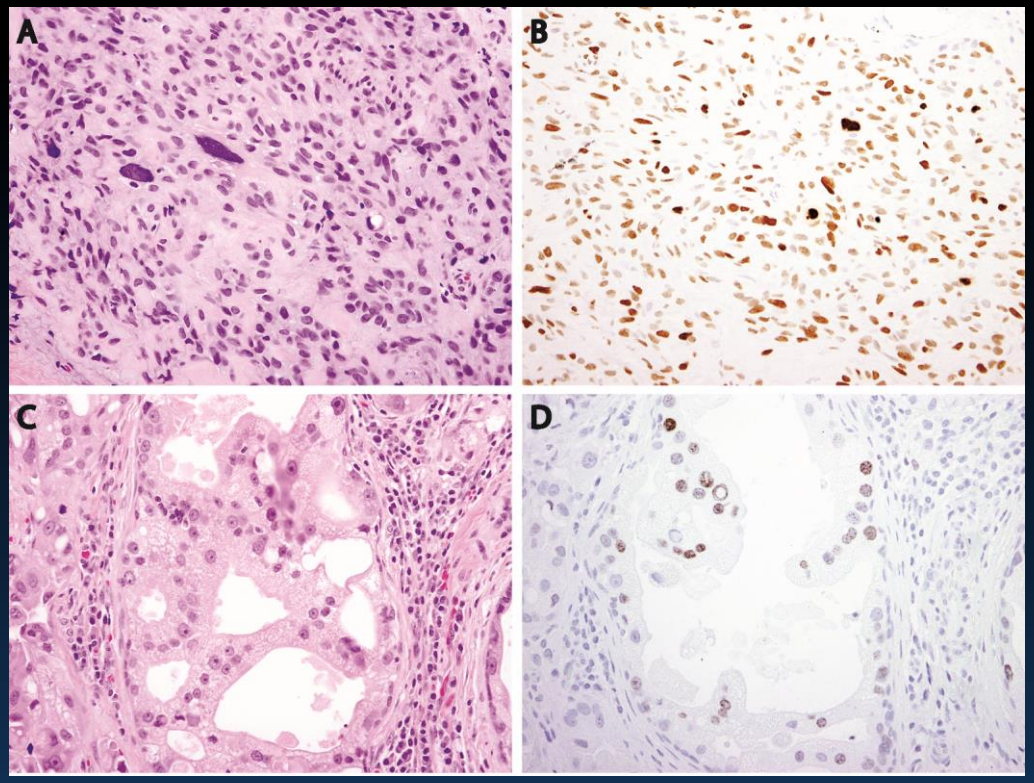
- Recurrent translocations:
  - 8q12 (*PLAG1* locus)
  - 12q13-15 (*HMGA2* locus)
  - Can FISH for *PLAG1*, *HMGA2*
- Alterations persist in carcinoma ex PA
  - Bahrami et al *Head Neck Pathol* (2012)
  - Katabi et al *Hum Pathol* (2015)

HMGA2 and PLAG1 in PA



Mito et al *Histopathology* (2017)

HMGA2 in Carcinoma ex PA



Mito et al *Histopathology* (2017)

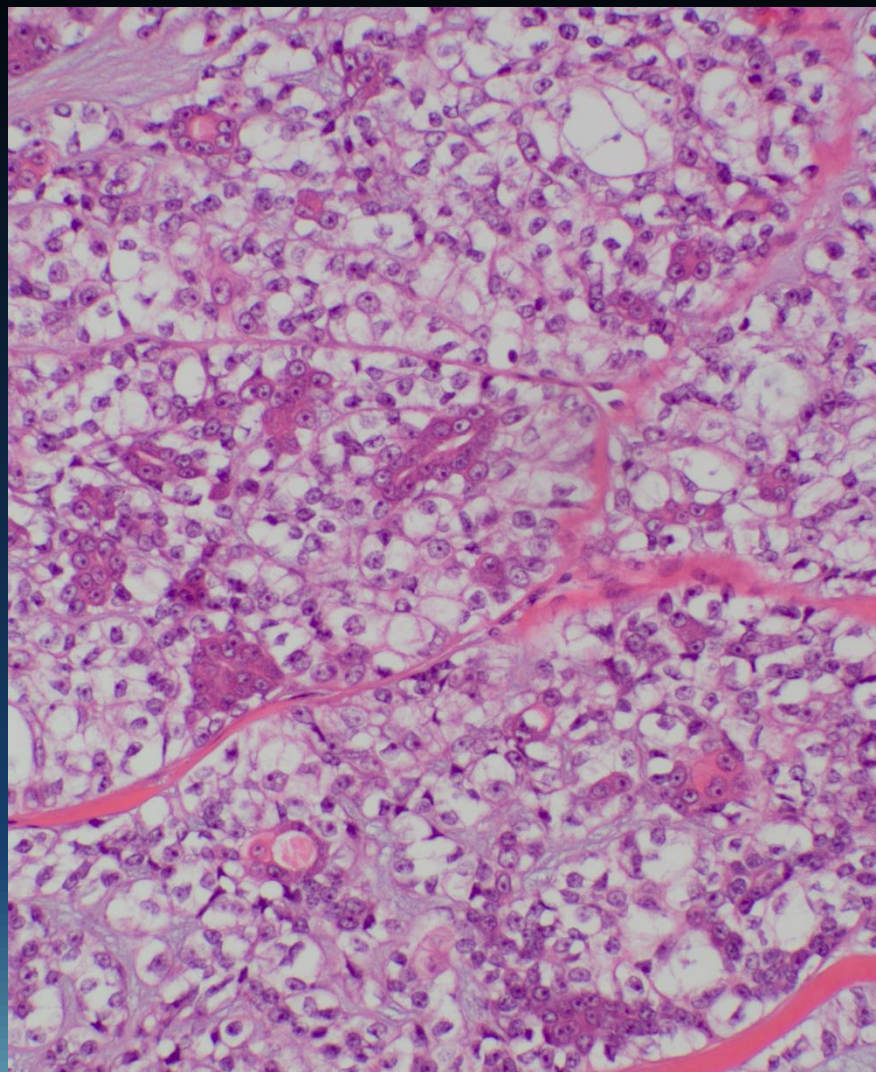
Tumor Type	Total Cases	HMGA2 POS only	PLAG1 POS only	Double POS	Double NEG
Pleomorphic Adenoma	55	11 (20)	28 (50.9)	8 (14.5)	8 (14.5)
Carcinoma ex-PA	29	4 (13.8)	7 (24.1)	3 (10.3)	15 (51.7)

Epithelial-myoepithelial carcinoma
Clinical

- 1% of salivary gland tumors
- 2:1 F:M
- Peak in 6th and 7th decades
- 60% parotid
- 40% recur
- 14% metastasize
  - Lymph nodes, lung, liver, kidney
- 80% 5 yr survival

Epithelial-myoepithelial carcinoma
Pathology

- Biphasic tumor
  - Inner layer of ductal cells
  - Outer layer of clear myoepithelial cells
- Perineural and vascular invasion common



Epithelial-myoepithelial carcinoma Genetics

- Lack distinct genetic alterations
- Subset harbor *MYB* translocations
  - "Hybrid" tumors (3 of 4)
  - Higher grade tumors (2 of 7)
- Many are likely carcinoma ex PA
  - Up to 80%

Bishop and Westra *Am J Surg Pathol* (2018)
El Hallani et al *Am J Surg Pathol* (2018)

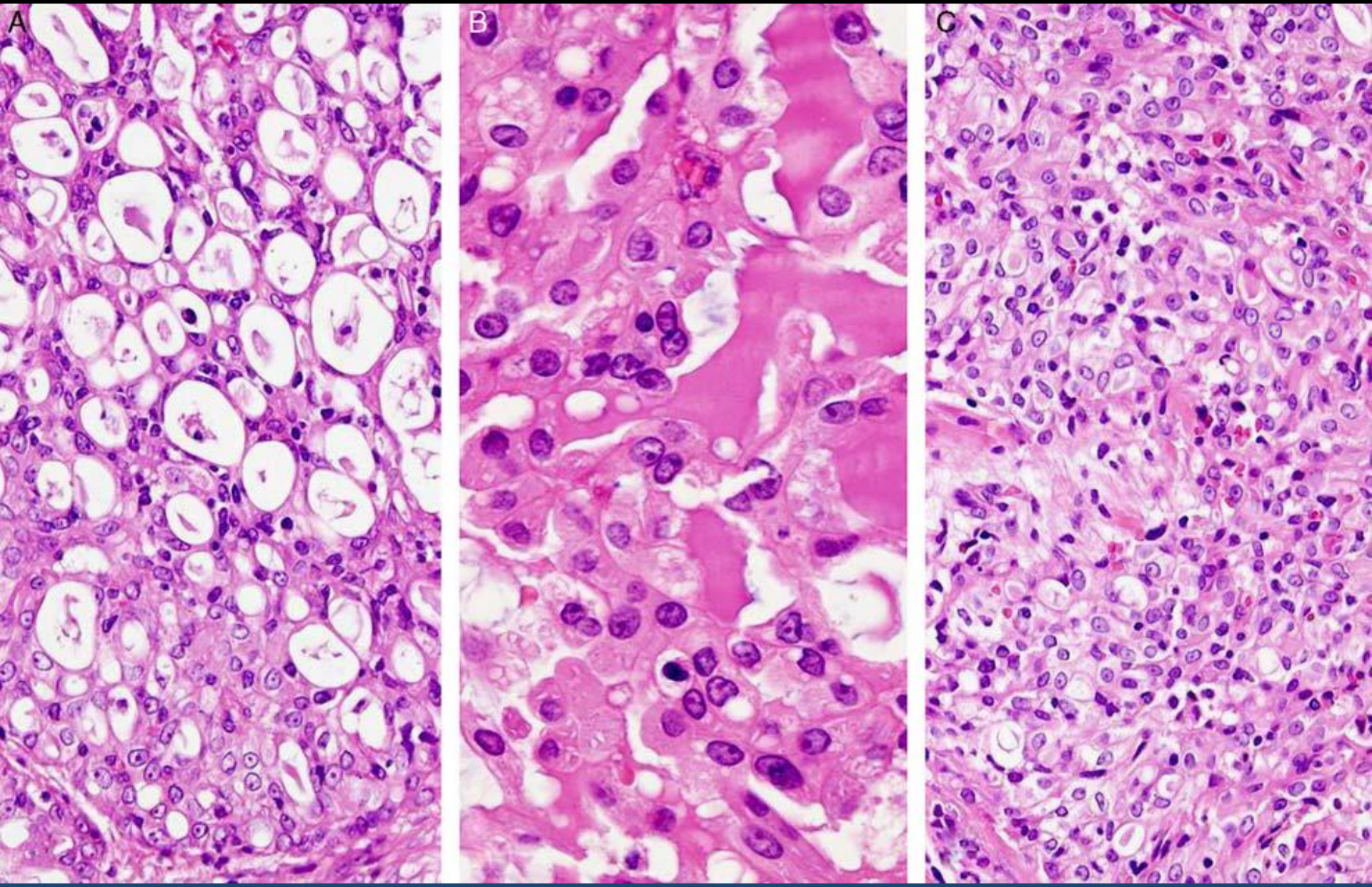
ORIGINAL ARTICLE

Mammary Analogue Secretory Carcinoma of Salivary Glands, Containing the *ETV6-NTRK3* Fusion Gene: A Hitherto Undescribed Salivary Gland Tumor Entity

Alena Skálová, MD, PhD,† Tomas Vanecek, PhD,‡ Radek Sima, MSc,‡ Jan Laco, MD,§ Ilan Weinreb, MD,‖ Bayardo Perez-Ordonez, MD, FRCPC,‖ Ivo Starek, MD, PhD,¶ Marie Geierova, MD,# Roderrick HW. Simpson, MD,** Fabricio Passador-Santos, MD, †† Ales Ryska, MD, PhD,§ Ilmo Leivo, MD, †† Zdenek Kinkor, MD, PhD,† and Michal Michal, MD**

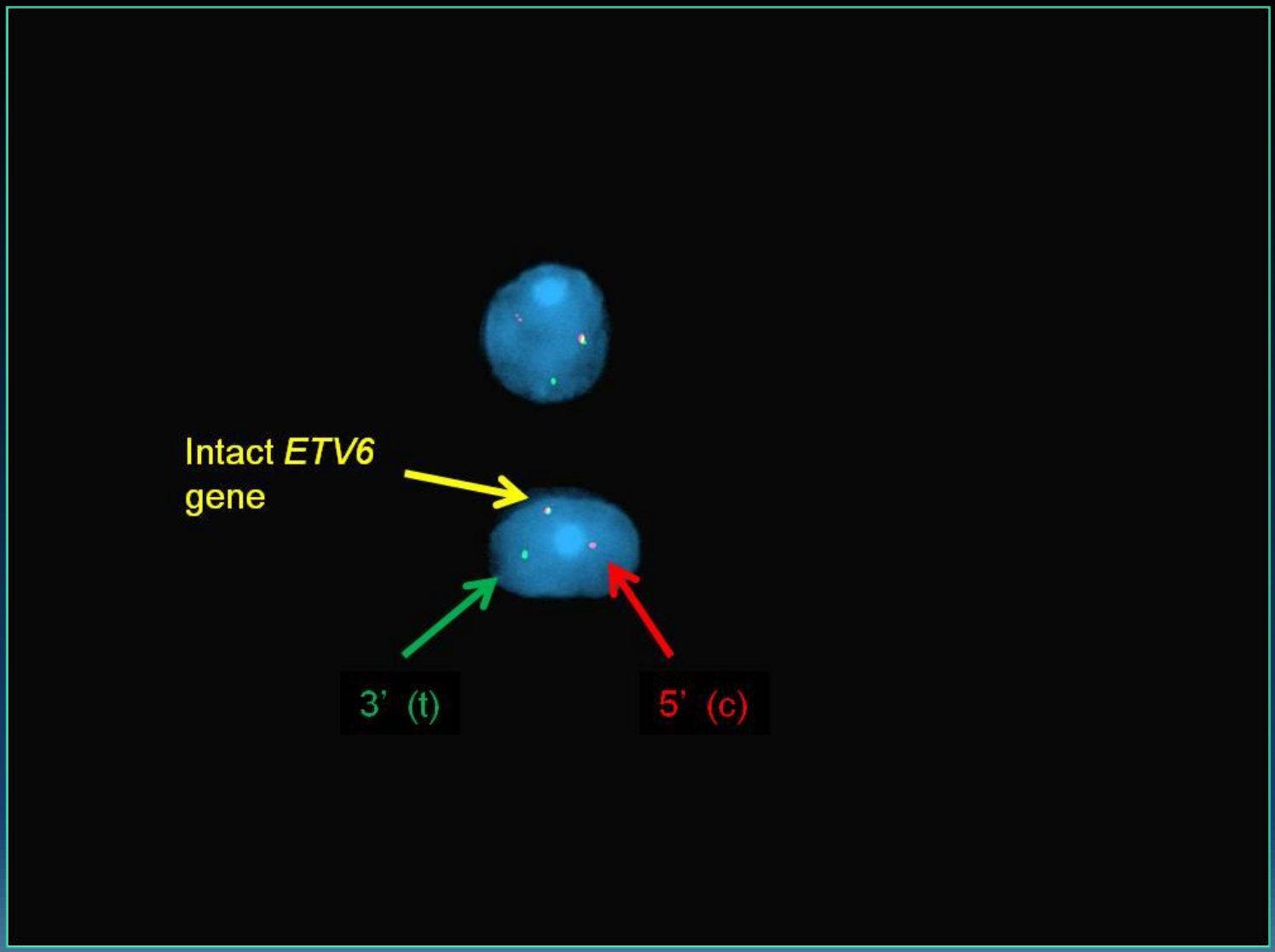
Am J Surg Pathol (2010)

- 16 salivary gland tumors morphologically similar to secretory carcinoma of the breast

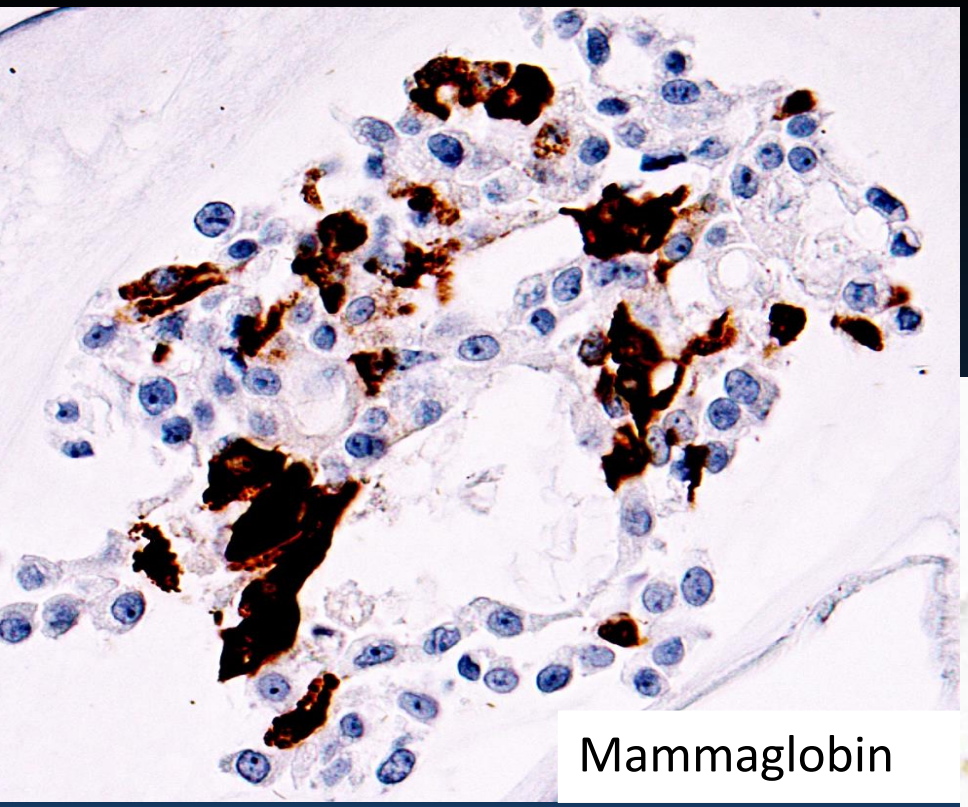


Skalova et al *Am J Surg Pathol* (2010)

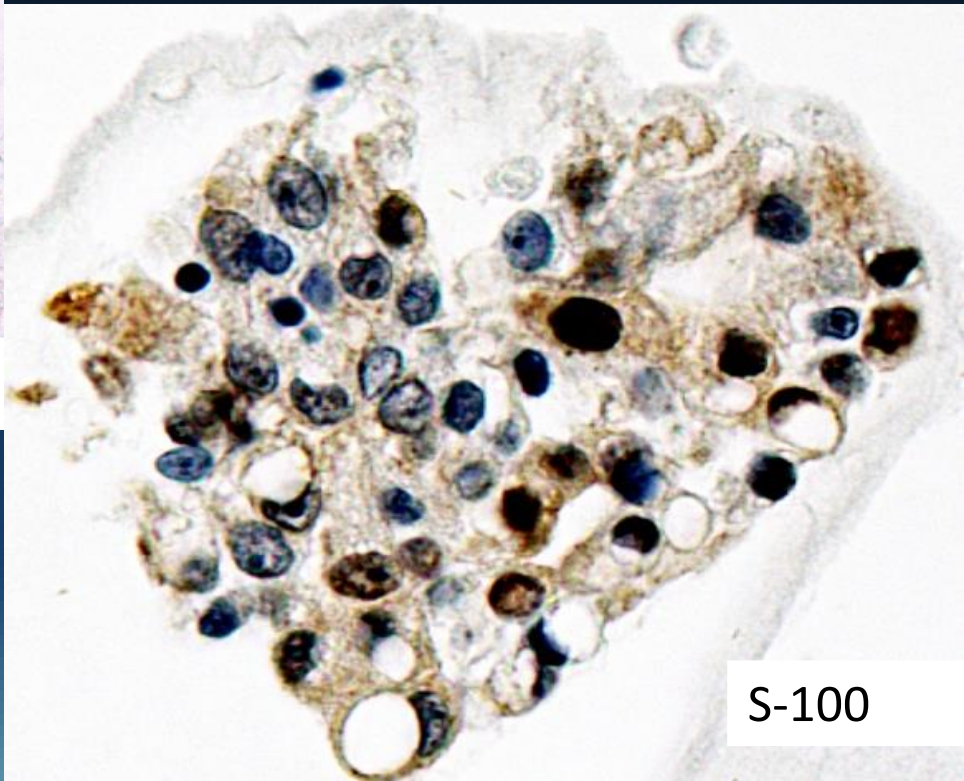
Secretory Carcinoma



Secretory Carcinoma
Immunohistochemistry

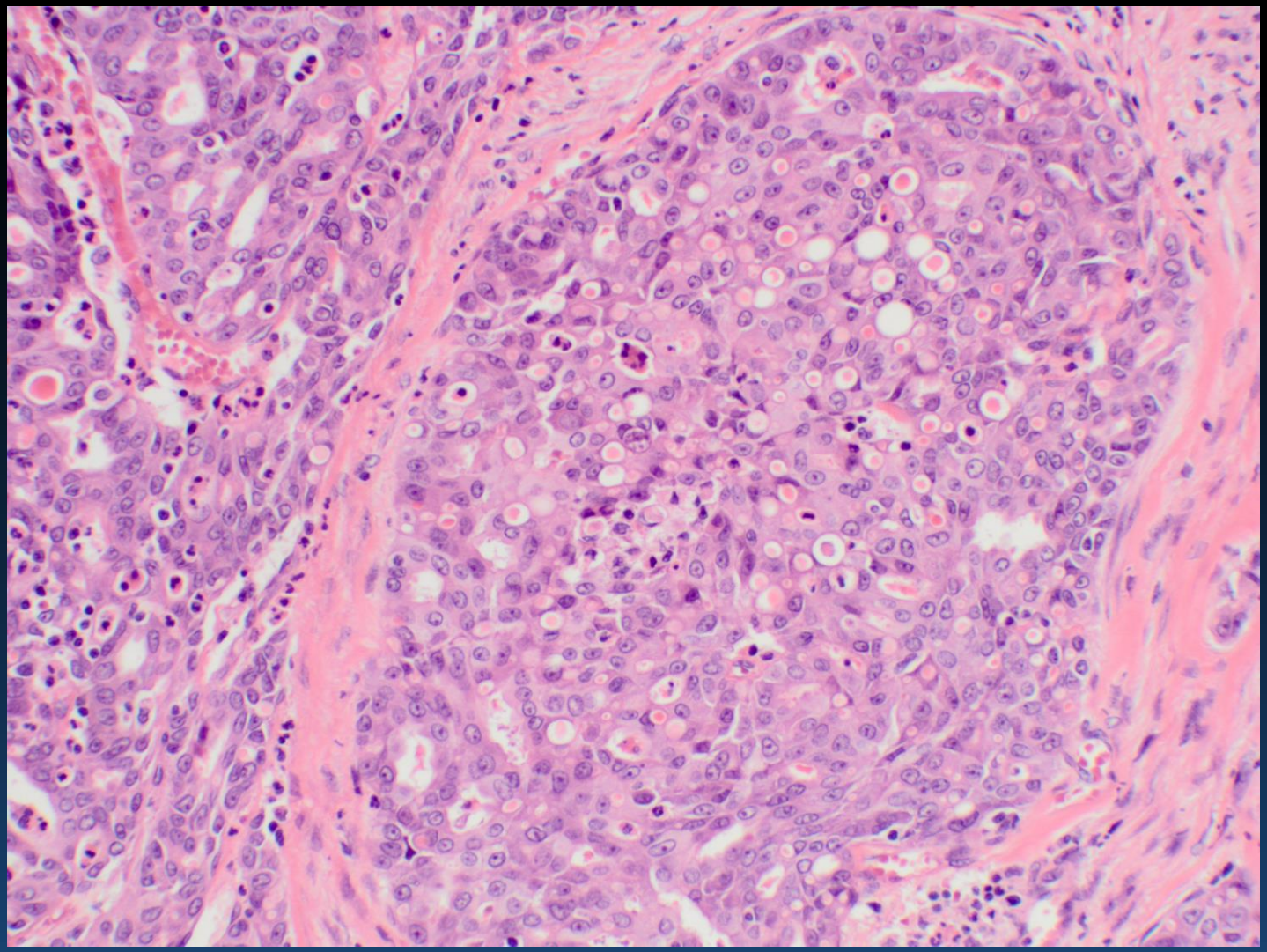


Mammaglobin



S-100

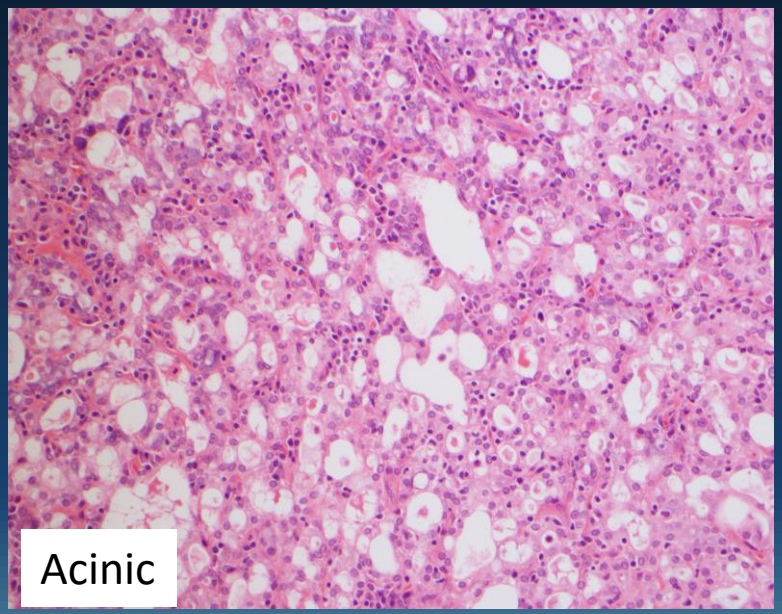
Secretory Carcinoma of Thyroid

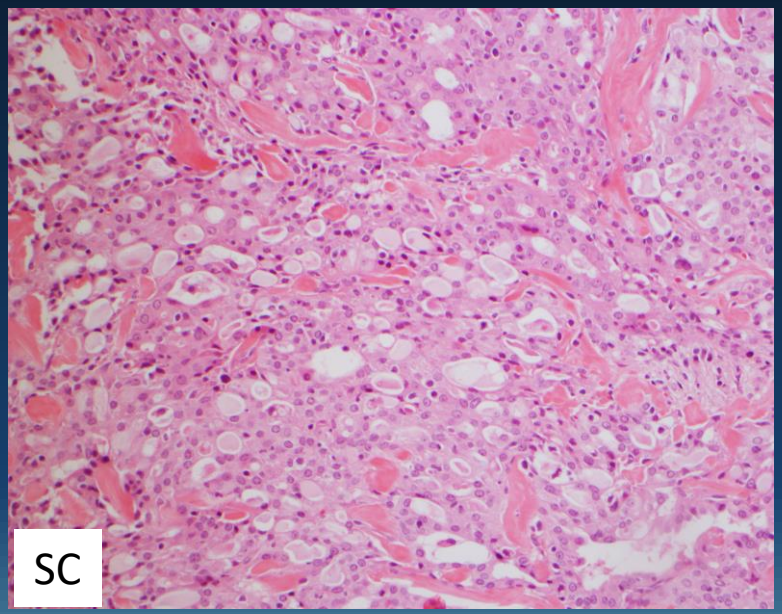


Dettloff et al *Head and Neck Pathol* (2016)
Dogan et al *Mod Pathol* (2016)
Wu et al *Histopathology* (2017)

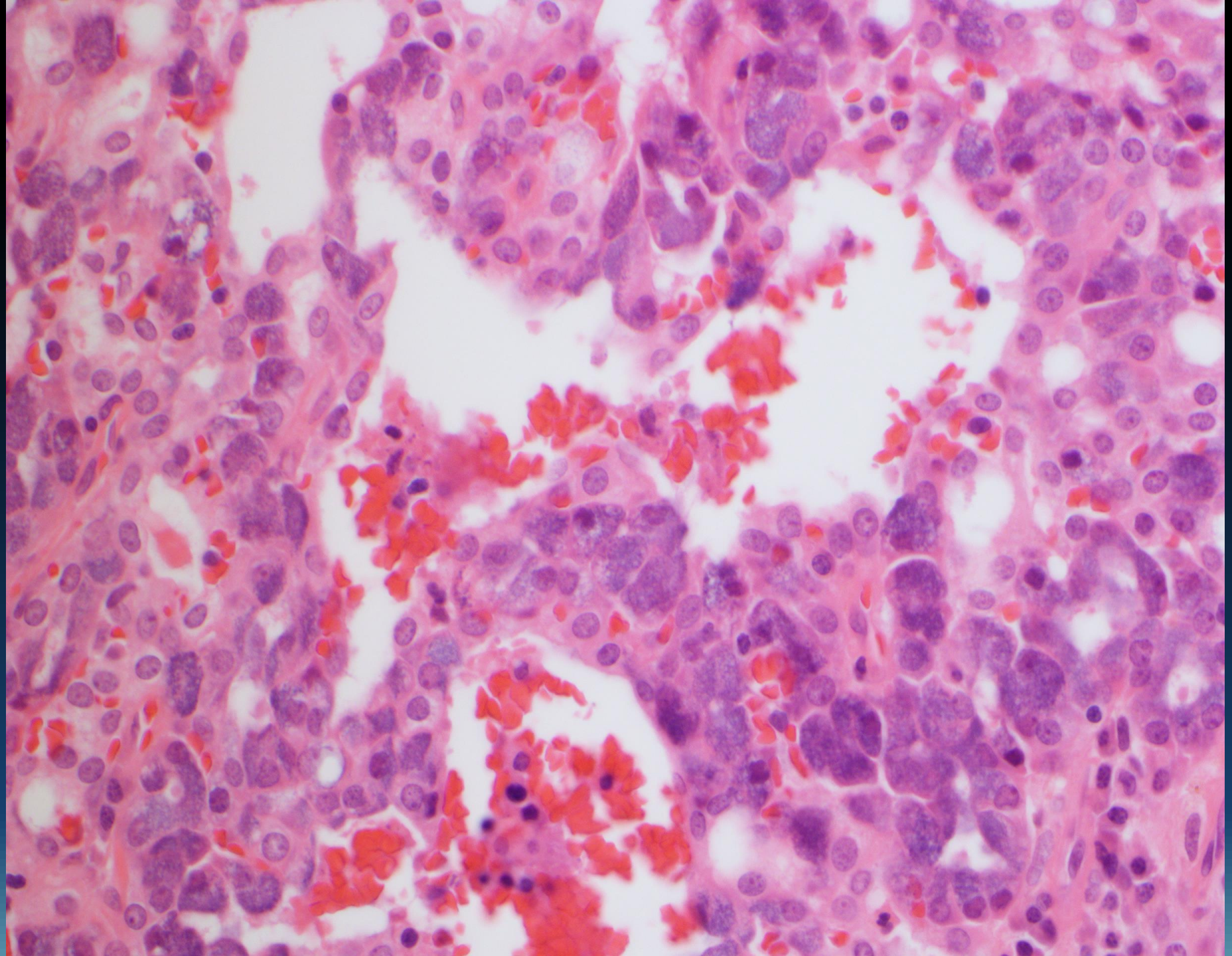
Acinic cell carcinoma

- Corollary to the discover of secretory carcinoma
  - Most ACCs not in parotid are actually SC



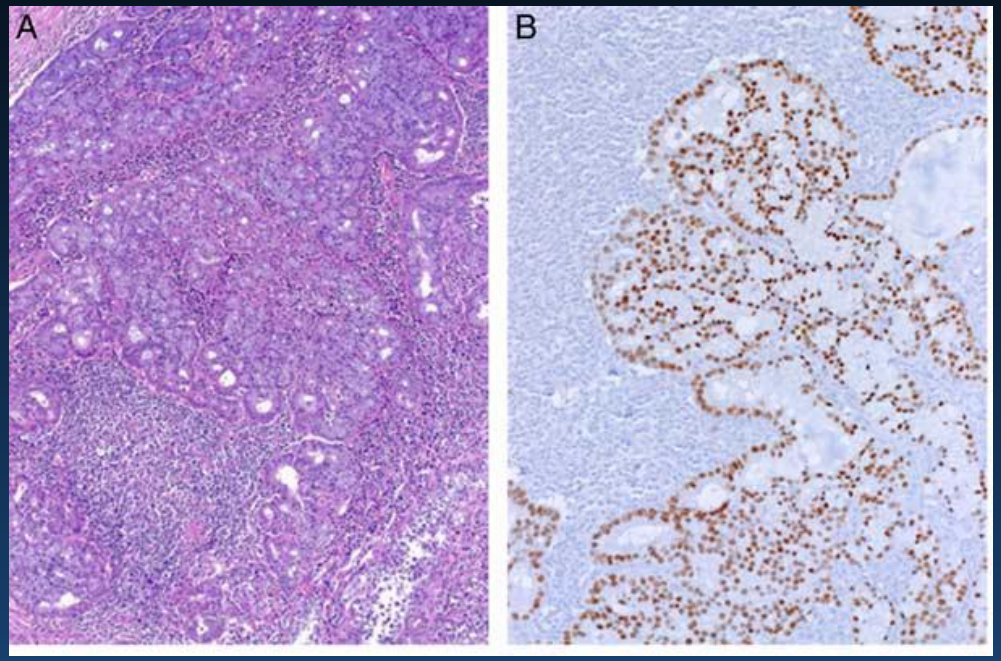


Bishop et al *Am J Surg Pathol* (2013)

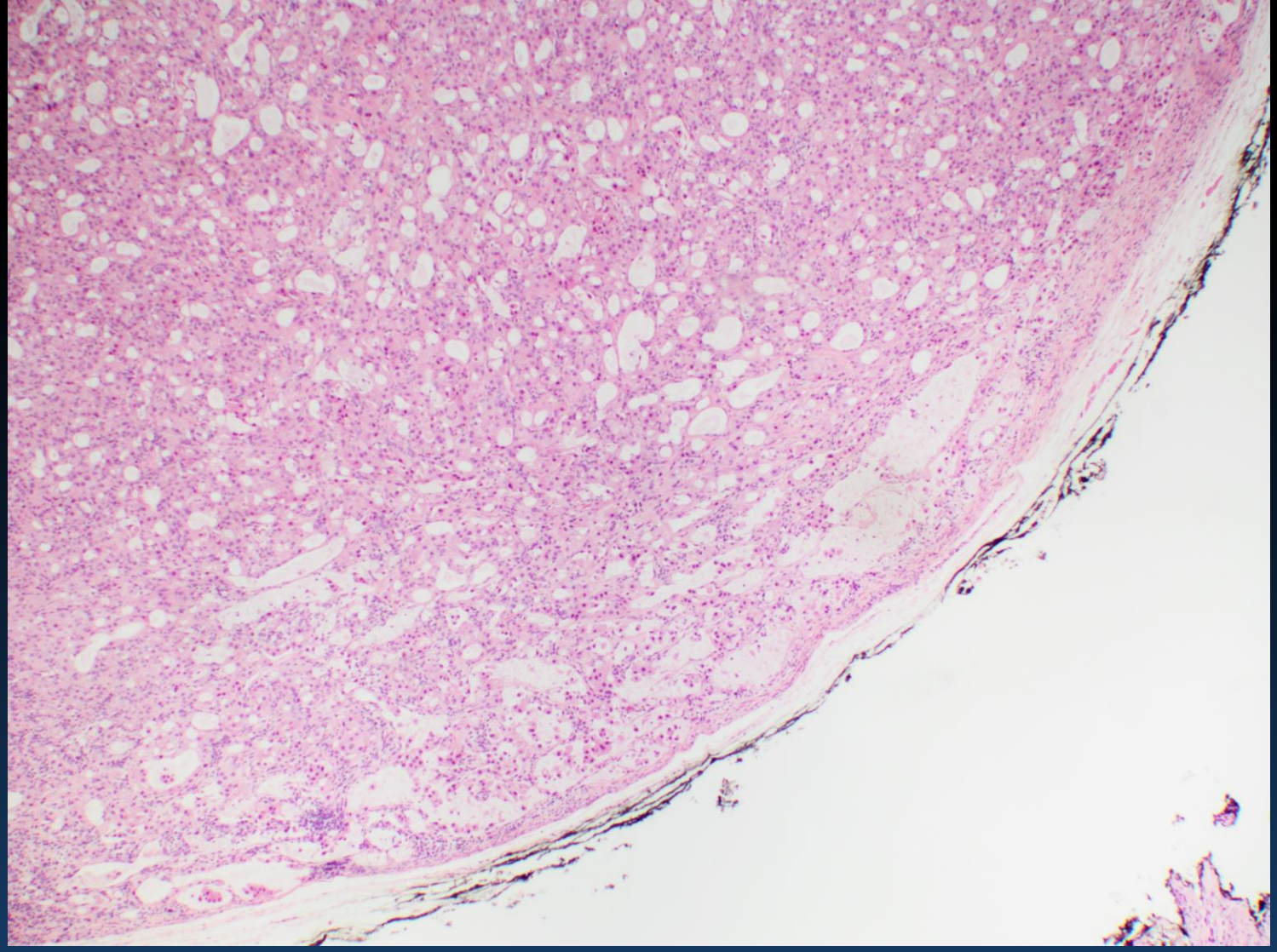


Acinic cell carcinoma
Genetics

- Recently discovered to harbor a recurrent t(4;9)(q13;q31) translocation involving NR4A3 locus
- NR4A3 immunohistochemistry is sensitive and specific marker

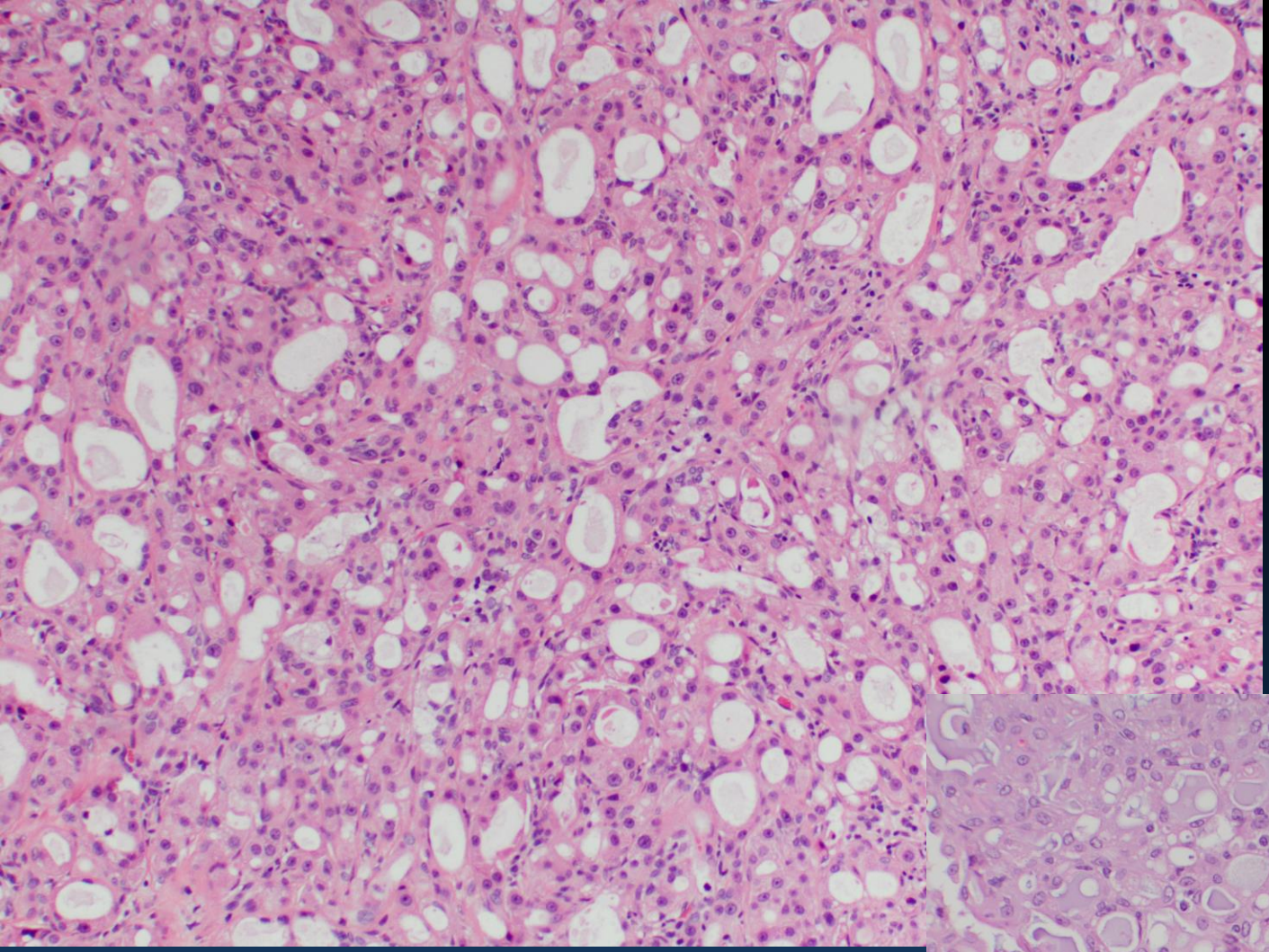


Haller et al *Nature Commun* (2019)
Haller et al *Am J Surg Pathol* (2019)



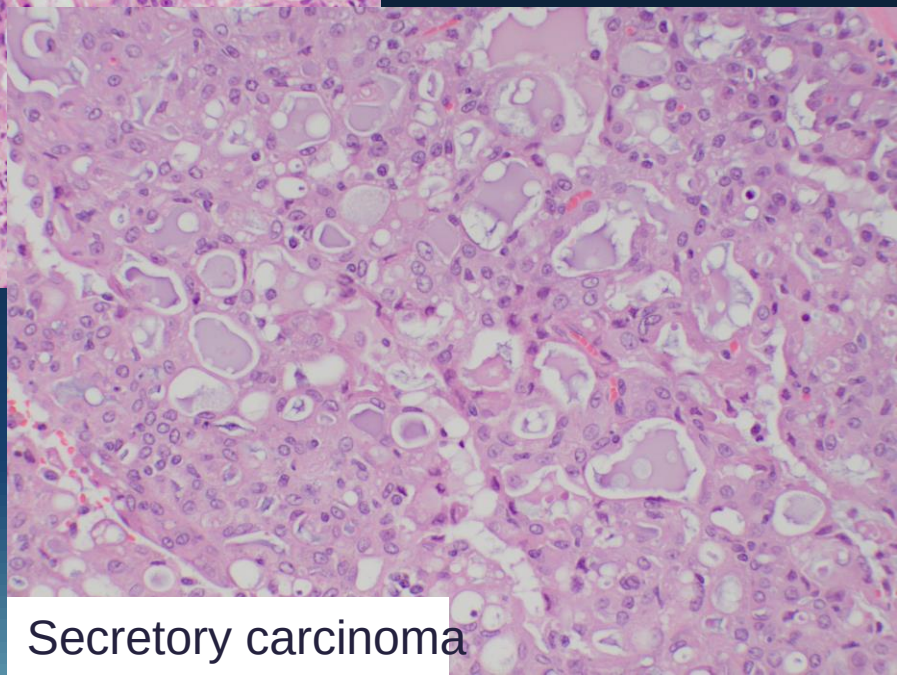
Case History

77 year old male with a buccal mucosal mass

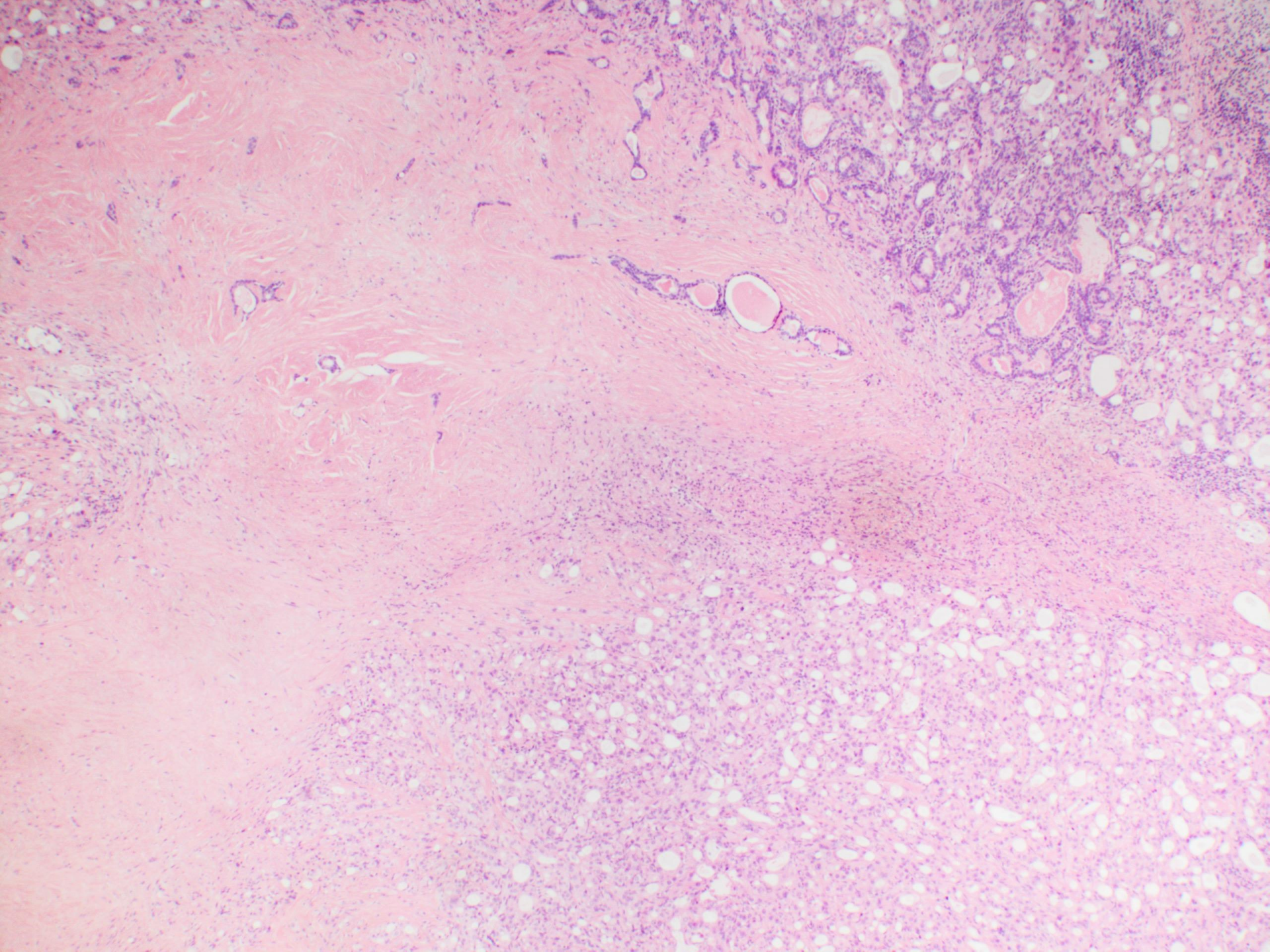


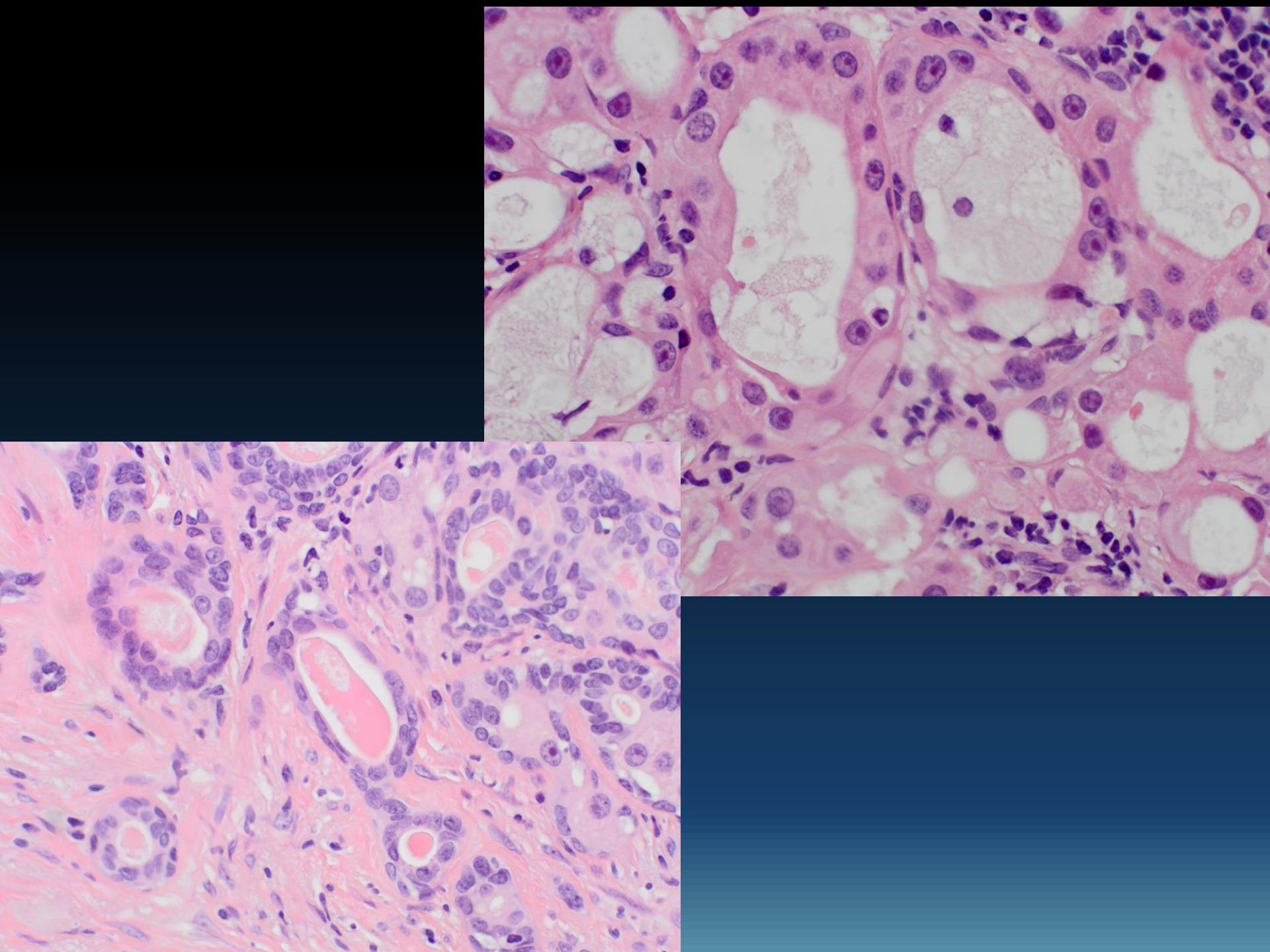
Secretory carcinoma?

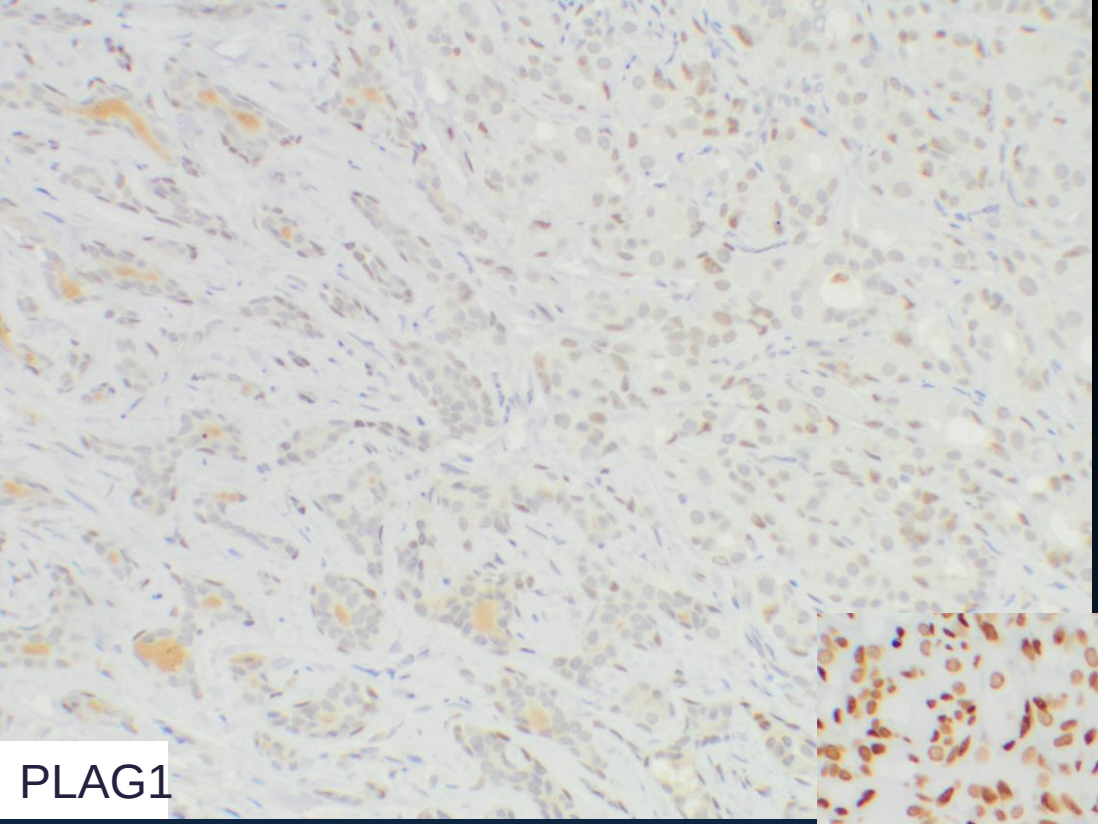
S100 and mammaglobin+



Secretory carcinoma

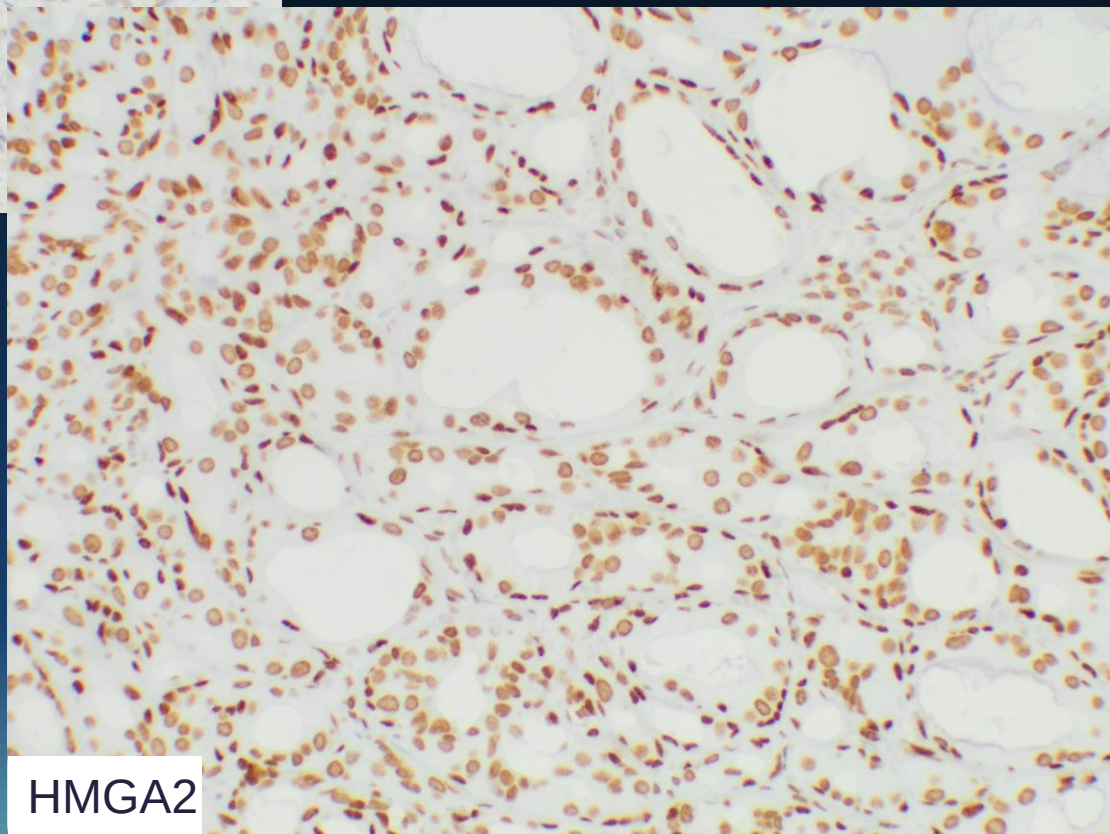






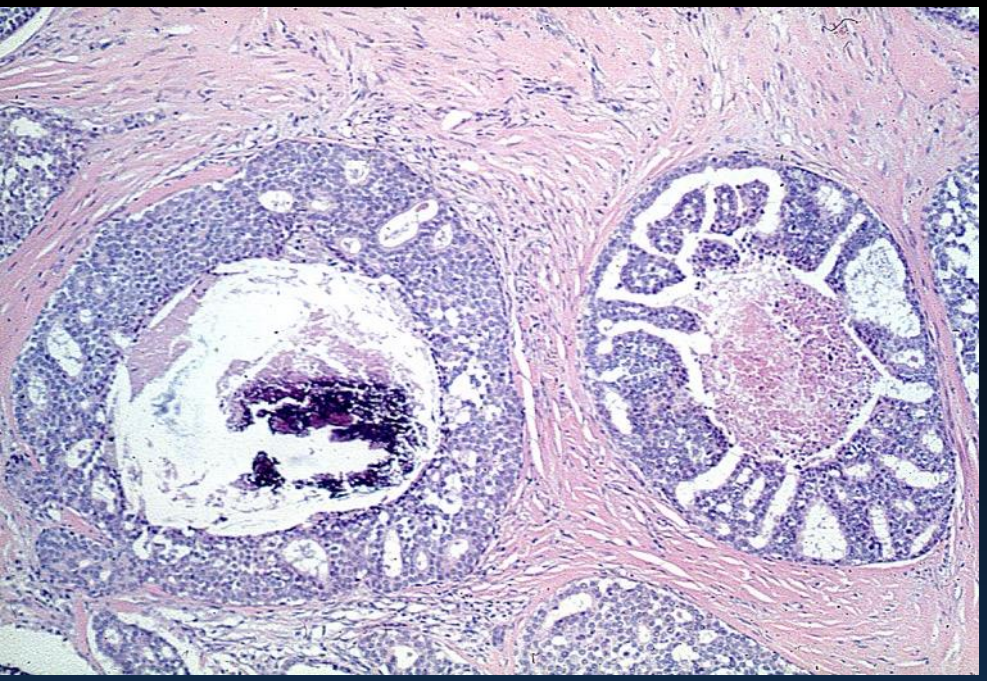
PLAG1

Carcinoma ex pleomorphic adenoma

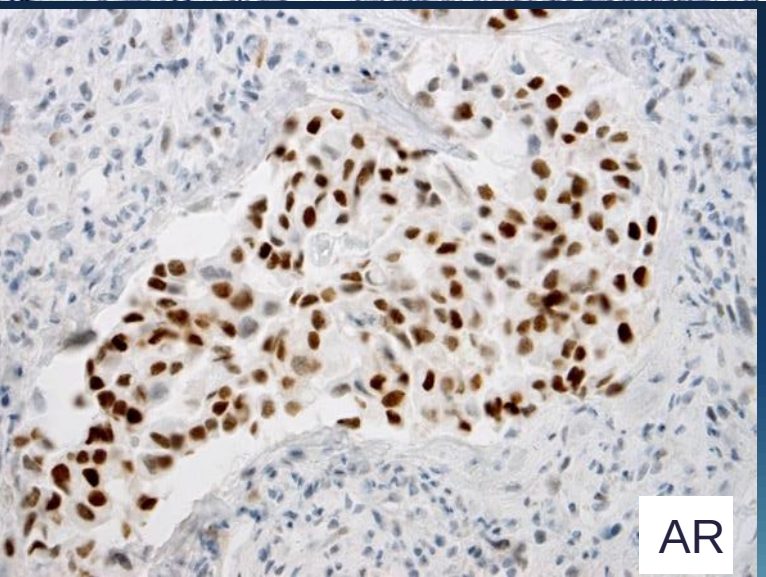


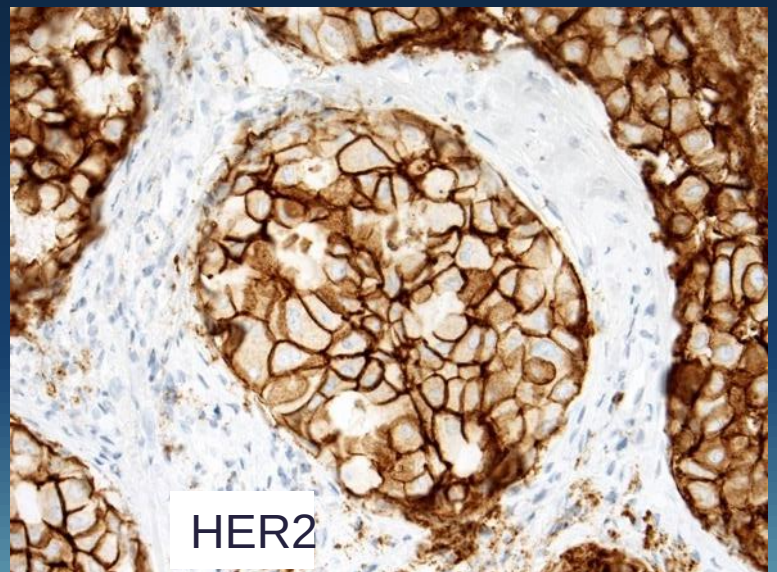
HMGA2

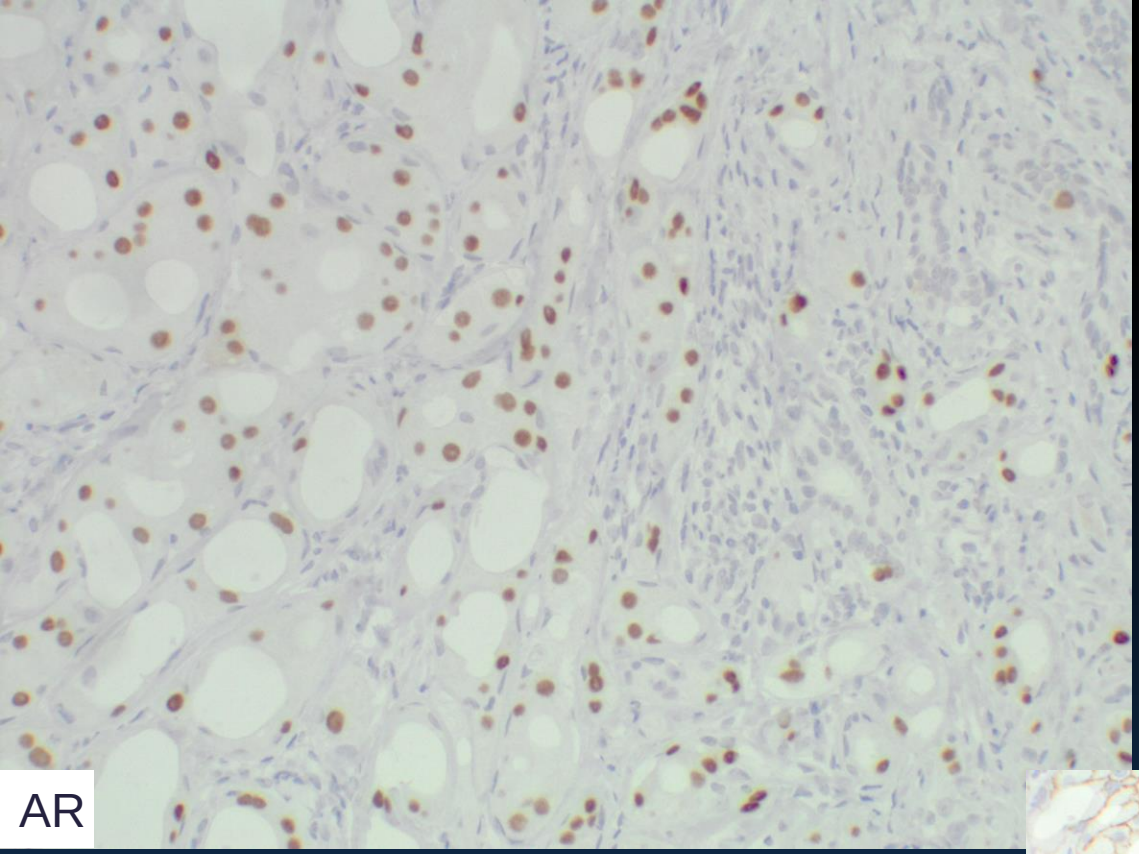
Salivary Duct Carcinoma



- AR+, subset HER2+
- Subset are SDC ex PA
  - PLAG1 or HMGA2 expression if rearrangement present
  - Precursor PA may not be sampled and/or focal



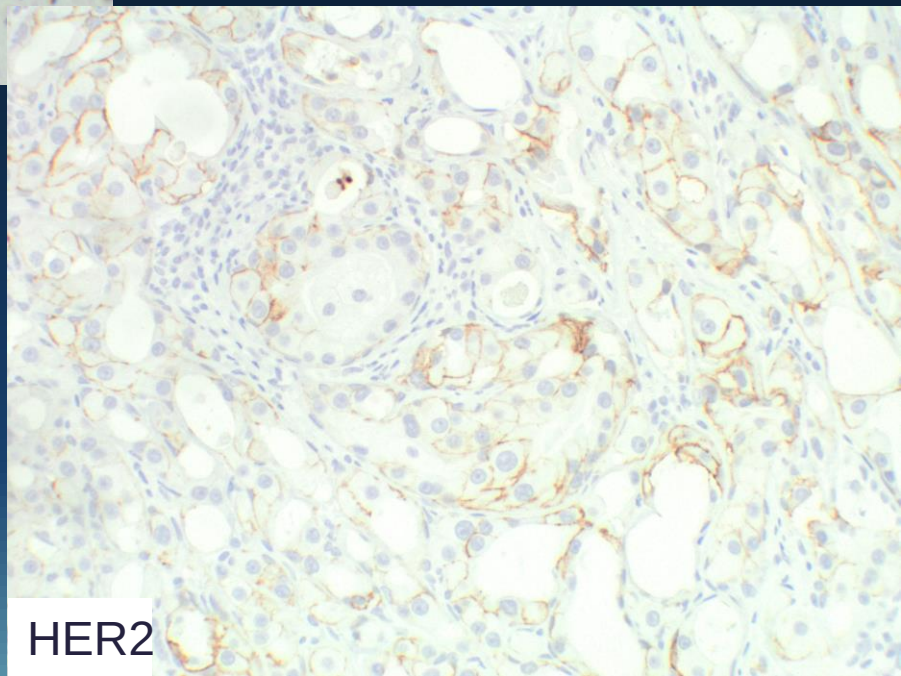




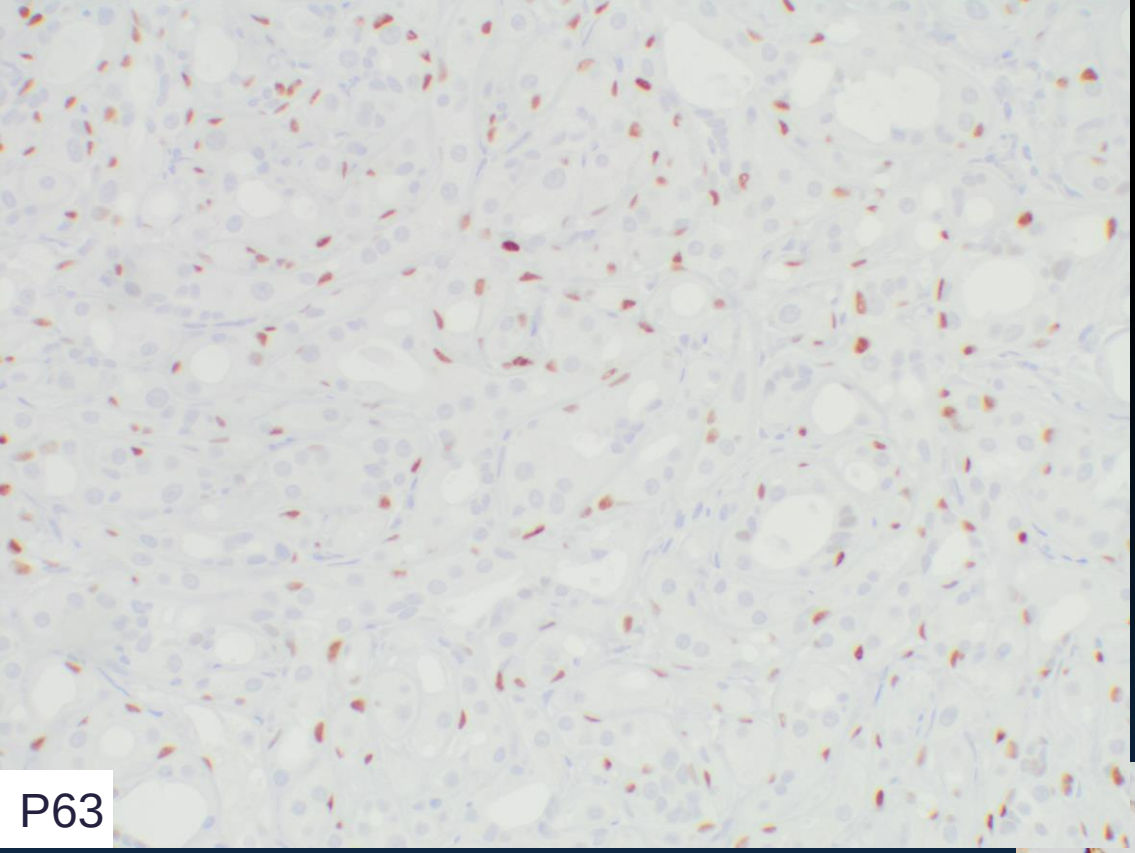
AR

Carcinoma ex pleomorphic adenoma

Salivary duct carcinoma
ex pleomorphic adenoma



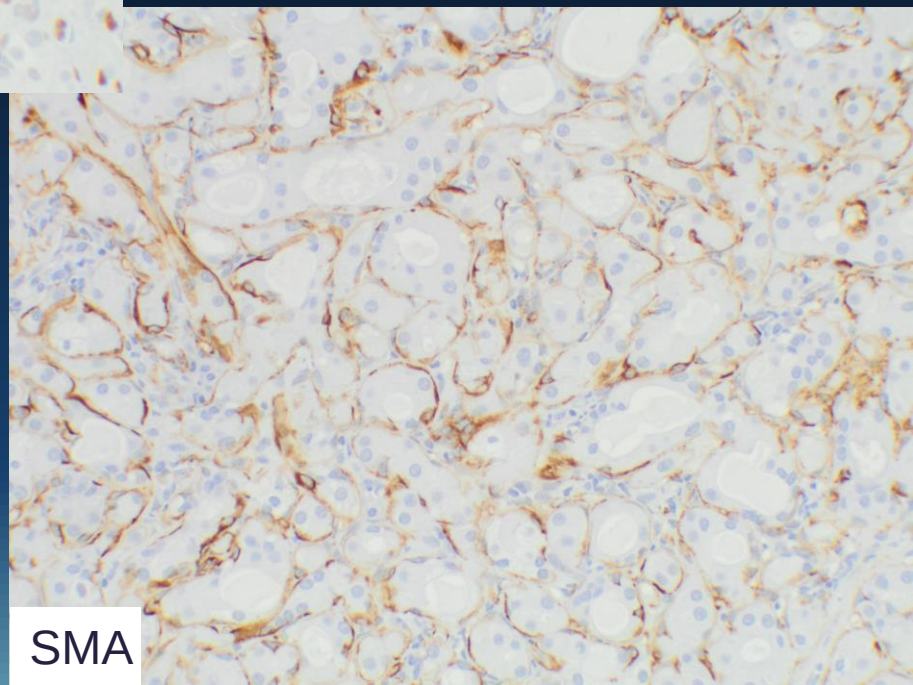
HER2



P63

Salivary duct carcinoma
ex pleomorphic adenoma

Intraductal salivary duct carcinoma
ex pleomorphic adenoma



SMA

Salivary Gland Tumor Ancillary Studies

Tumor	Genetic Alteration	Genes Involved	FISH Probe	IHC Markers
Pleomorphic Adenoma (and Carcinoma ex PA)	Translocation 8q12 Translocation 12q13-15	*PLAG1* *HMGA2*	*PLAG1* *HMGA2*	PLAG1 + HMGA2 +
Adenoid Cystic Carcinoma	t(6;9)(q22-23;p23-24)	*MYB-NFIB*	*MYB*	MYB +
Mucoepidermoid Carcinoma	t(11;19)(q21;p13) t(11;15)(q21;q26)	*CRCT1-MAML2* *CRCT3-MAML2*	*MAML2*	p63/p40+
Secretory Carcinoma	t(12;15)(p13;q25)	*ETV6-NTRK3*	*ETV6*	S100+, mammaglobin+ Pan-TRK+
Acinic Cell Carcinoma	t(4;9)(q13;q31)	*NR4A3*	*NR4A3*	NR4A3+
Clear Cell Carcinoma	t(12;22)(q13;q12)	*EWSR1-ATF1*	*EWSR1*	
Polymorphous Adenocarcinoma	14q12 mutation	*PRKD* family		
Salivary Duct Carcinoma				AR+, HER2+
Basal Cell Adenoma	3p22.1 mutation	*CTNNB1*		Beta-catenin +
Microsecretory Carcinoma	t(5;18)(q14;q11)	*MEF2C-SS18*	*SS18*	

Conclusions

- Ancillary testing is increasingly useful for salivary gland and sinonasal tumors
  - Routine diagnosis
  - Refining recognized entities
  - Recognizing new entities
  - Therapeutic potential through targeting of potentially actionable mutations