Salivary Gland Tumors

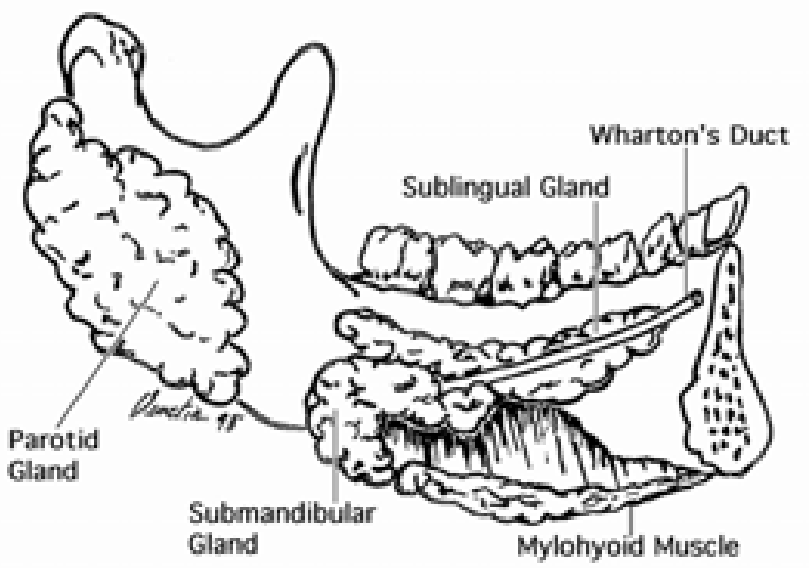
Haresh Mani
Inova Fairfax Hospital

Objectives

- Outline pathology of salivary gland neoplasms
- Form an approach to the practical diagnosis of salivary gland tumors
- Recent advances (new entities and molecular pathology)

Major salivary glands

- 3 large exocrine glands
  - Parotid (serous)
  - Submandibular (mixed)
  - Sublingual (mucous)

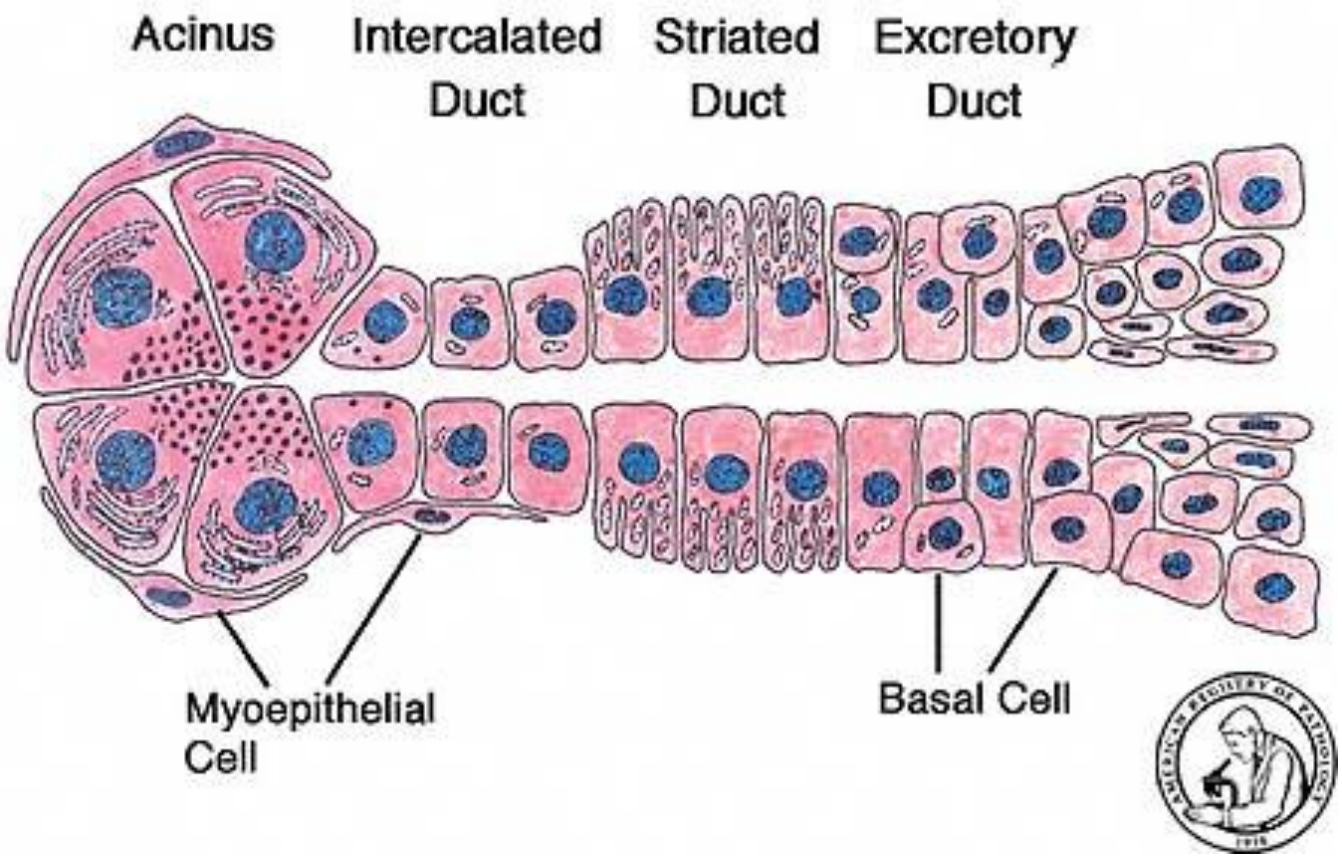


- Minor glands

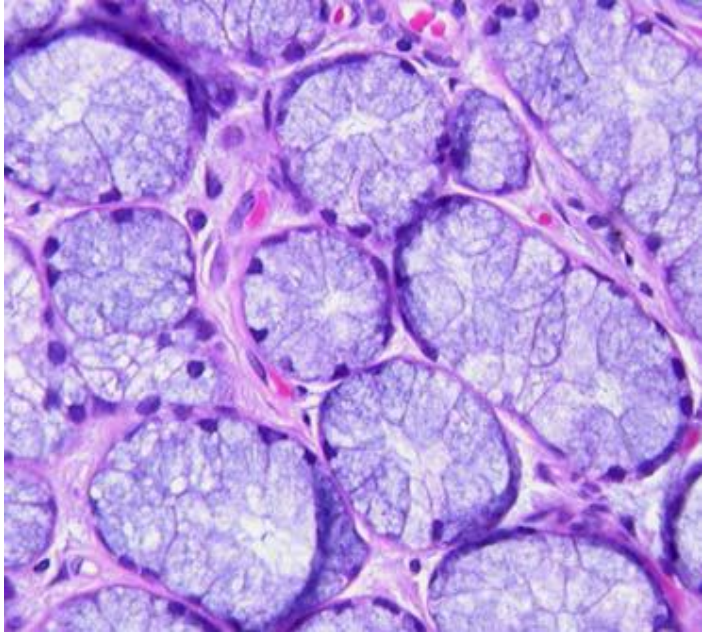
  throughout the upper aerodigestive tract

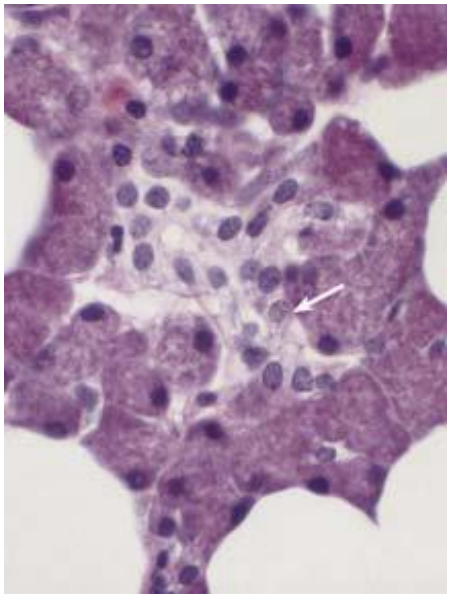
Salivary Gland Unit
(Origin of Salivary Gland Tumors)

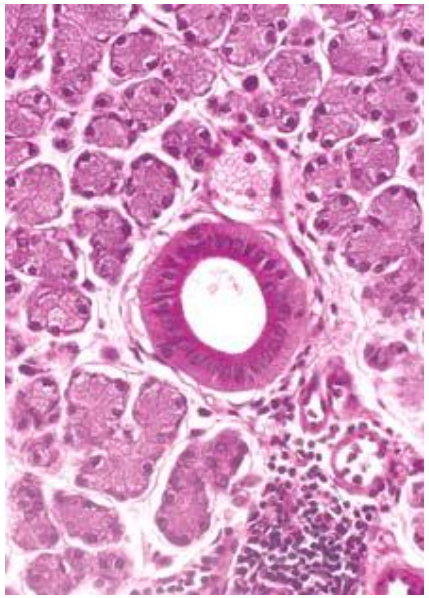
- The segments of the unit contain two cell layers
  - Inner (adluminal):
    - Acinous: serous and mucous cells
    - Duct luminal: cuboidal, columnar, and squamous epithelial
  - Outer (Abluminal):
    - Myoepithelial (acinus and intercalated duct)
    - Basal cell (excretory duct)
- Branching tubules open onto the mucosal surface

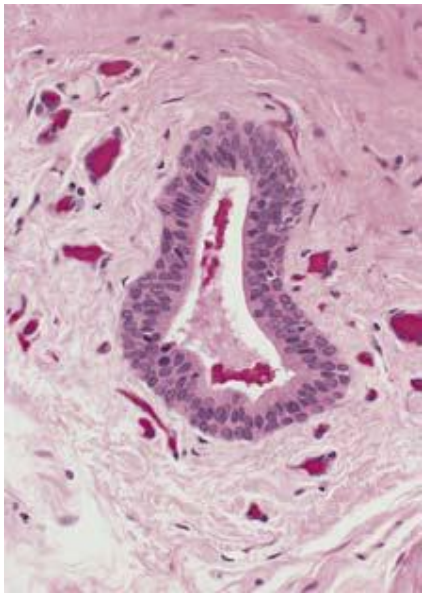


- Basic secretory unit: Acinus → intercalated duct →striated duct → excretory duct
- Acinar cells may be *serous, mucous* or mixed
- *Myoepithelial cells* surround the acini and have a contractile function.
- Acini → Lobule → Parenchyma









Classification

Benign Neoplasms

- Pleomorphic Adenoma
- Warthin Tumor
- Canalicular Adenoma
- Basal Cell Adenoma
- Oncocytoma
- Myoepithelioma
- Adenoma, Not Otherwise Specified
- Papillary lesions

Reactive Conditions

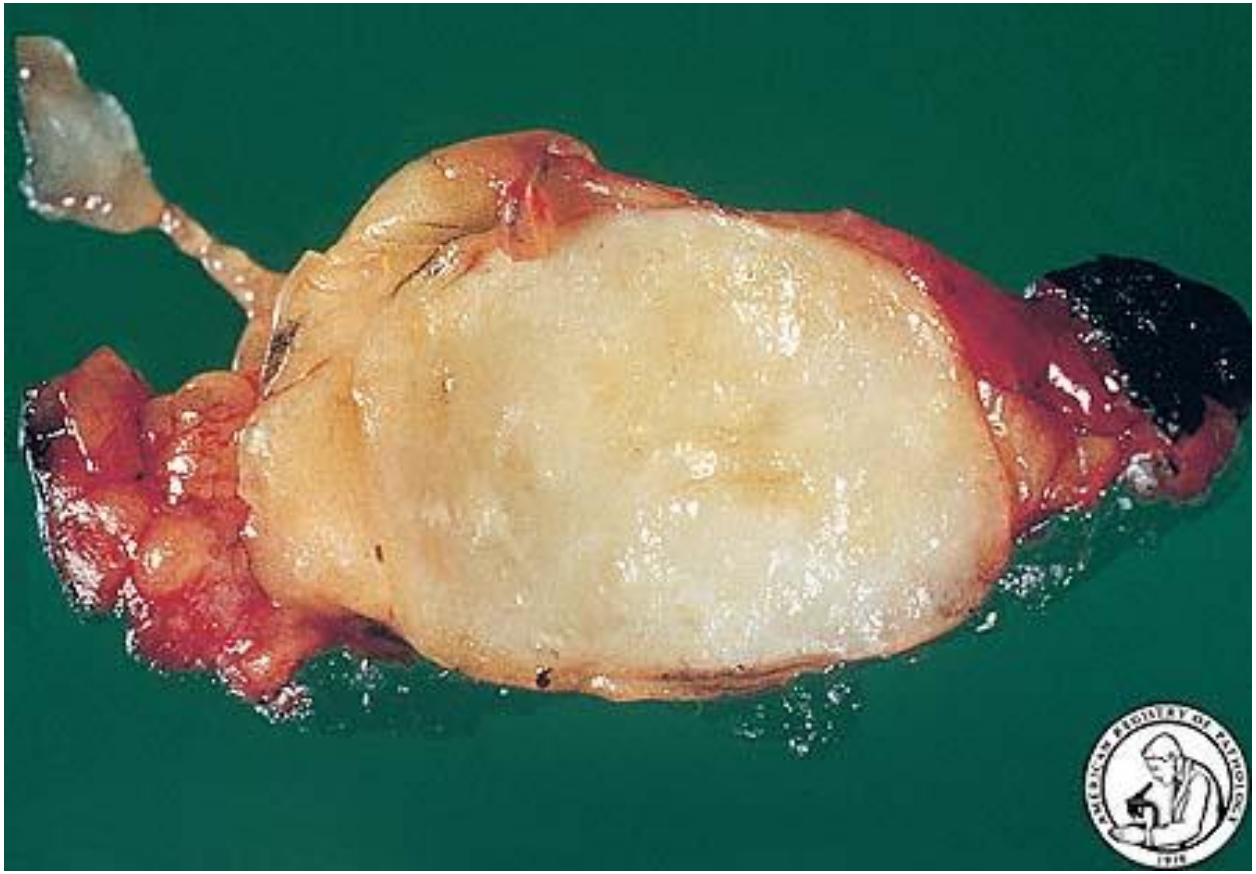
- Mucocele
- Sialolithiasis/Sialadenitis
- Necrotizing Sialometaplasia

Malignant Neoplasms

- Mucoepidermoid Carcinoma
- Acinic Cell Carcinoma
- Adenoid Cystic Carcinoma
- Polymorphous ADCa
- Carcinoma ex PA
- Adenocarcinoma Not Otherwise Specified
- Secretory Ca
- Clear cell Ca
- LGCC
- Salivary duct carcinoma
- EMC
- Others

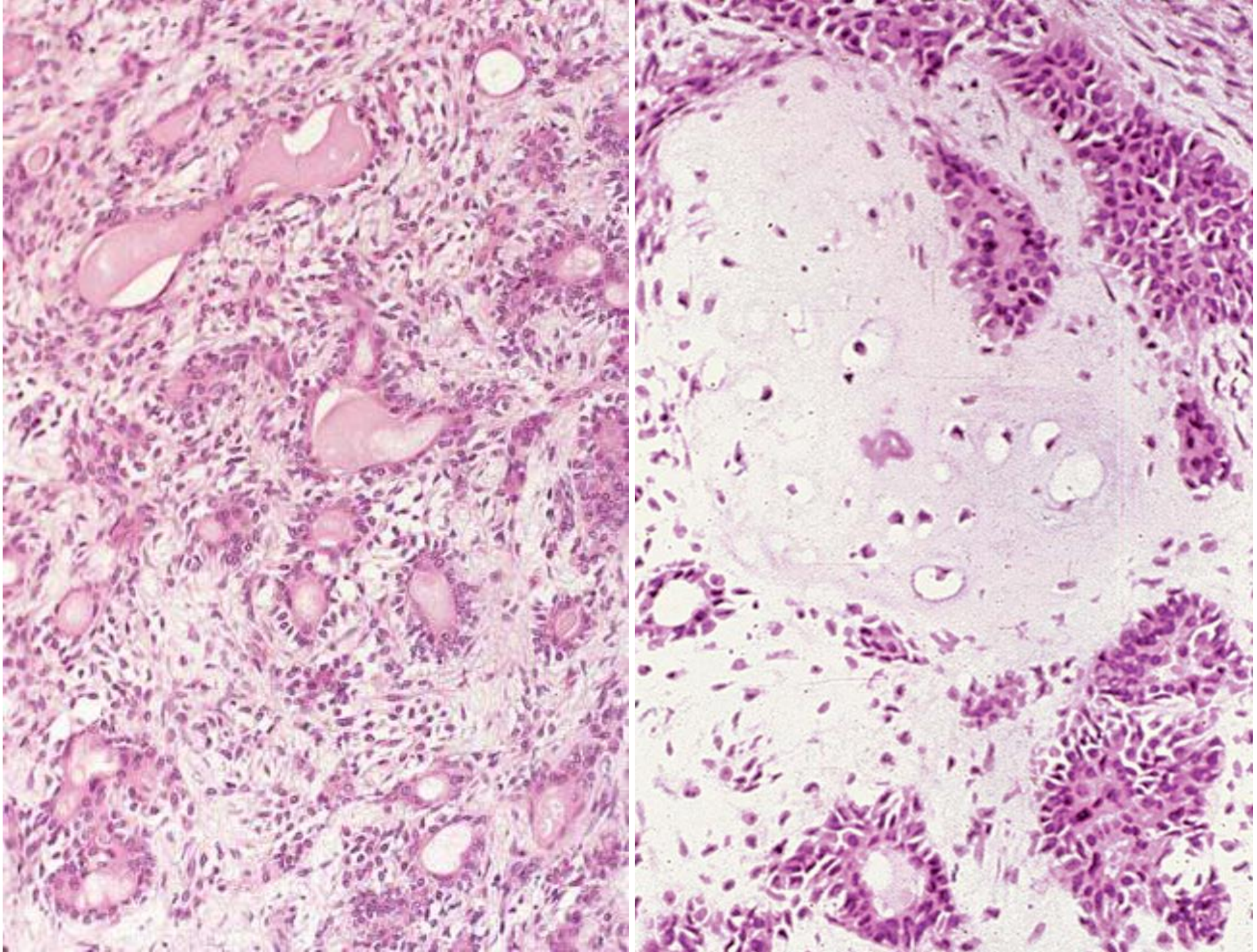
Pleomorphic Adenoma

- Circumscribed homogeneous tan-white frequently glistening, maybe partially myxoid



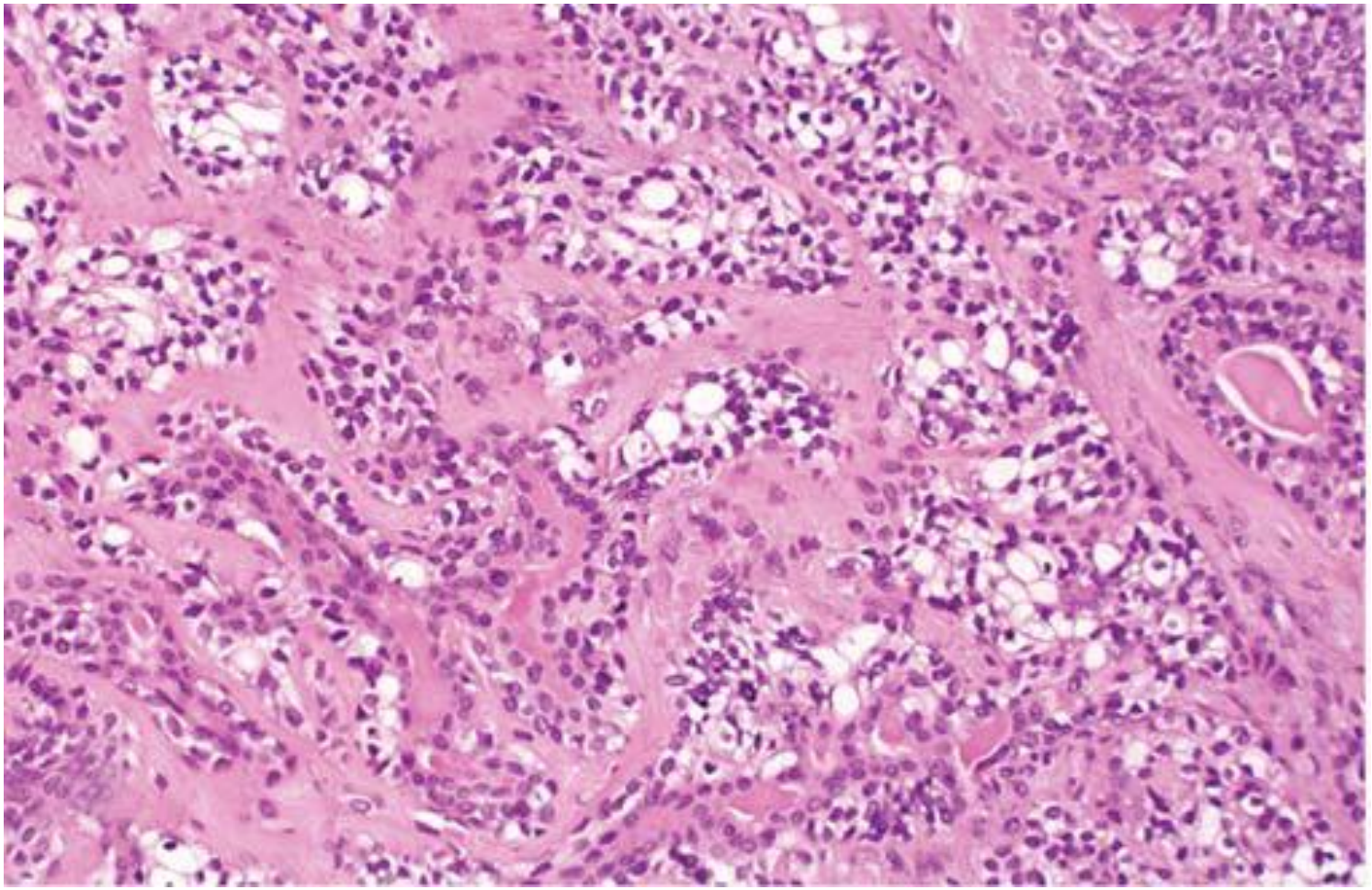
Pleomorphic Adenoma

- Epithelial and myoepithelial differentiation
  - Epithelial differentiation: Well formed ducts associated with non-ductal cells
  - Non-ductal cells (myoepithelial cells): spindle, round, stellate, plasmacytoid, polygonal, clear
- Stroma
  - Myxoid, hyaline, cartilaginous, osseous stromal differentiation (?modified myoepithelial)



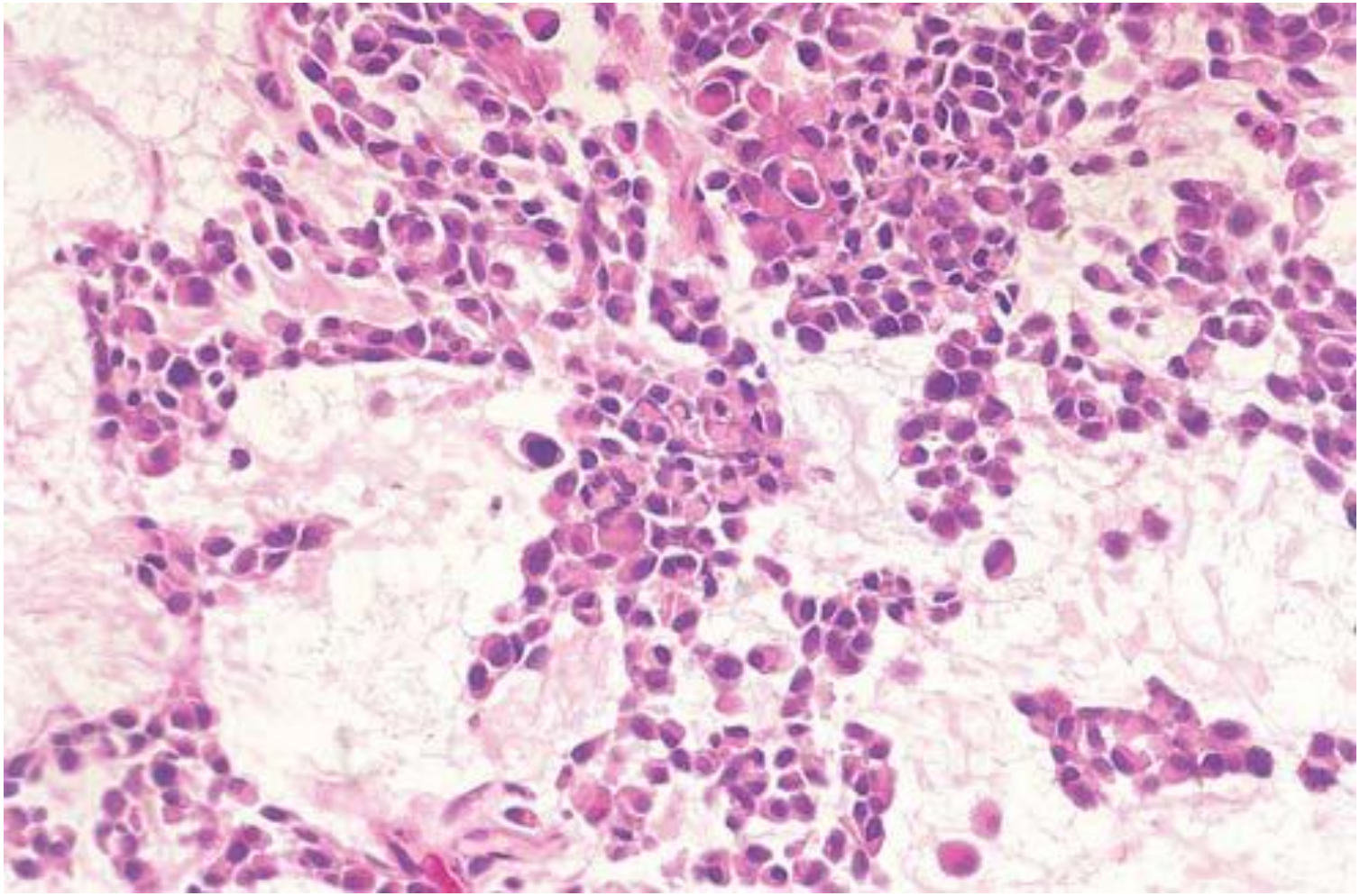
Pleomorphic Adenoma

- Clear cells



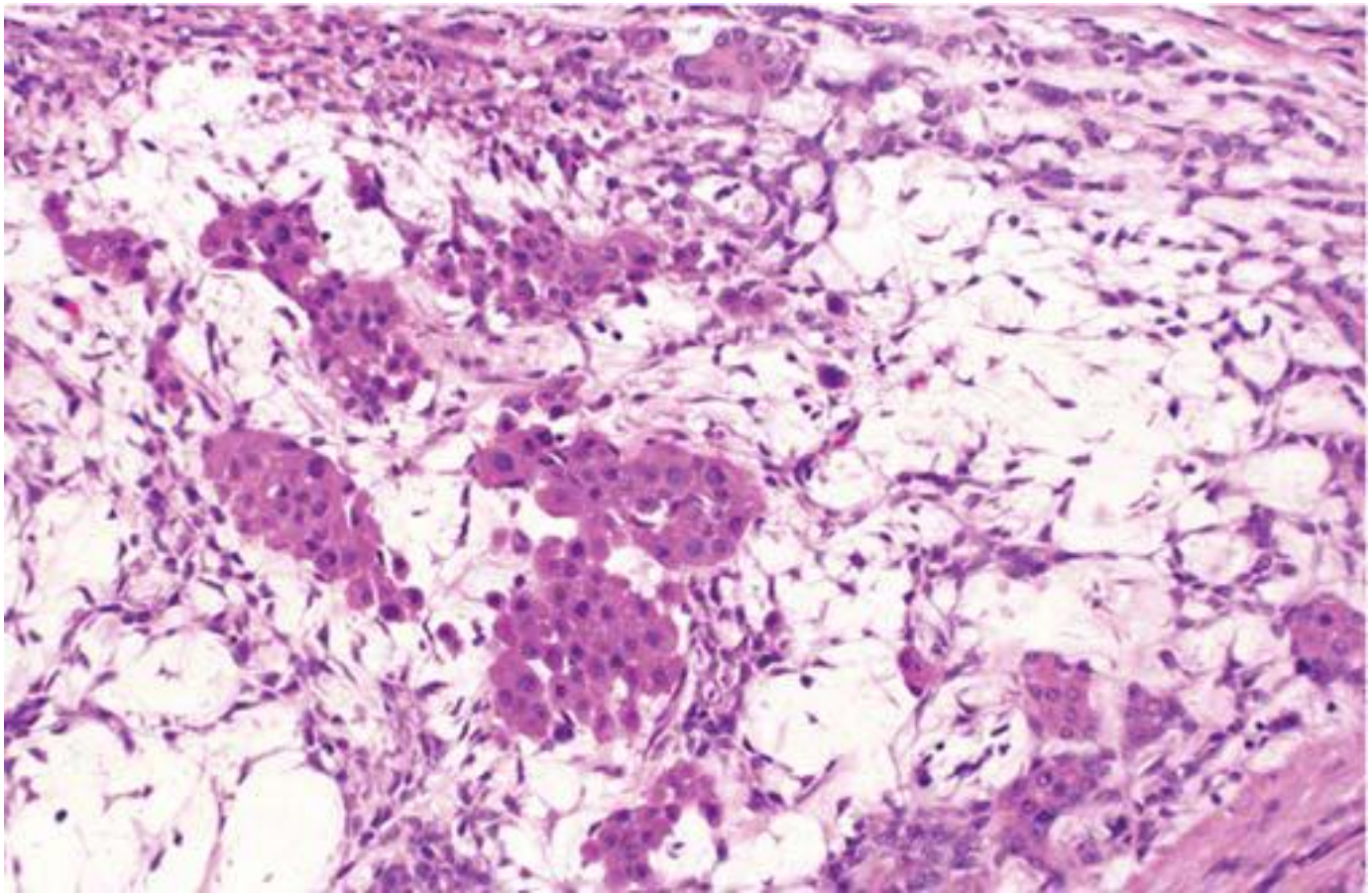
Pleomorphic Adenoma

- Plasmacytoid cells



Pleomorphic Adenoma

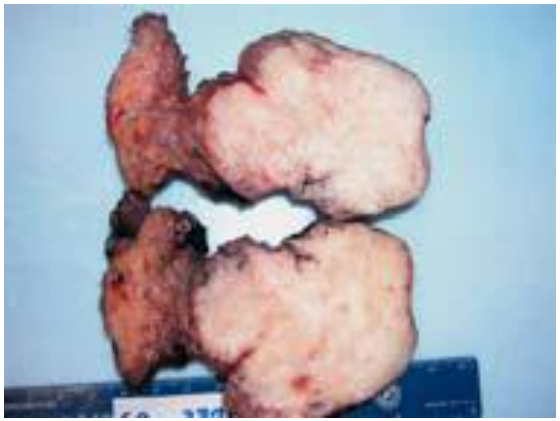
- Oncocytic features

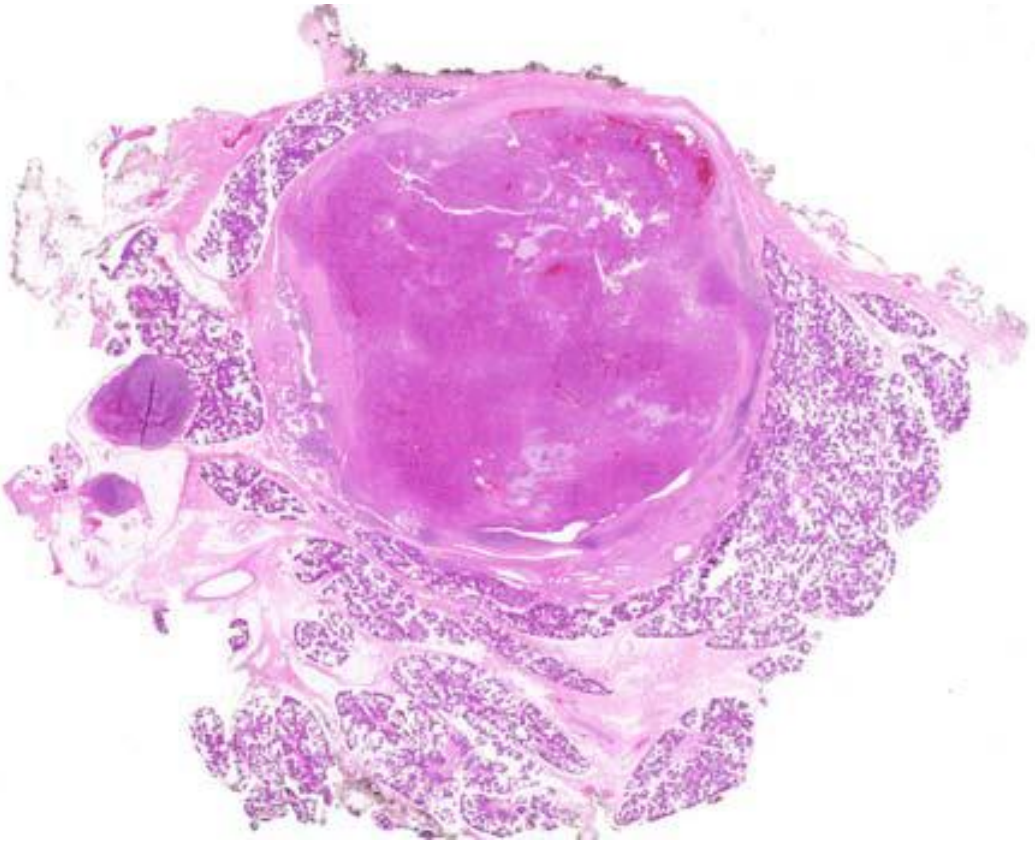


Atypical / Malignant Features

- Tumor extending through the capsule
  - acceptable in the absence of cellular atypia
- Hypercellularity
  - acceptable in the absence of cellular atypia
- Absence of capsule with tumor abutting parenchyma
  - acceptable with absence cellular atypia
- Multiple foci in normal parenchyma if discrete and circumscribed without atypia
  - acceptable in recurrent adenoma

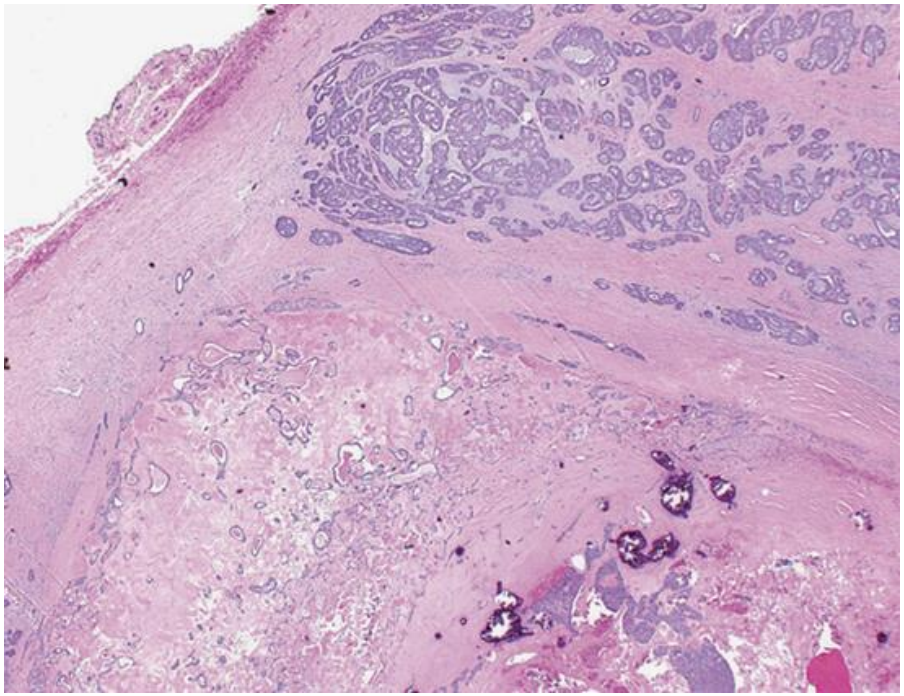
PA

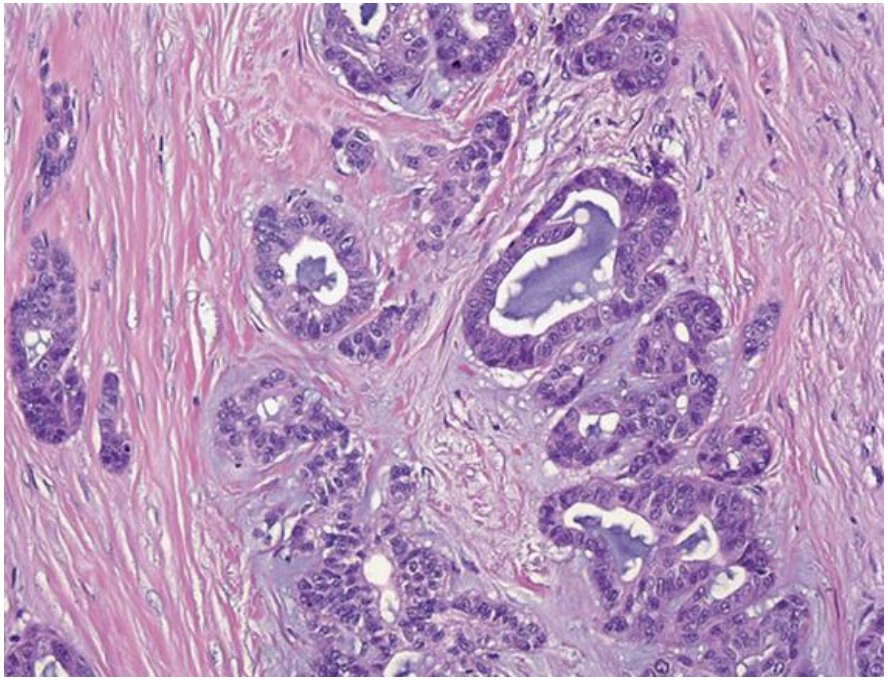


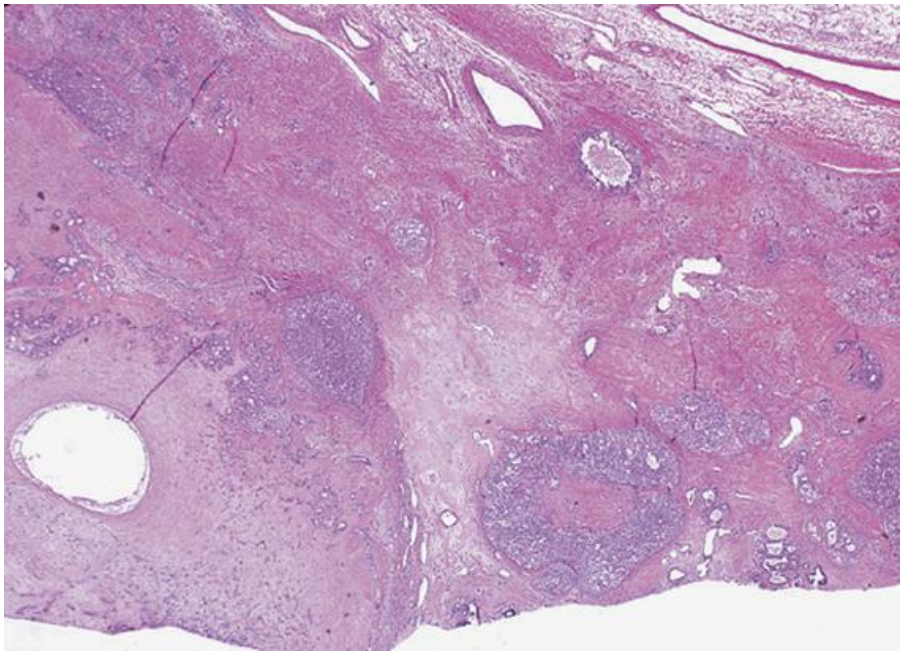


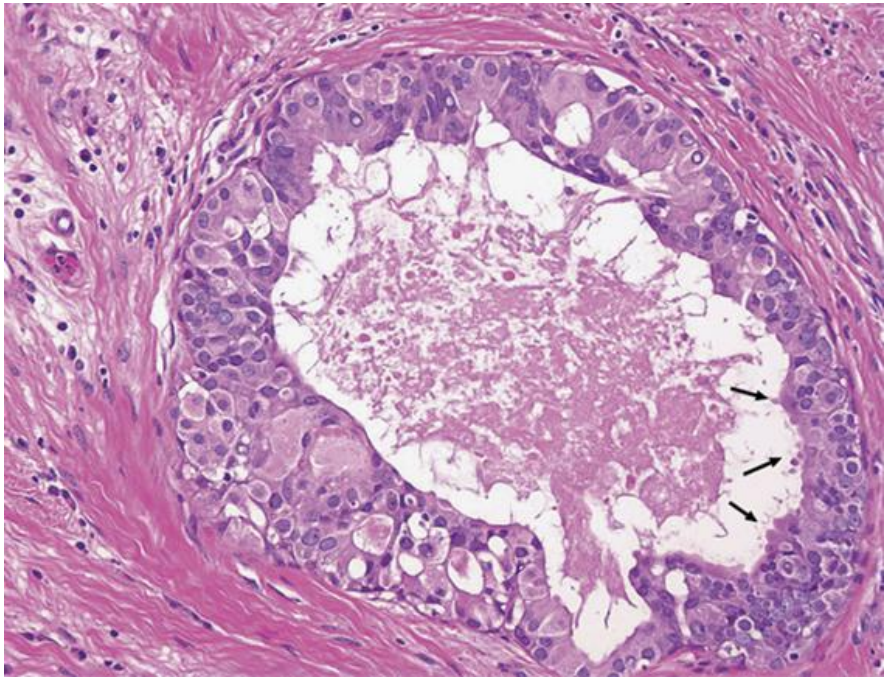
Ca-ex-PA

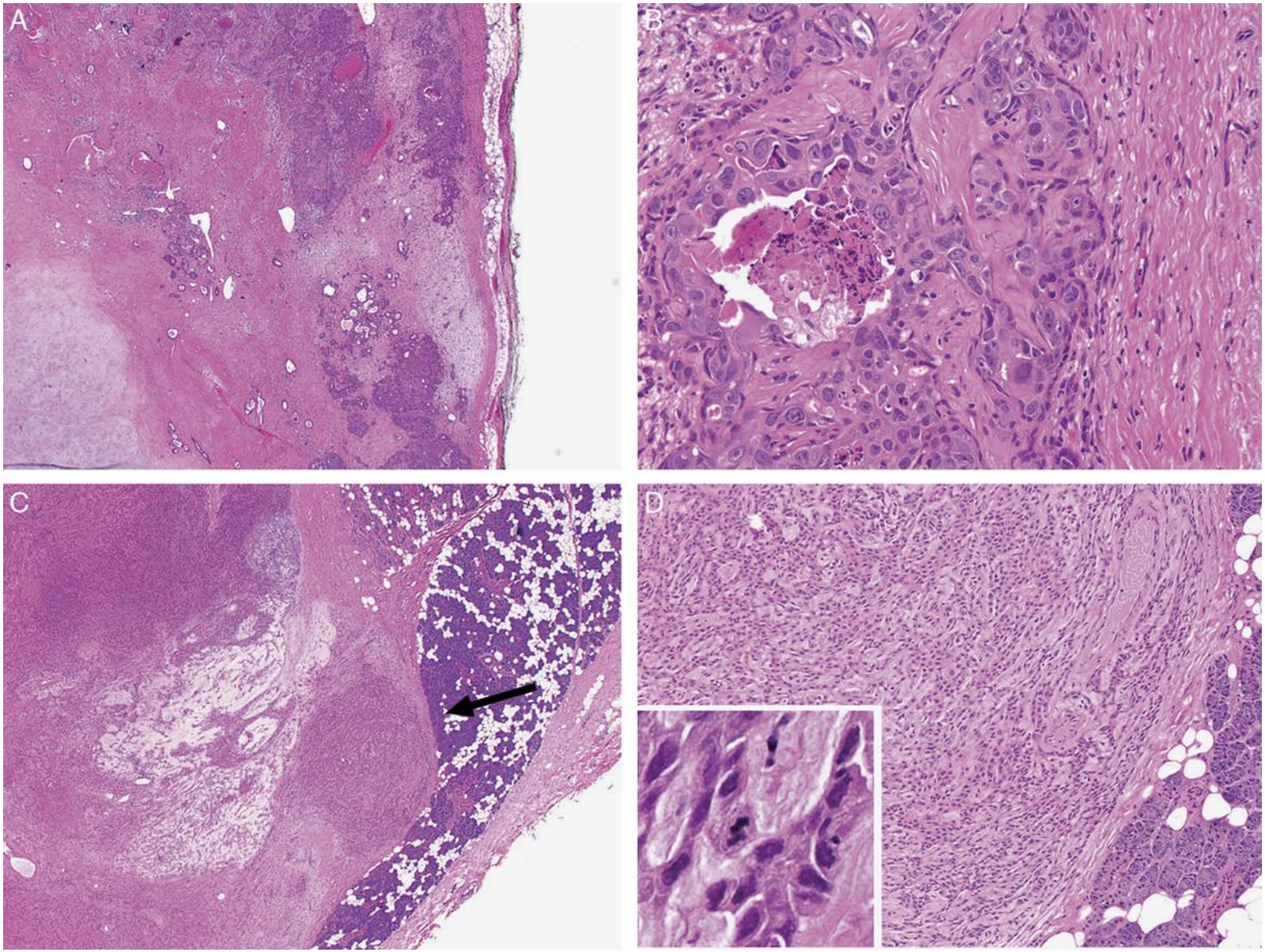
- May be true Ca-ex-PA
  - Identifiable PA component
- May be carcinosarcoma
- Benign PA may metastasize (avg interval of 20 yrs, with 20% mortality)
- Ca-ex-PA may be classified as
  - In-situ (no invasion, has myoepithelial cells, cytologic anaplasia)
  - Intracapsular (no invasion, no myoep cells)
  - Minimally invasive (invasion up to 8mm); >1.5 cm invasion is associated with metastasis







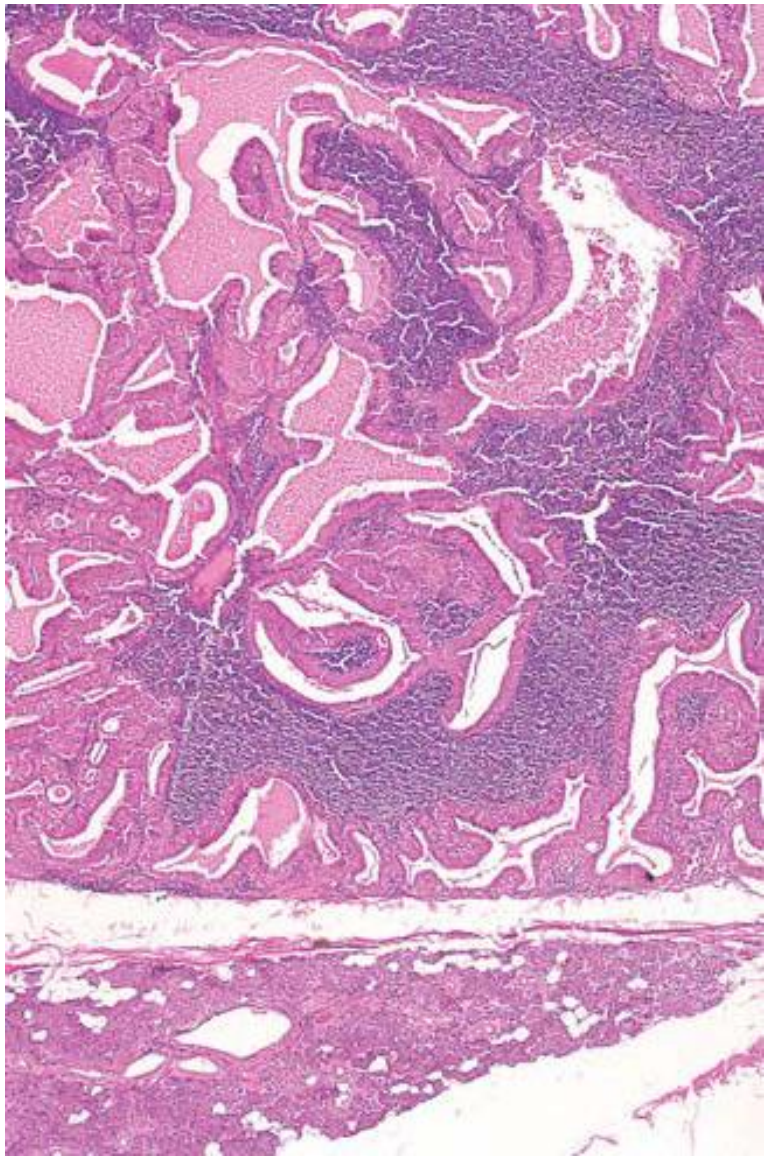


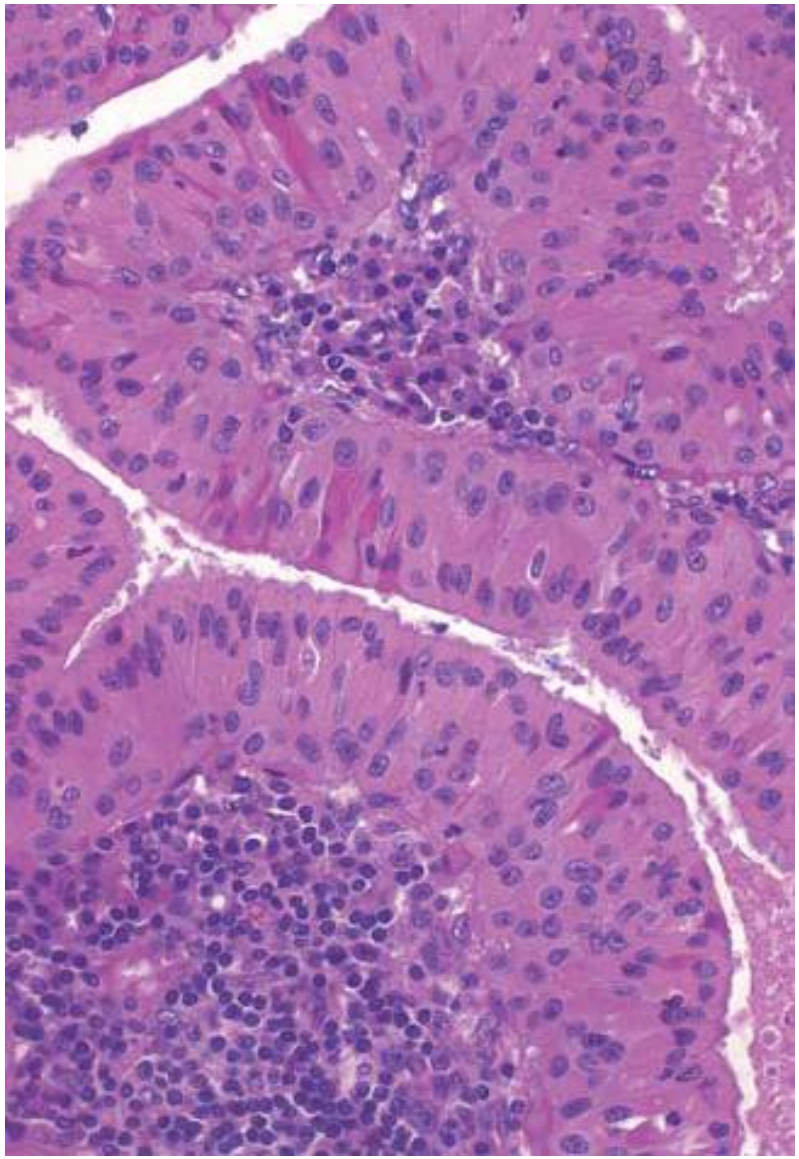


Seethala R. Advances in Anatomic Pathology. 18(1):29-45, January 2011.

Warthin Tumor

- Bilayered columnar and basaloid oncocytic epithelium with extensive follicle containing lymphoid tissue
- Theories:
  - Metaplastic process with secondary lymphoid reaction
  - Heterotopic salivary ducts within lymphoid tissue or lymph nodes
  - Epithelial neoplasm or hyperplastic proliferation with lymphocytic response
- Parotid- bilateral and multifocal tumors
- Papillary cystadenoma lymphomatosum is not recommended because of the potential confusion of the term with other lymphadenomas





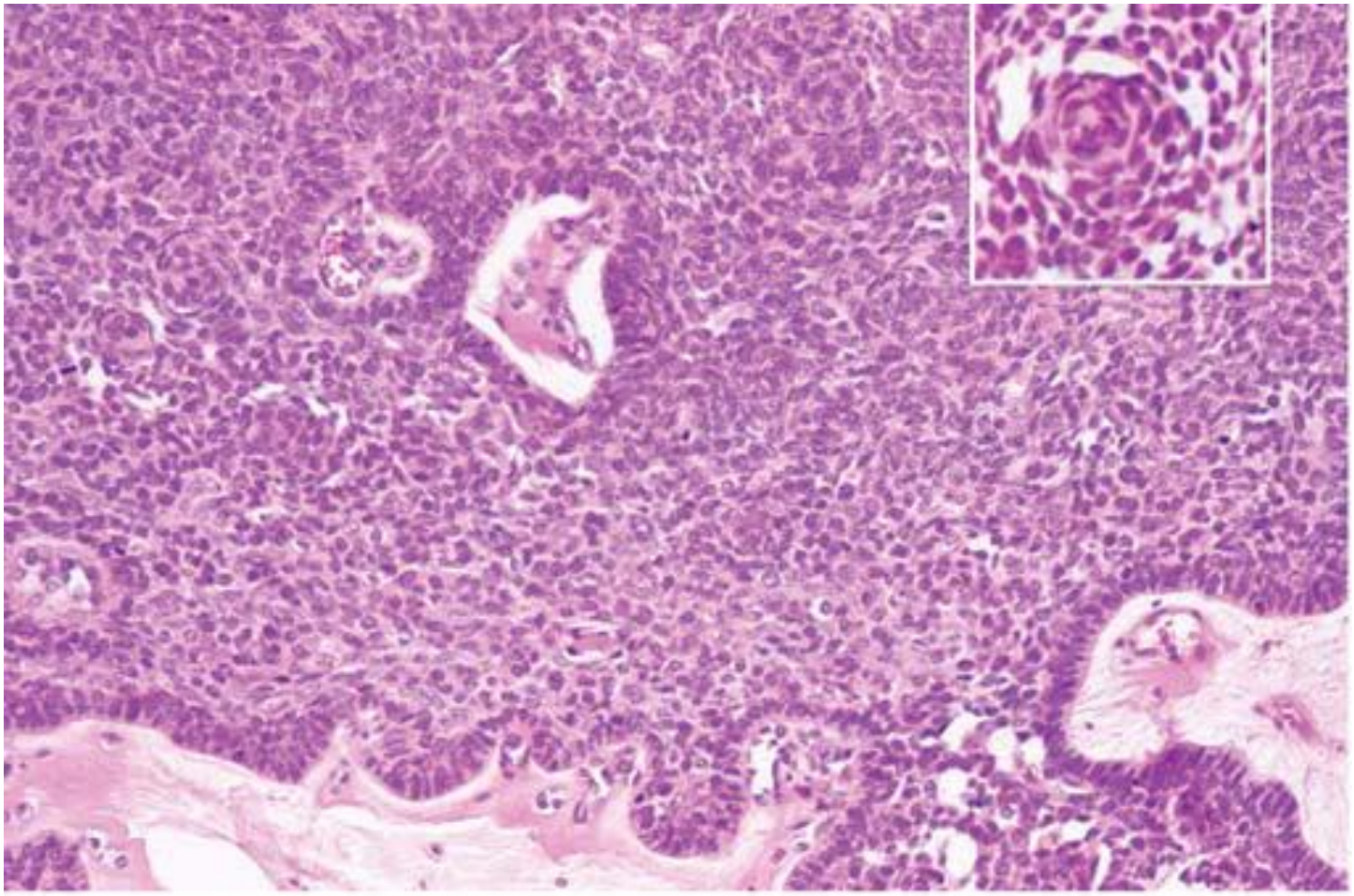
D/D lymphoepithelial cyst

Basal Cell Adenoma

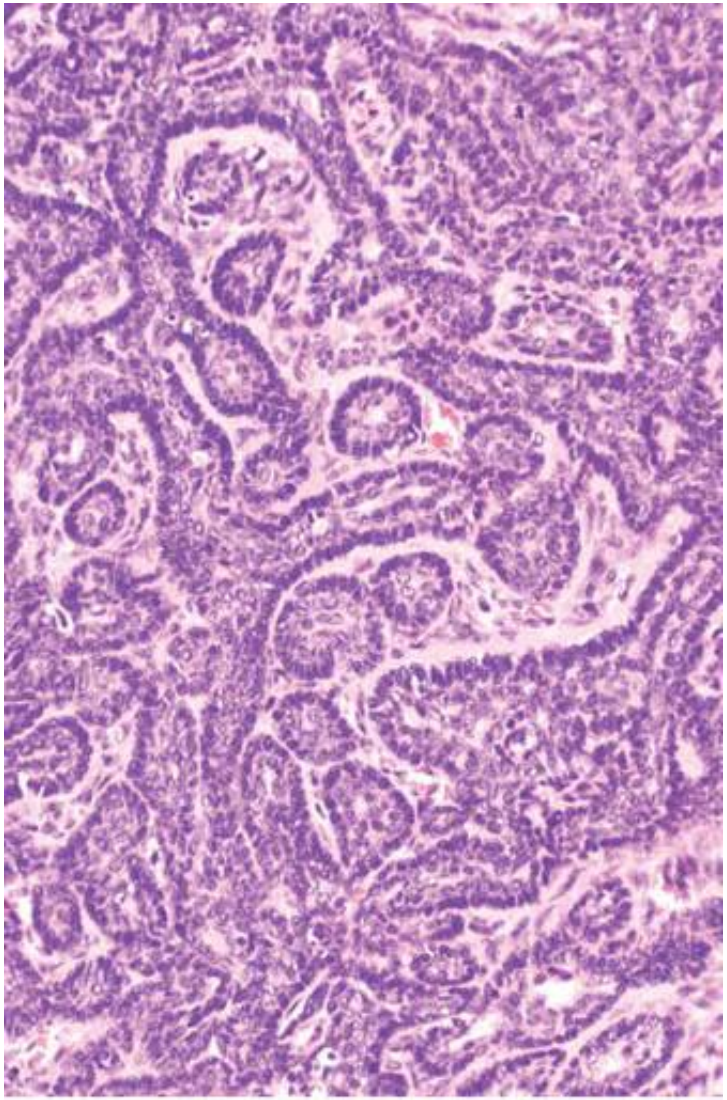
- Monomorphic adenoma (old terminology) – monomorphous proliferation of basaloid cells
  - Varying numbers of basal, ductal, and myoepithelial differentiated cells
- Architecture - Solid, trabecular, tubular, and membranous patterns
- Membranous pattern has a higher recurrence rate

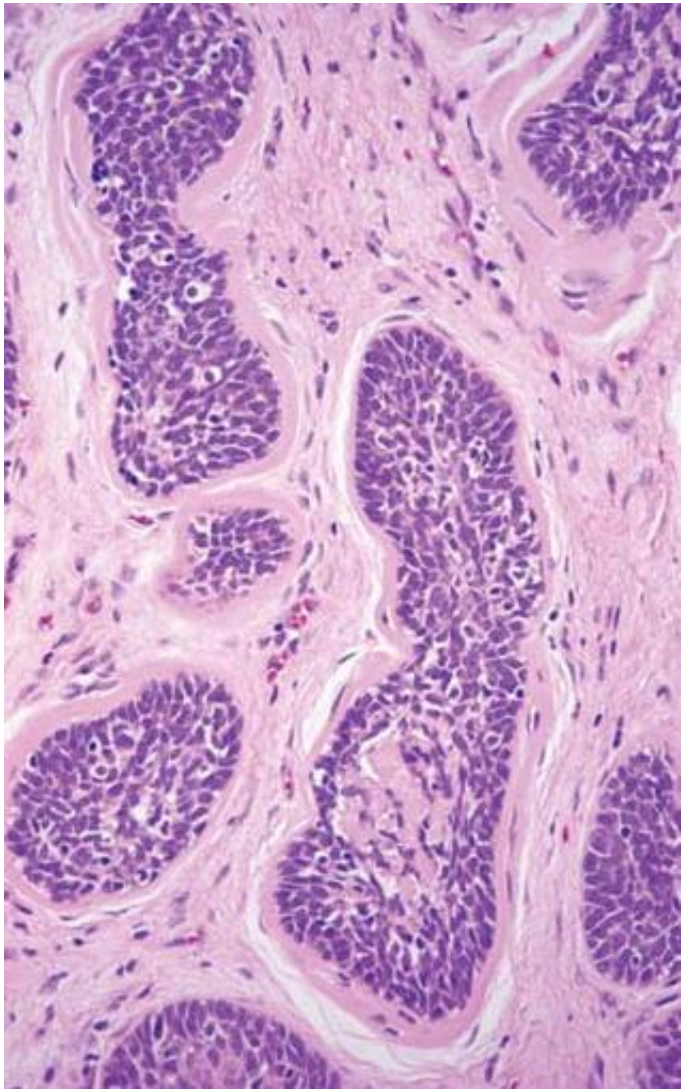
Basal Cell Adenoma

- Basal cell proliferation in a trabecular-type pattern



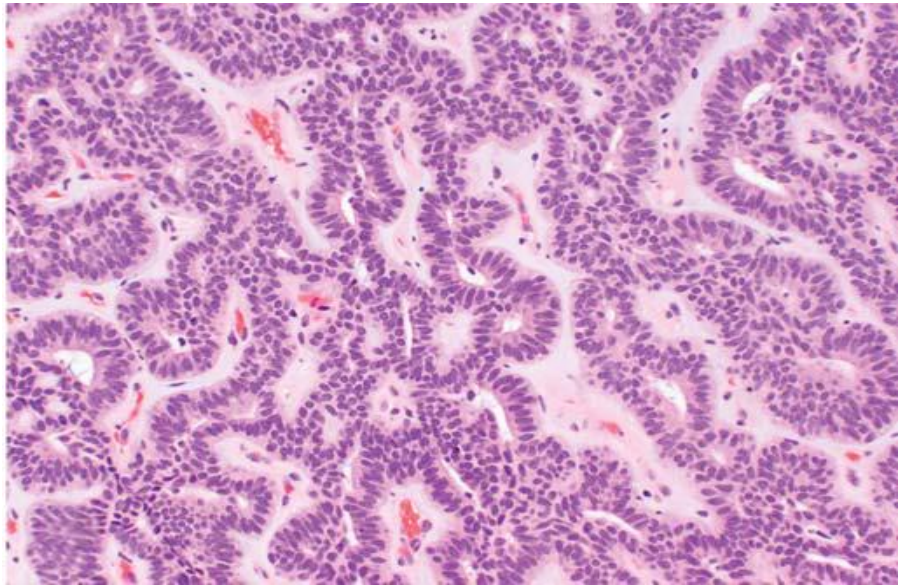
Basal Cell Adenoma

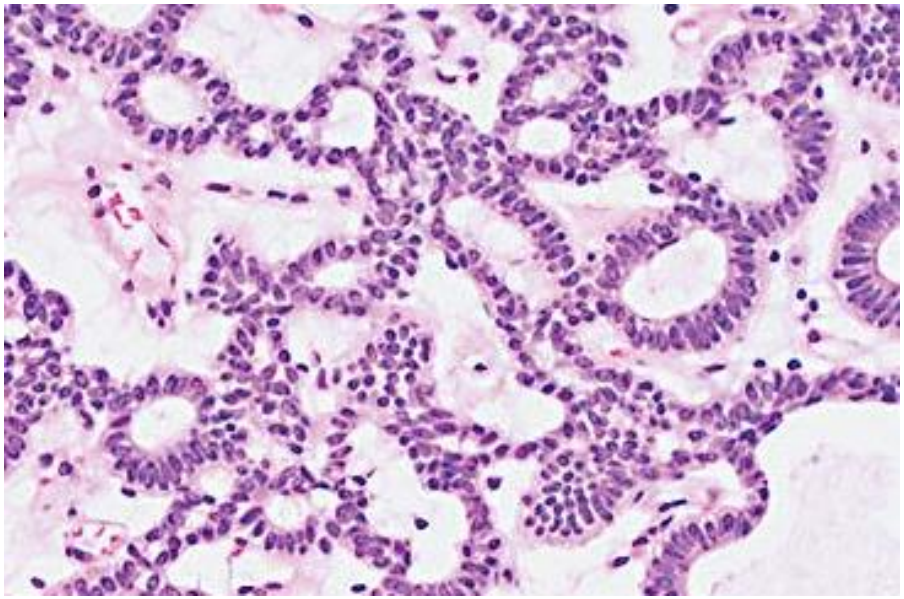




Canalicular Adenoma

- Upper lip and adjacent buccal mucosa, frequently multifocal
- Rows of columnar epithelial cells lining the canaliculi are alternately apposed and separated
- Forming microcysts with “beads on a string” appearance

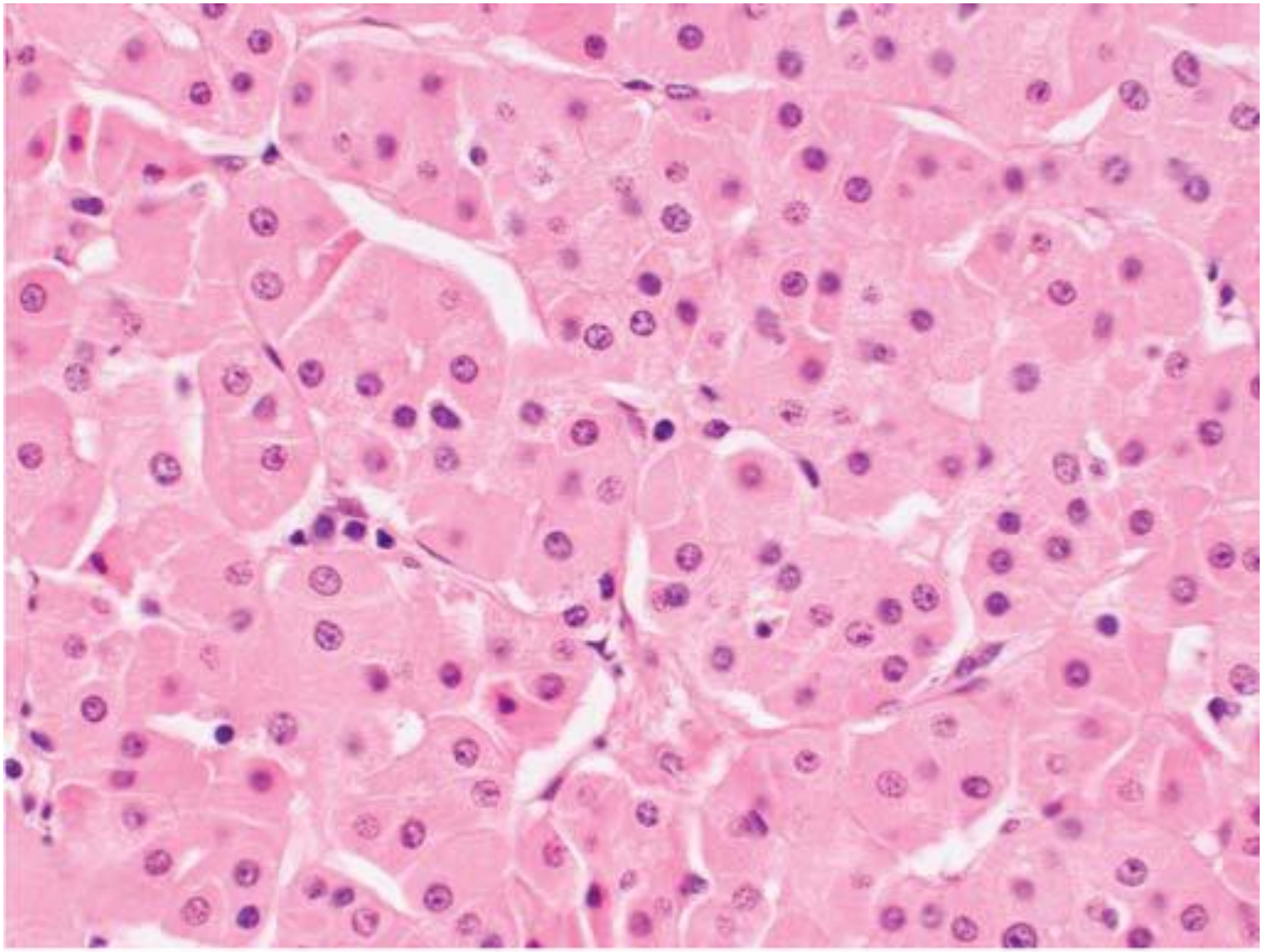




Oncocytoma

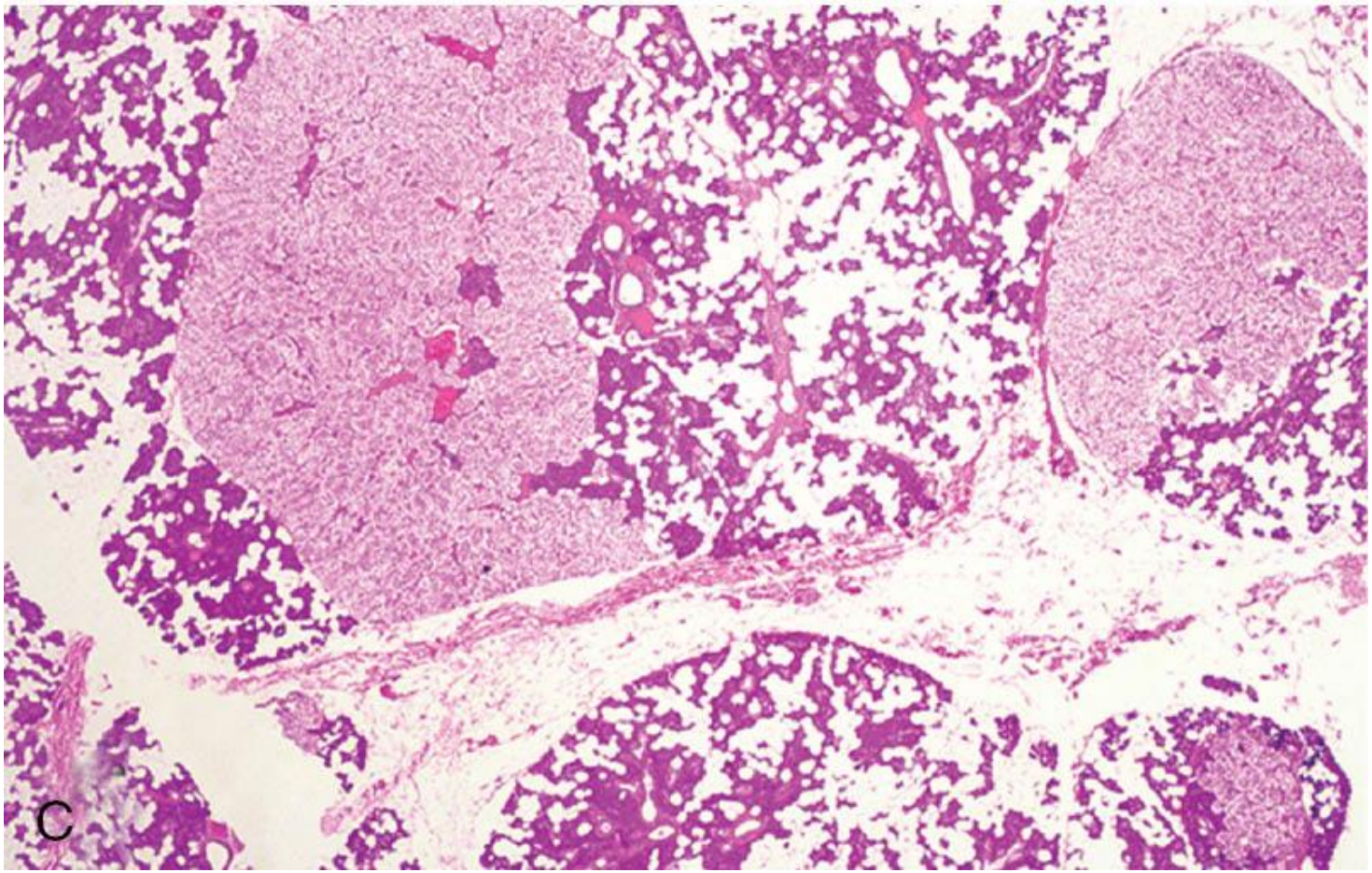
- Oncocytic metaplasia – aging process, older individuals
- Accumulation of atypical mitochondria
  - Accumulations of smooth endoplasmic reticulum, lysosomes, or secretory graduals can mimic the granular cytoplasm
- Clear cells – glucagon accumulation with mitochondria lateral or basilar
- Architecture – organoid, cords, thin fibrous strands
- Many other tumors have foci of oncocytic metaplasia

Oncocytoma



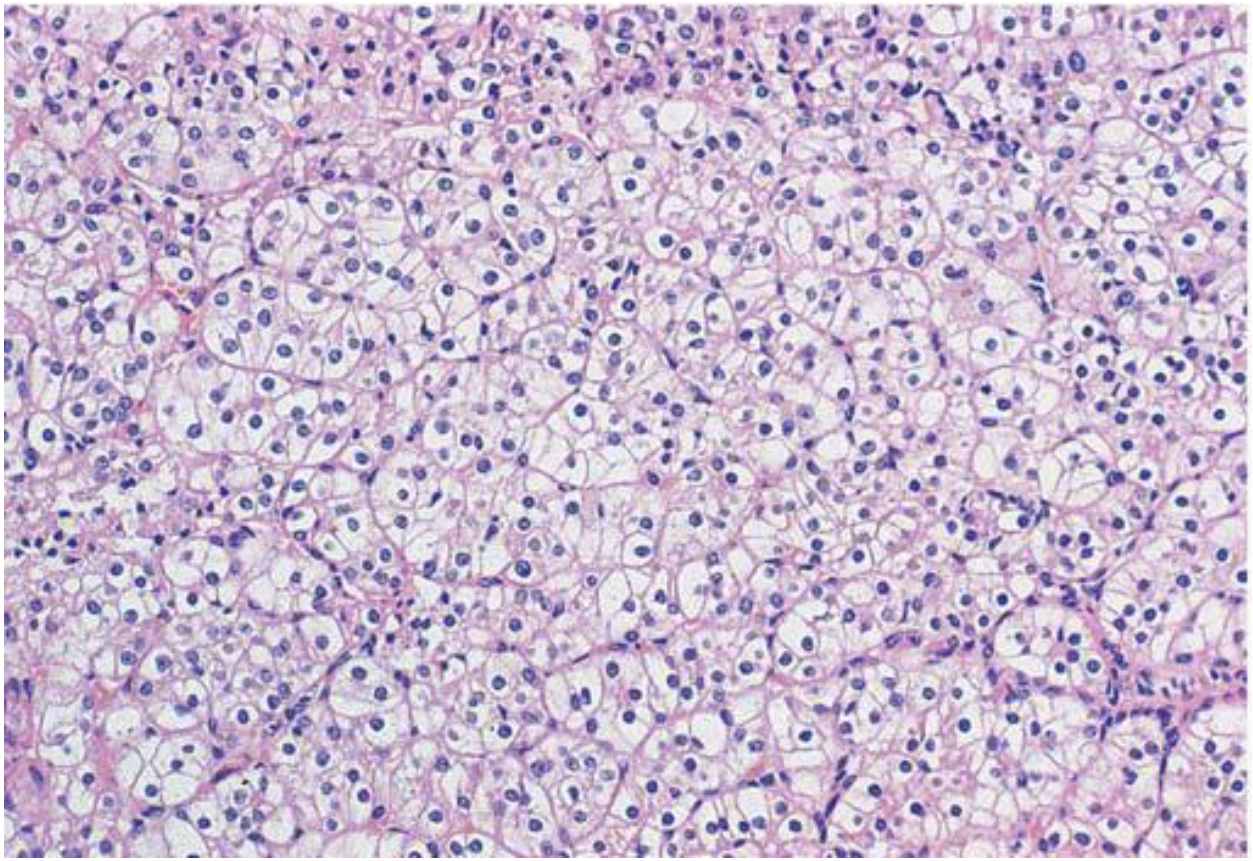
Nodular Hyperplasia (Oncocytosis)

- Nodules scattered amid parotid parenchyma



Oncocytoma

- Oncocytes appearing as clear cells with the mitochondria pushed around the edges of the cytoplasm

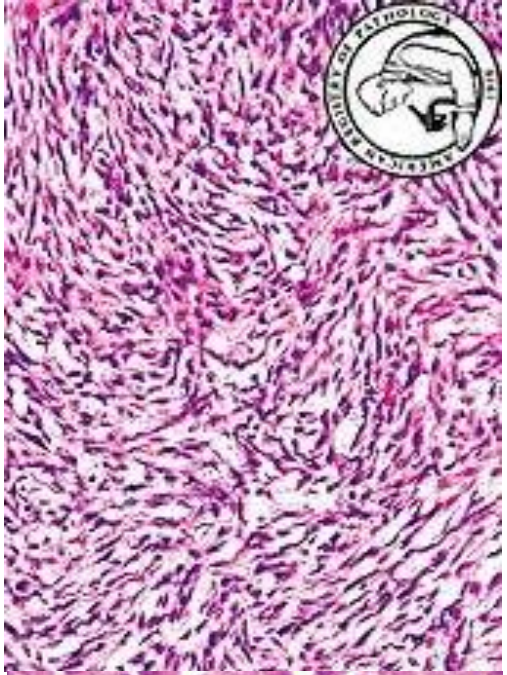


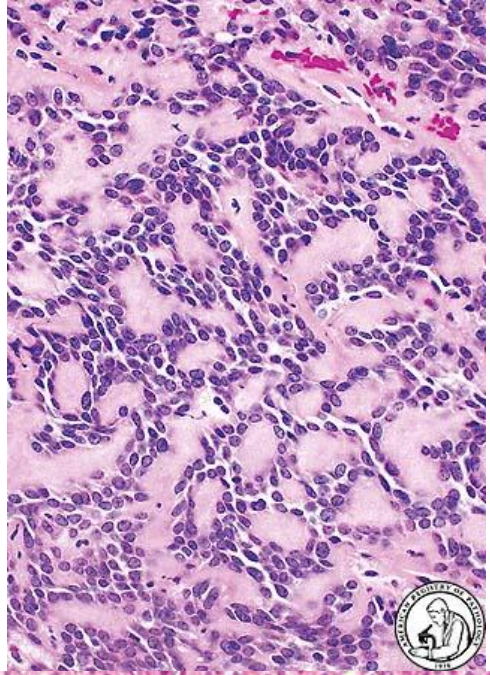
Myoepithelioma

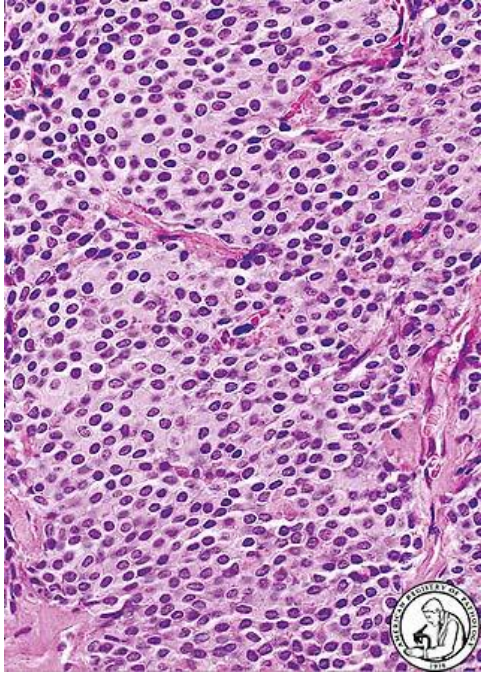
- Differentiated from pleomorphic adenoma by the absence of ductal formation and chondroid component
- Usually hypercellular with amorphous, hyaline or mucoid stroma
- Spindle, epithelioid, plasmacytoid cell variance
- Variety of architectural patterns

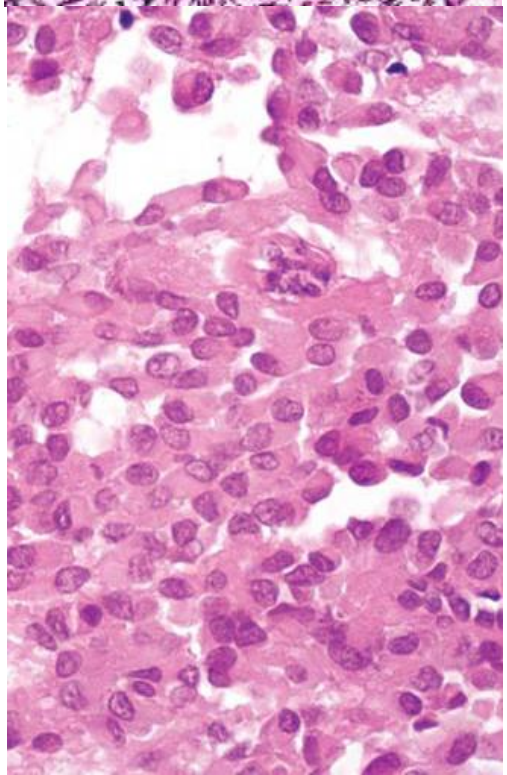
Myoepithelioma

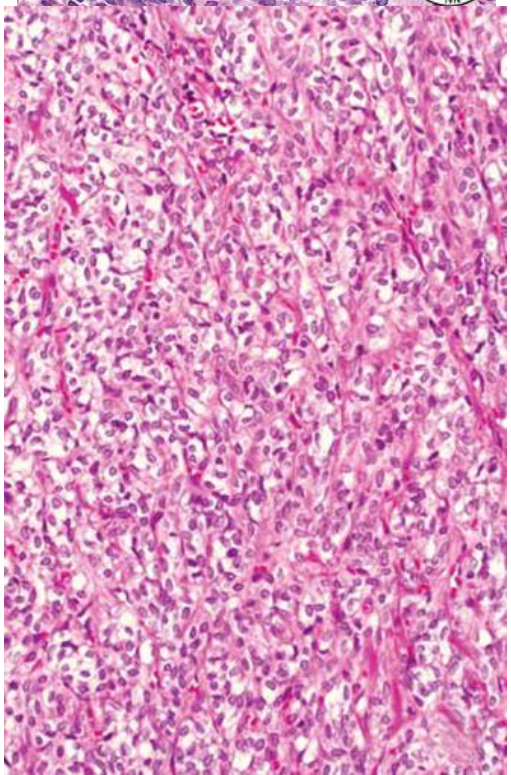
- Well circumscribed nodule

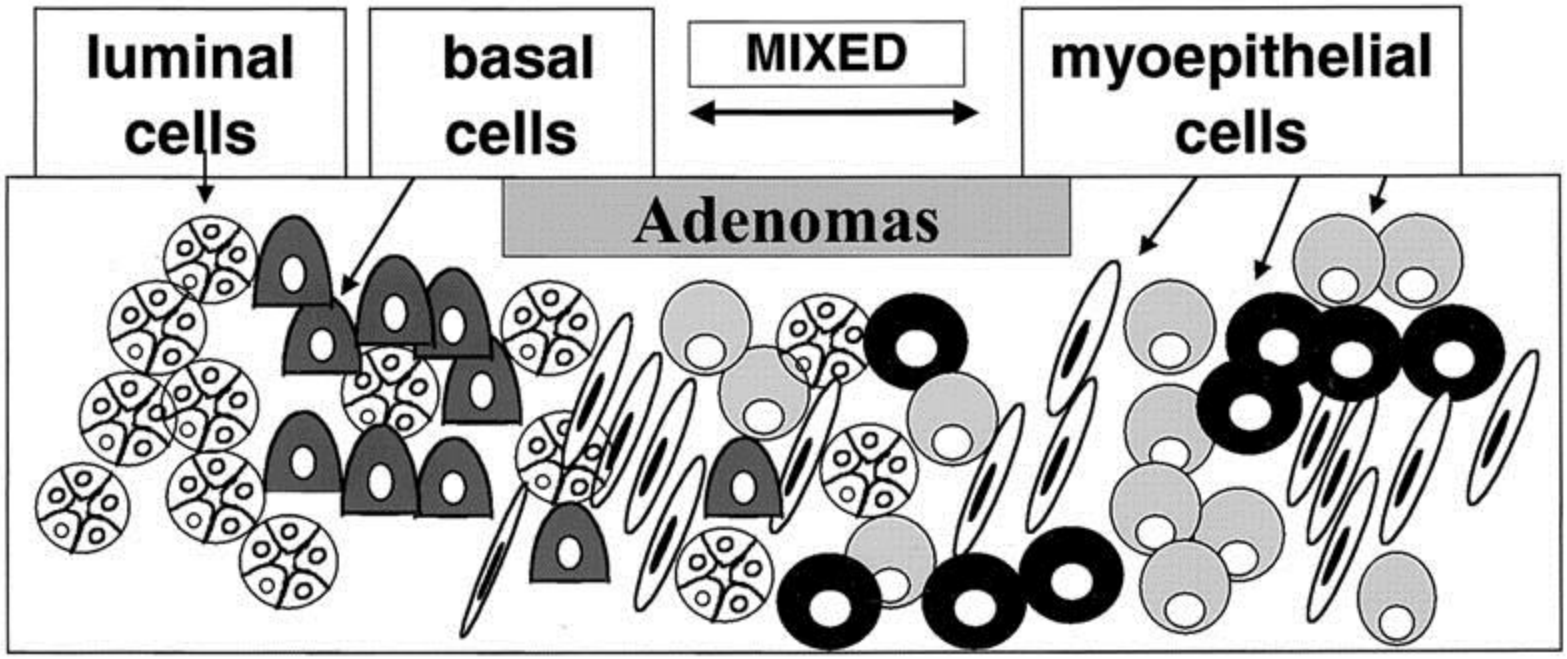












canalicular adenoma

myoepithelioma

pleomorphic adenoma

basal cell adenoma

cellular / myoepithelial predominant pleomorphic adenoma

Zarbo RJ, *Mod Pathol 2002;15(3):298–323*

Sebaceous Adenoma & Sebaceous Lymphadenoma ~ Rare

- Sebaceous cells are normally seen in the parotid as well as in the oral mucosa and less frequently in the submandibular gland

- Sebaceus Adenoma – squamous epithelial nests with some sebaceus differentiation in a fibrous stroma

- Sebaceous Lymphadenoma – dense lymph node stroma with germinal follicles and nests of squamous epithelium, sometimes sebaceus differentiation

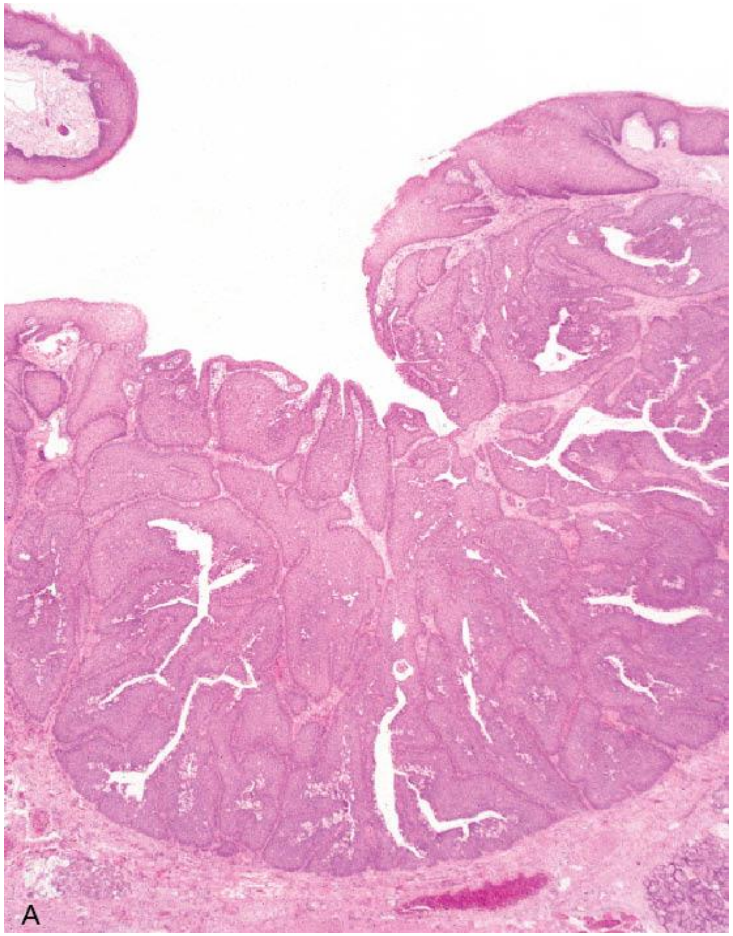
Cystadenoma

- Frequently in the parotid gland, circumscribed, usually small columnar lined cysts, frequently lacking intervening stroma

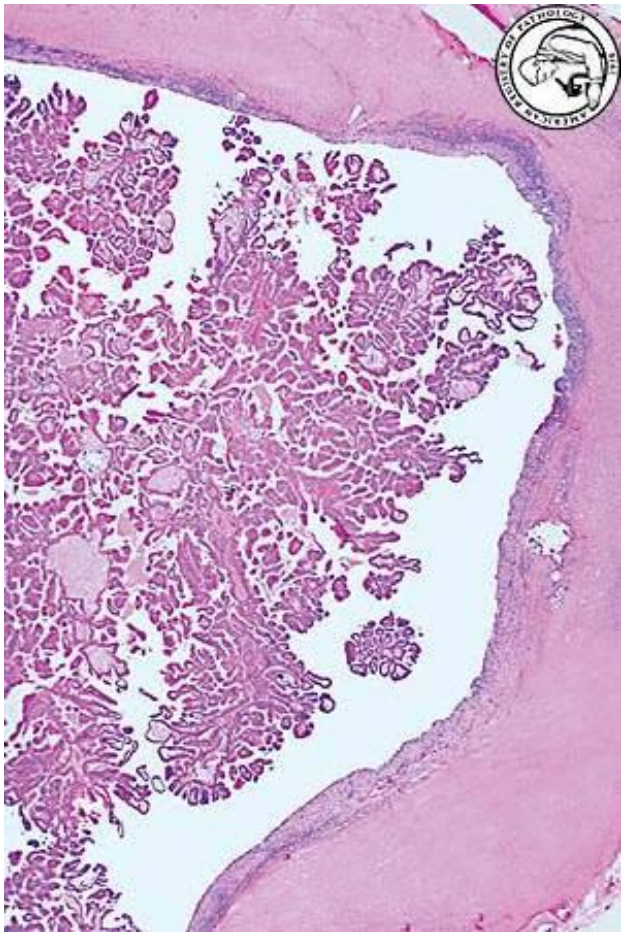
- Maybe unicystic and papillary, contains small ductal structures, lining cell hyperplasia and varying cell types

Ductal Papillomas

Inverted ductal papilloma

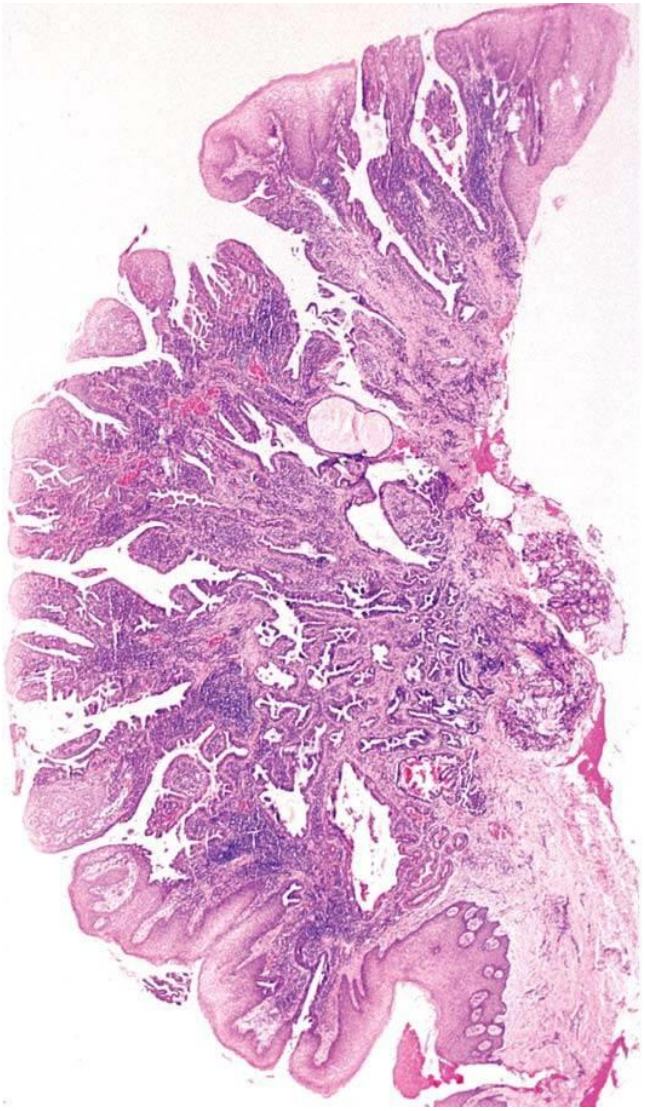


Intraductal papilloma



Sialadenoma Papilliferum

- Benign rare exophytic (papillary squamous) and endophytic (salivary duct) proliferation of the oral squamous mucosa



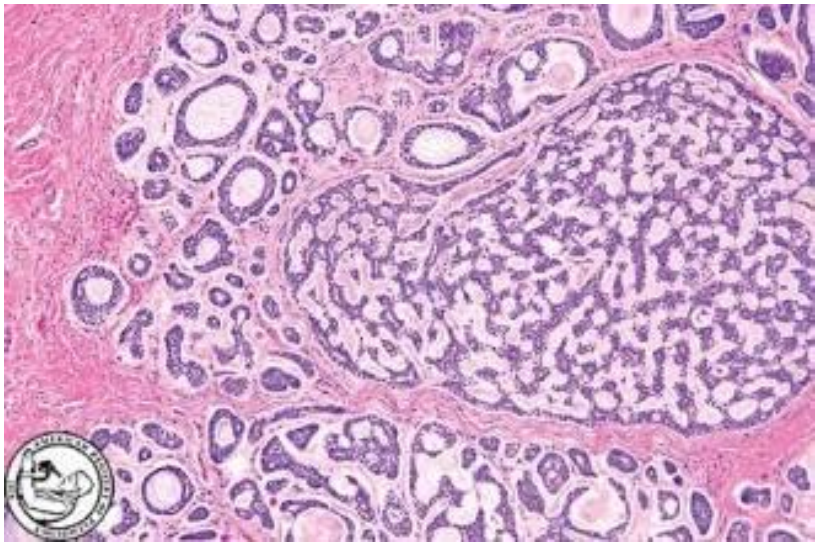
Salivary Gland Tumors
Malignant

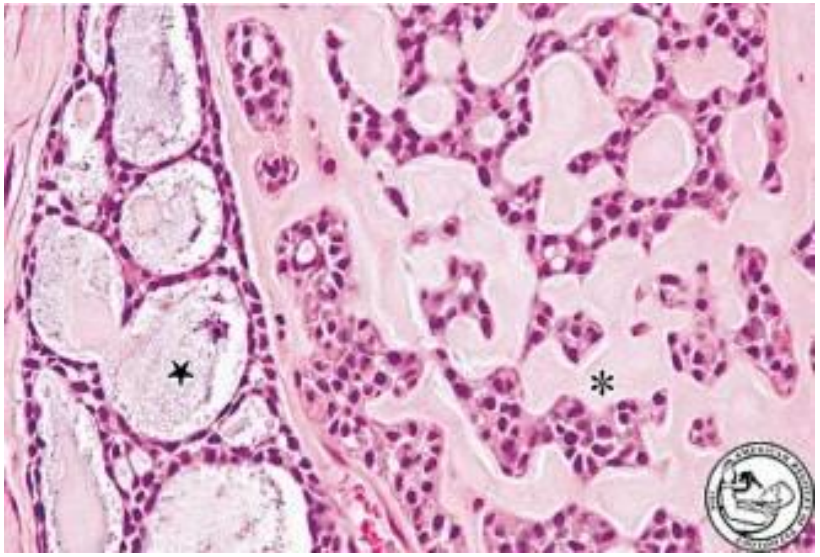
Adenoid cystic carcinoma

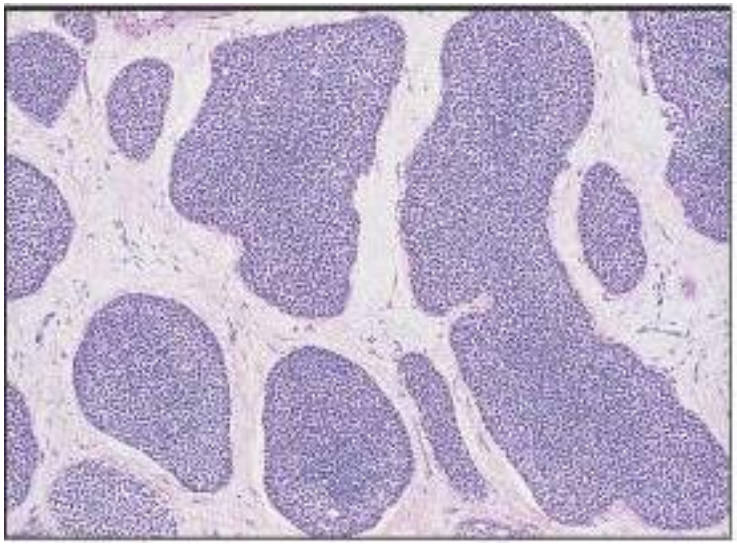
- 10% of all and 30% of minor salivary gland tumors
- 10-20% 10-yr survival and 30% 5-yr survival
- Metastases to lung, brain, bone, liver
- Outcome depends on histology, clinical stage and recurrences

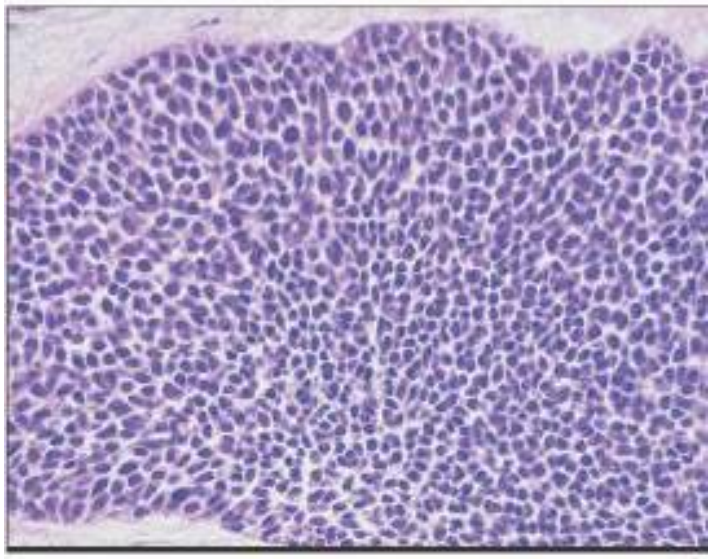
- Myoepithelial cells
  - Angulated hyperchromatic nuclei
  - Clear cytoplasm
  - Molding
- Ductal cells
- Spaces with matrix
  - Mucopolysaccharide that could be hyalinized, mucoid or myxoid
- Growth patterns
  - Tubular, cribriform and solid (more aggressive)
- t(6;9) MYB-NFIB fusion transcripts (MYB IHC)

Adenoid Cystic Carcinoma









Grade	Perzin et al[41] and Szanto et al[42]	Grade	Spiro and Huvos[39]
1	Predominantly tubular, no solid component	1	Mostly tubular or cribriform (no stipulations on minor solid components)
2	Predominantly cribriform, solid component < 30% acceptable		
3	Solid component > 30%		
		2	50% solid
		3	Mostly solid

Seethala,R. Advances in Anatomic Pathology. 18(1):29-45, January 2011.

Ad CC Pattern based D/D

Solid

- Basal cell ADC (no chondromyxoid matrix)
- Basaloid SqCC (in-situ component and keratinization)
- High grade NEC

Tubular/cribriform

- PA
- PLGA
- EMC
- Other clear cell neoplasms

Polymorphous Adenocarcinoma

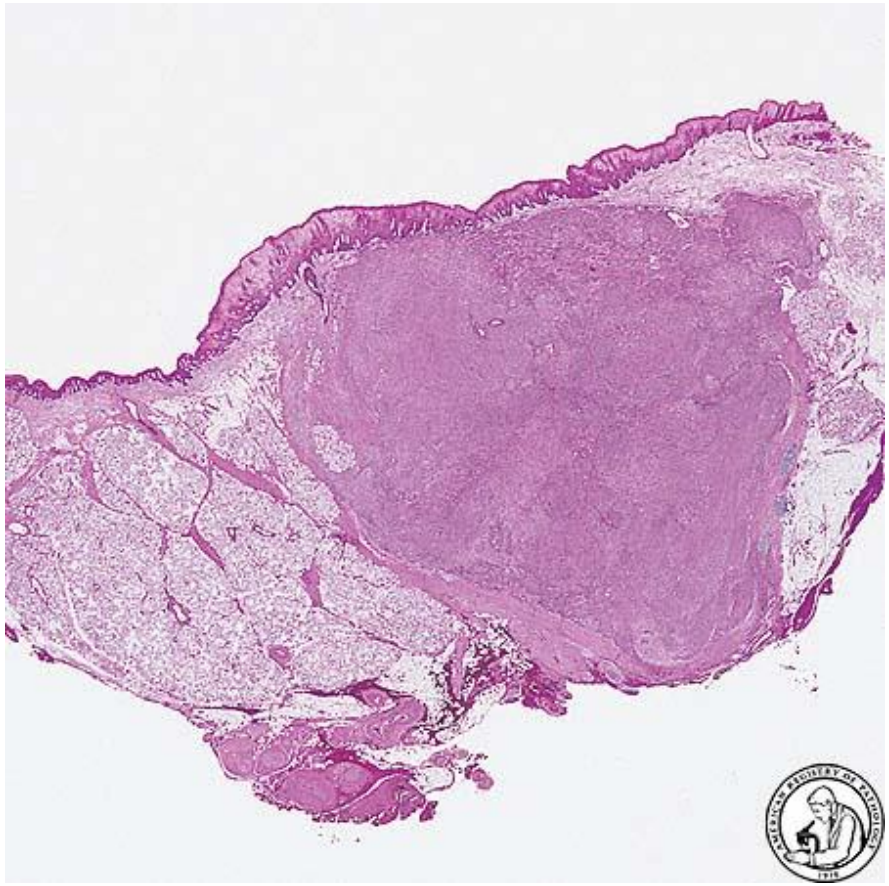
- Classic location in the palate

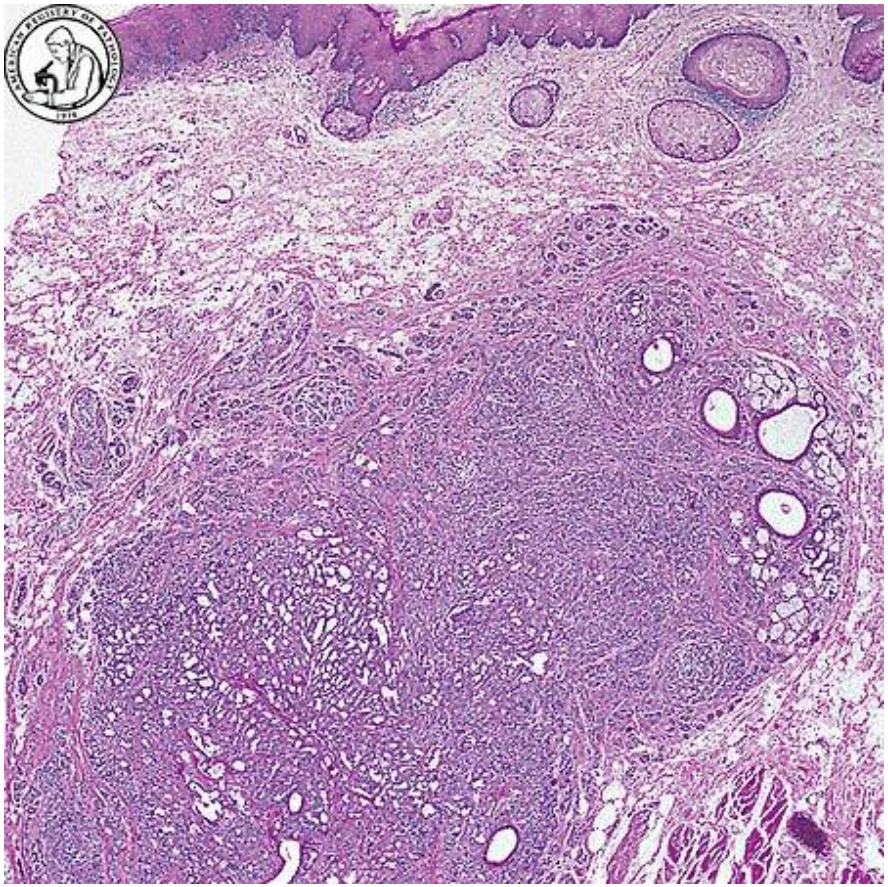
Polymorphous Adenocarcinoma

- Low grade minor salivary gland tumor of the palate, buckle mucosa, and lip
  - Bland cells forming tubules and ducts in a variety of growth patterns
- The tumor has the highest frequency of perineural invasion of any salivary gland tumor and common perivascular invasion
- Some patients have recurrences after many years but distant metastasis is rare

Polymorphous Adenocarcinoma

- Low power showing partially circumscribed but unencapsulated tumor

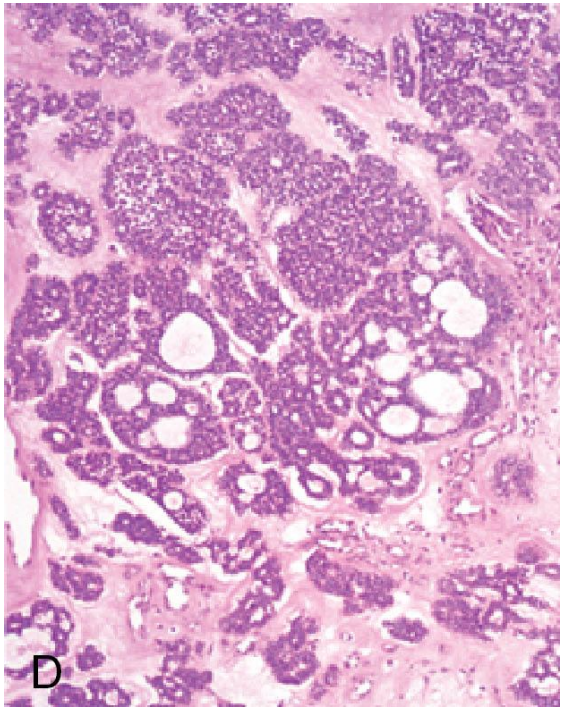




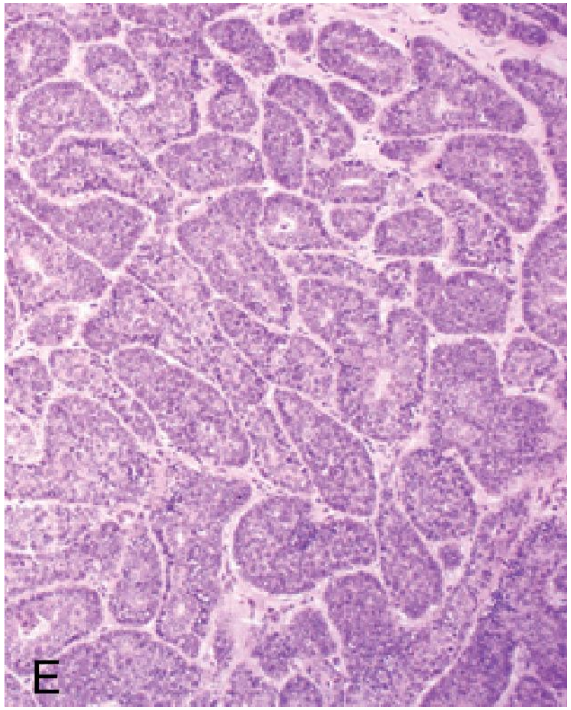
Polymorphous Low-Grade Adenocarcinoma

Patterns

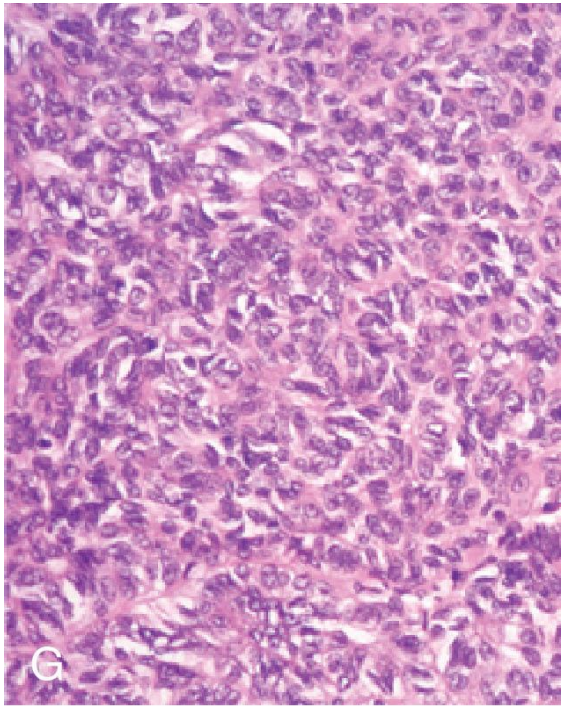
- Cribriform



- Solid



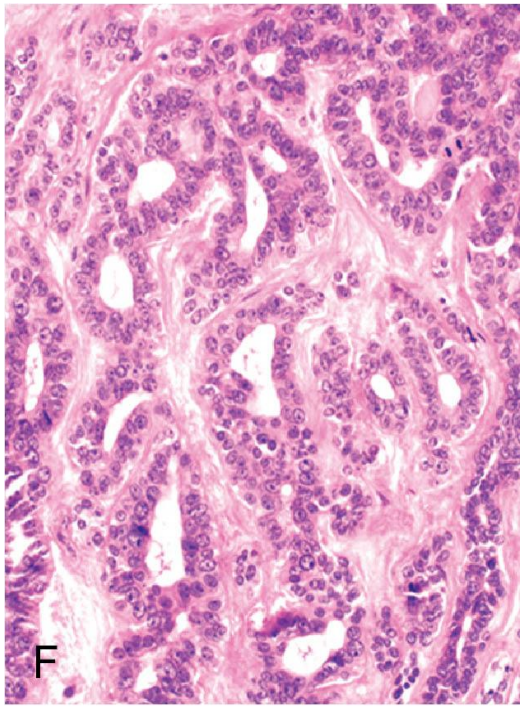
- Solid



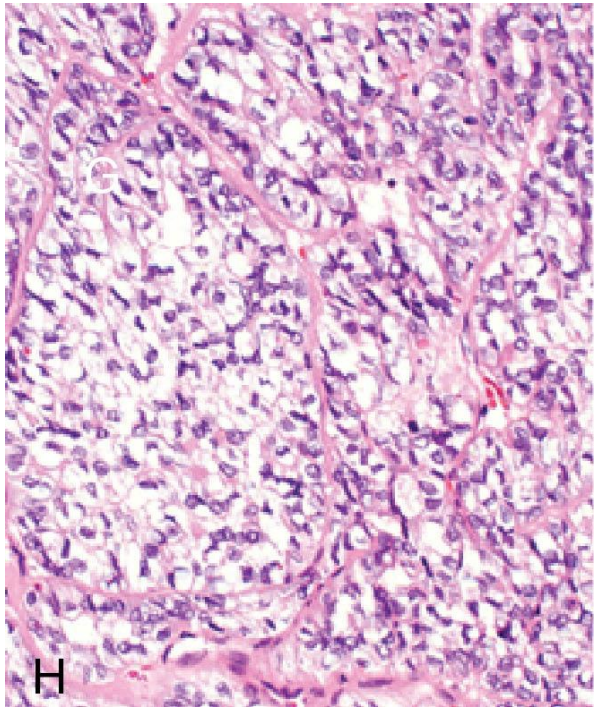
Polymorphous Low-Grade Adenocarcinoma

Patterns

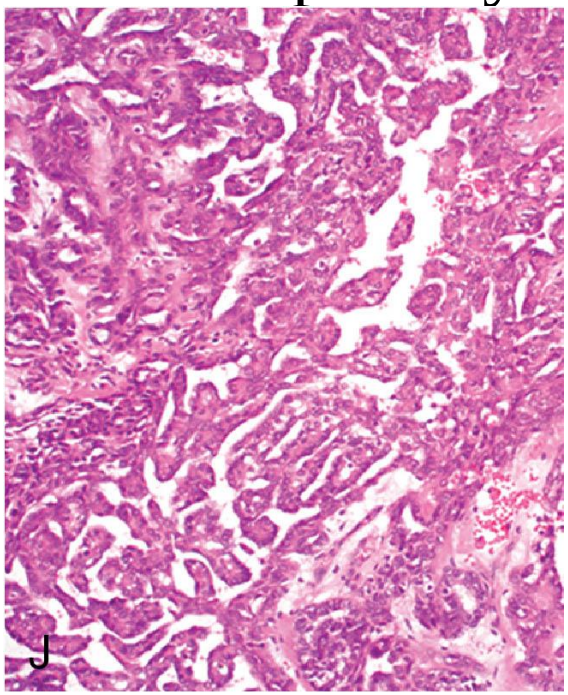
- Ductal



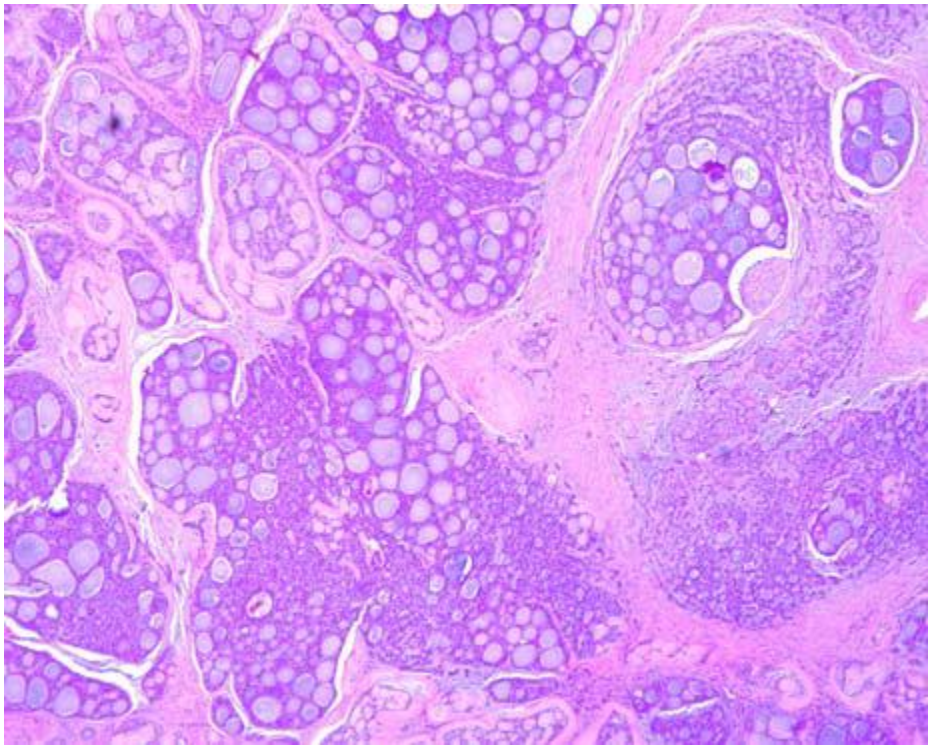
- Clear Cell

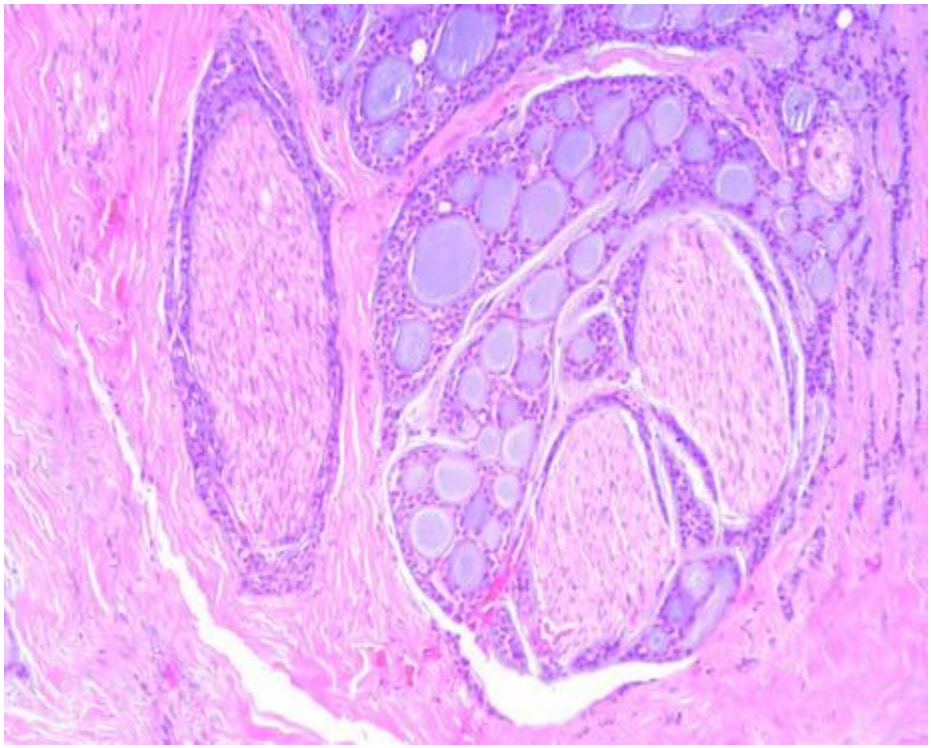


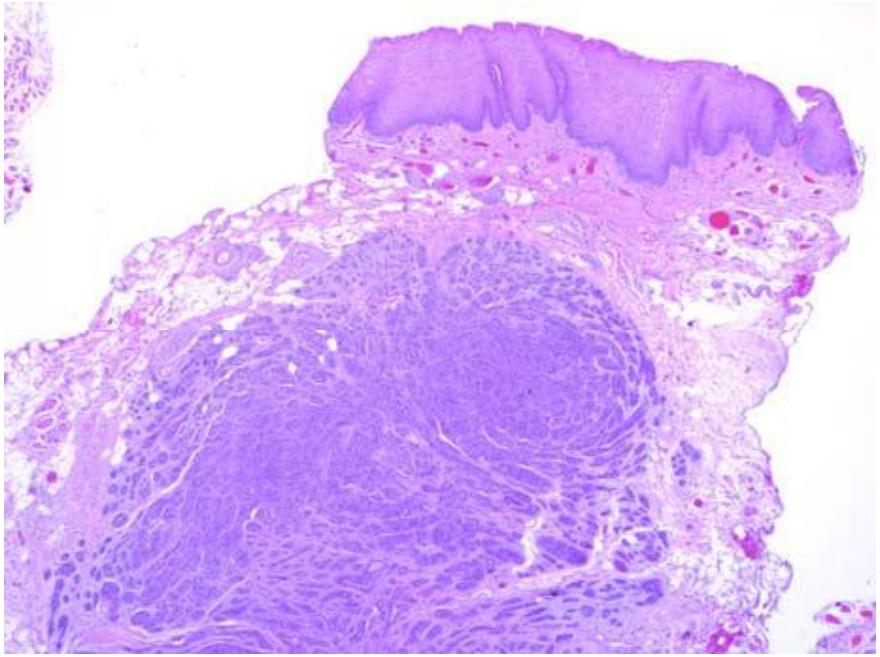
- Micropalliary

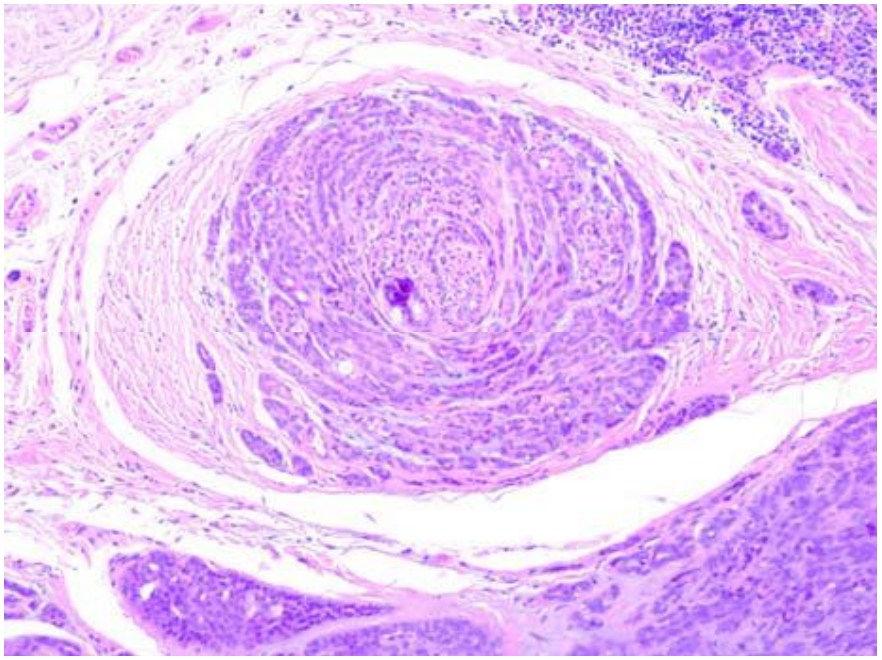


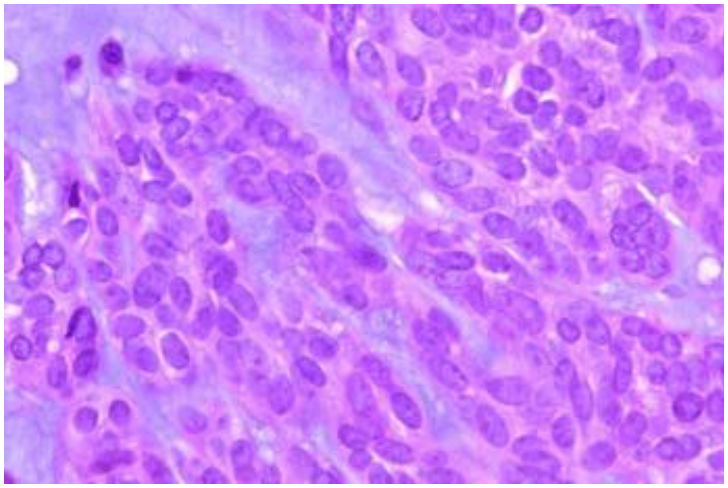
PLGA or ADCC

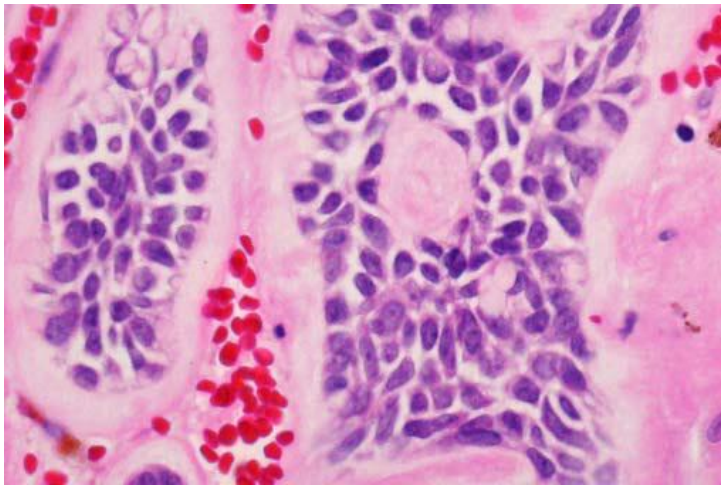










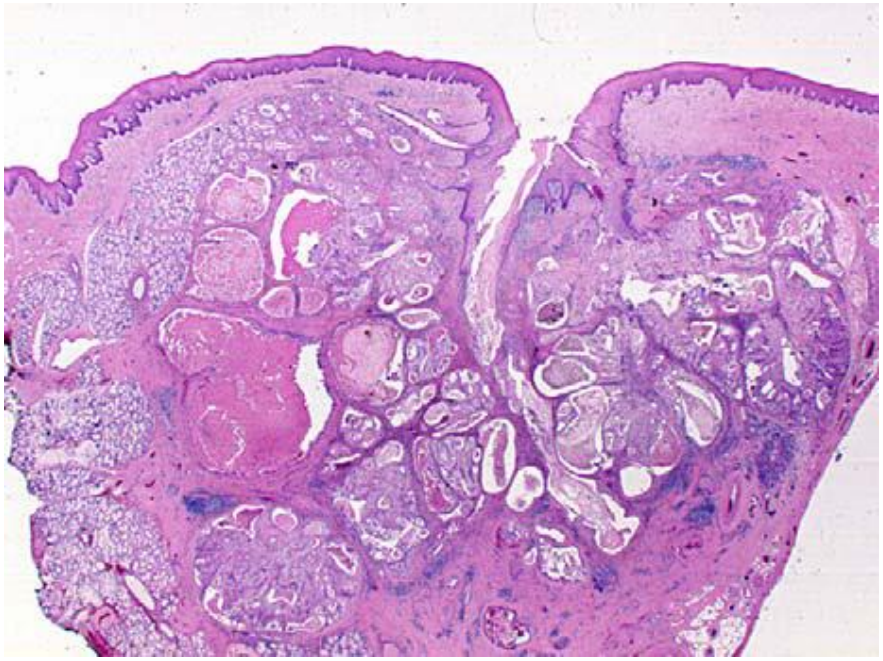


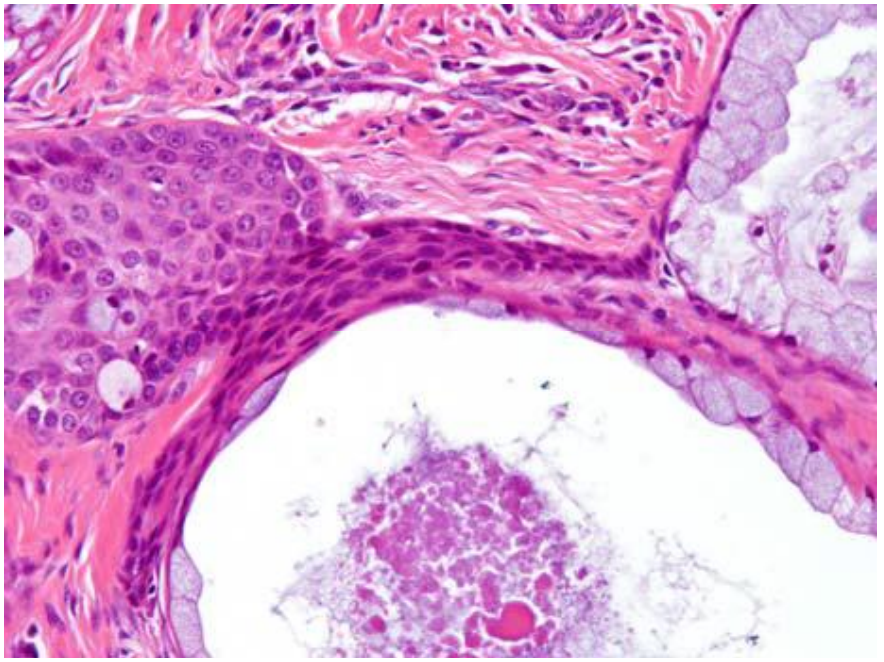
Mucoepidermoid Ca

- Most common malignancy in both adults and children
- Major:minor glands 50-50
- About 10% mortality
- Histologic grading has prognostic significance (low grade 98% and high grade 60% 5-yr survival)

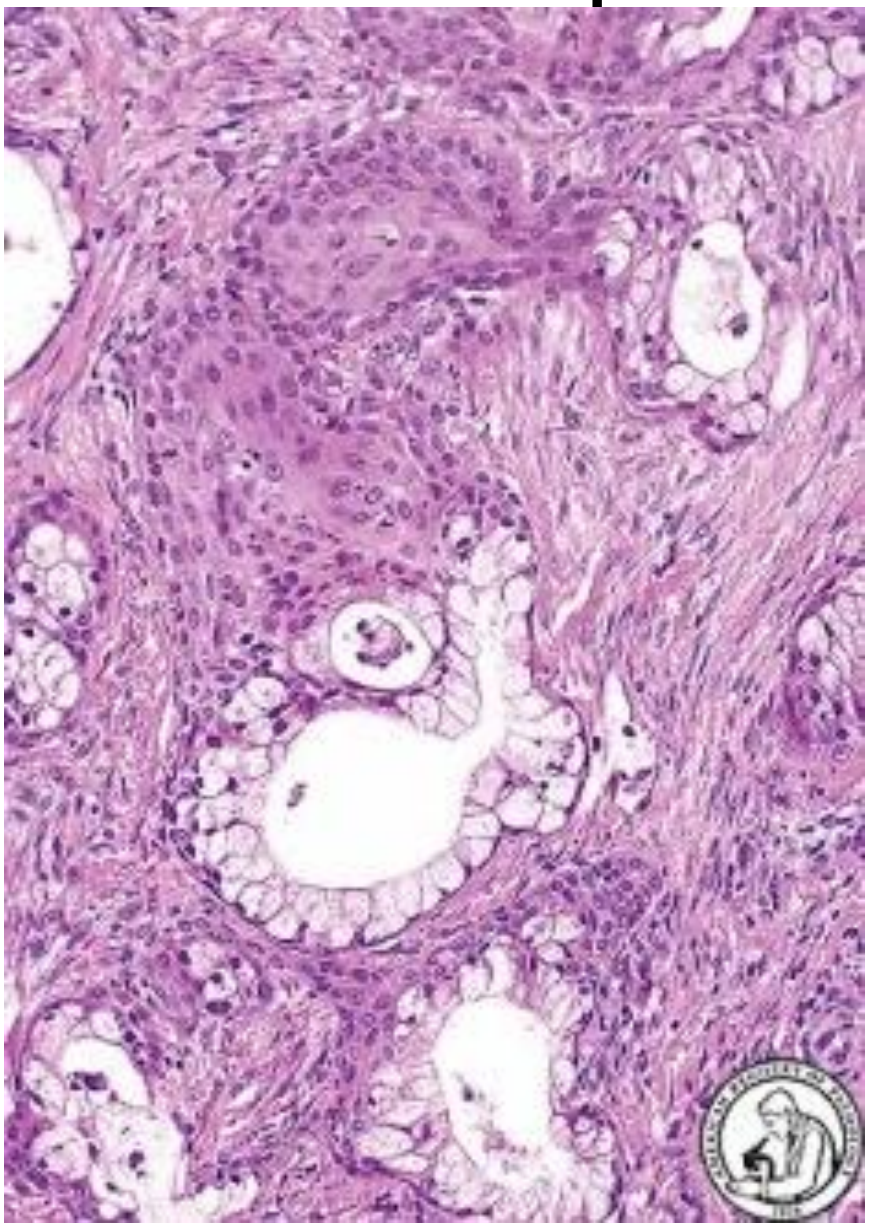
- Cell types: mucinous, squamous, intermediate

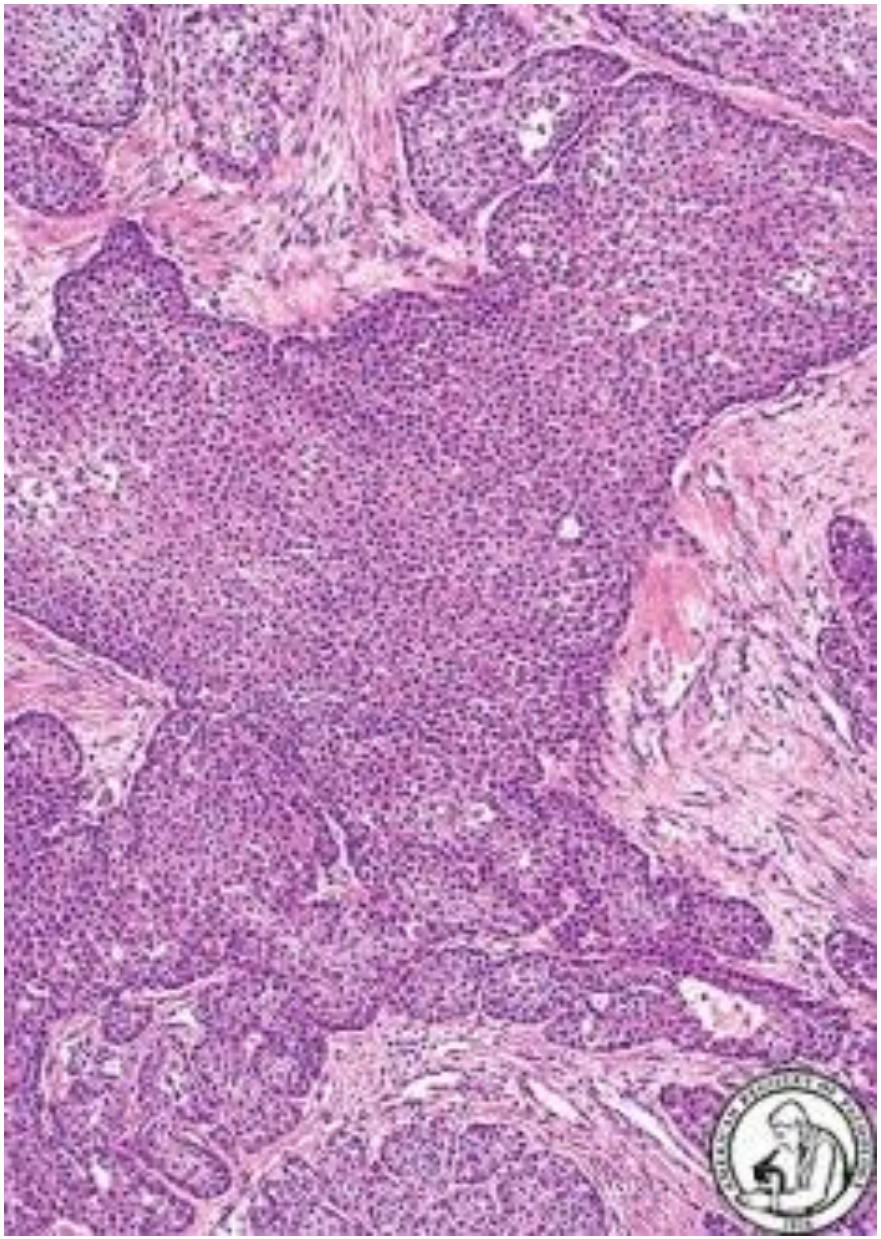
  Oncocytic, Clear cell
- t(11;19) MECT1-MAML2
- High grade MEC D/D
  - SqCC (keratinization)
  - Salivary duct Ca (papillary or cribriform growth, necrosis)
  - Ca-ex-PA
  - Metastases



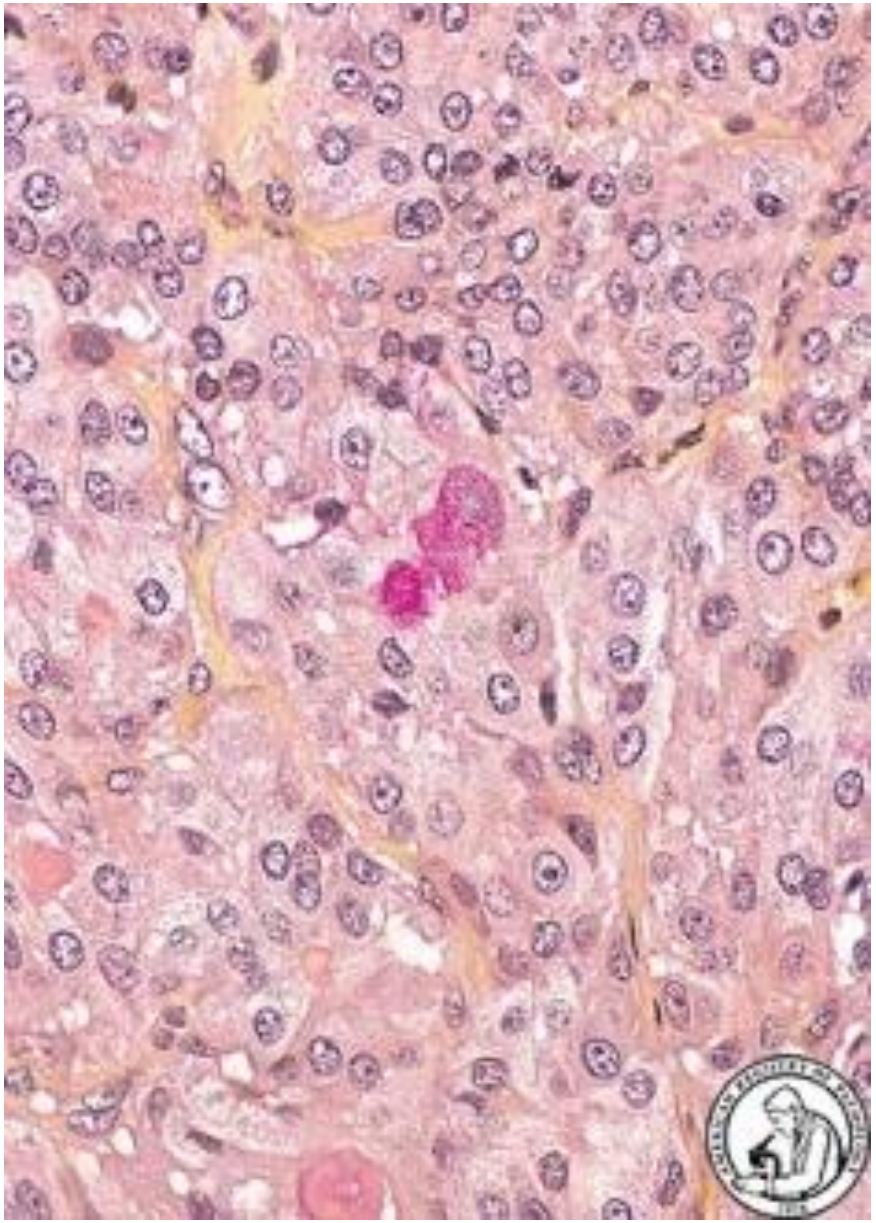


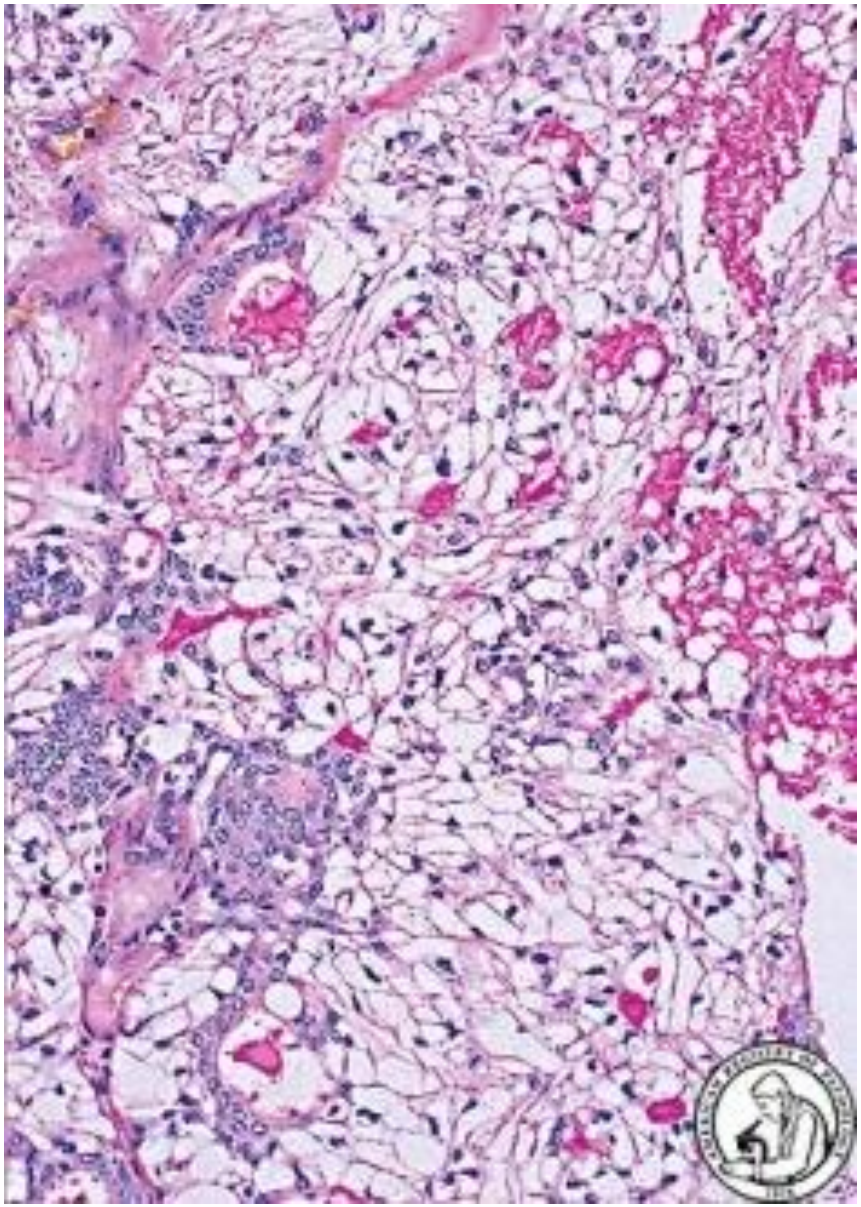
Mucoepidermoid Carcinoma





Mucoepidermoid Carcinoma



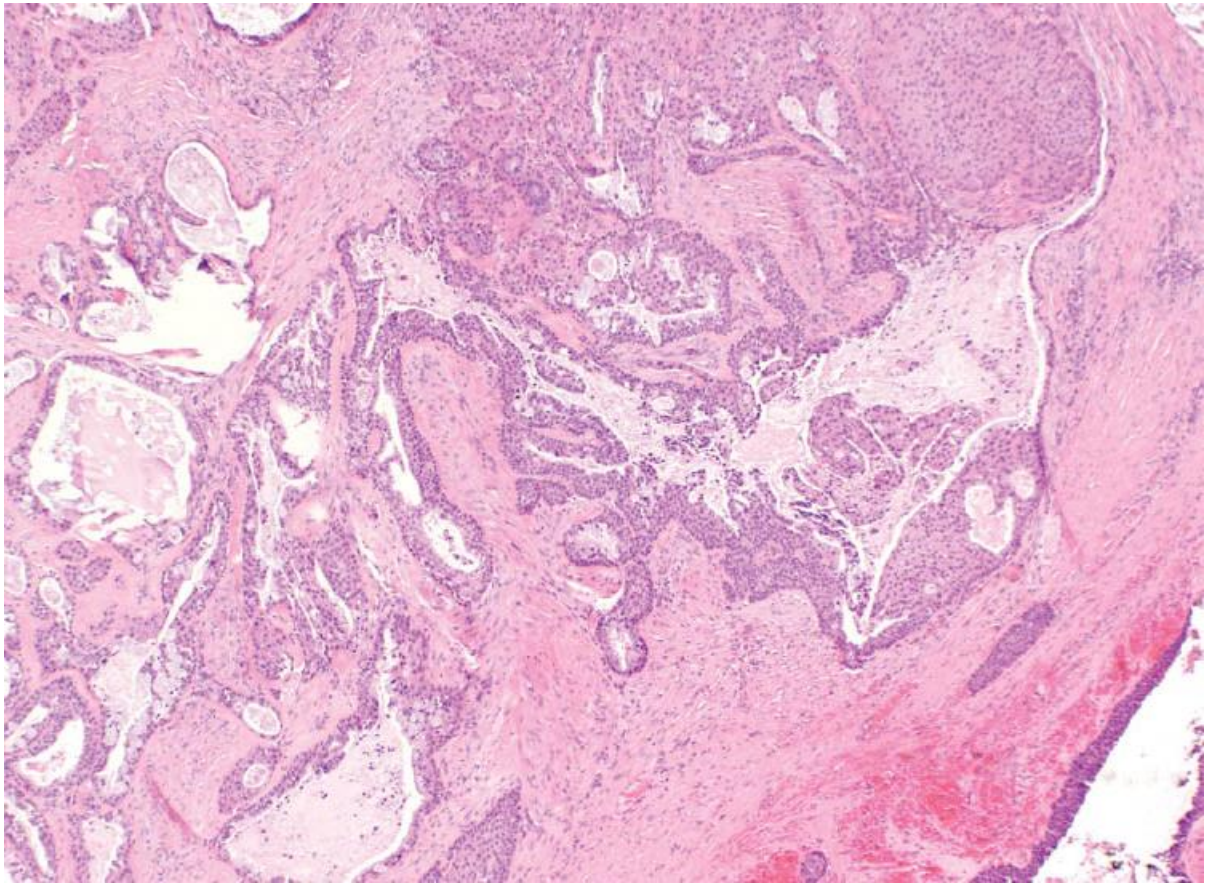


Mucoepidermoid Carcinoma

- Grading is related to behavior and prognosis with low-grade having a good prognosis and high-grade having a poor prognosis
  - Submandibular gland tumors are the exception as they are more aggressive including those with low-grade histology
- The intermediate grade has a prognosis similar to low grade
  - This category allows for inter-observer variation and does not require division between low and high grade based on a single feature

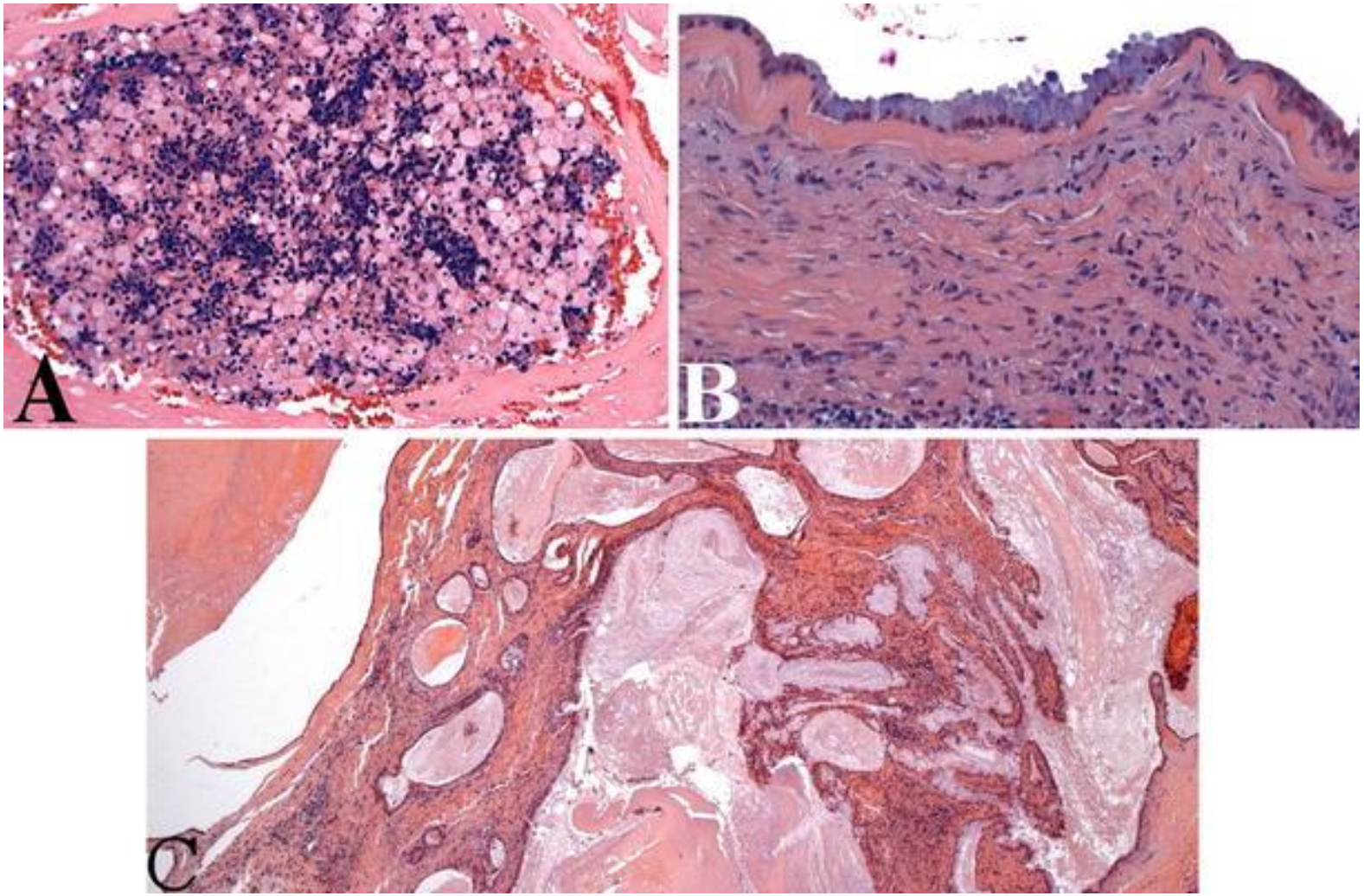
Mucoepidermoid Carcinoma
Low Grade

- Prominent cystic component



AFIP	***Points***	***Modified criteria, Brandwein 2001***	***Points***
Cystic component <20 %	+2	*Cystic component <25 %*	+2
Perineural invasion	+2	*Perineural invasion*	+2
Necrosis	+3	*Necrosis*	+3
≥4 mitoses/10 HPF	+3	*≥4 mitoses/10 HPF*	+3
Anaplasia	+4	*Anaplasia*	+4
		LVI	+3
		Aggressive pattern of invasion	+2
		Bony invasion	+3
Low-grade	**0-4**	***Low-grade***	**0**
Intermediate-grade	**5-6**	***Intermediate-grade***	**2, 3**
High-grade	**7-14**	***High-grade***	**≥ 4**

Missed diagnoses



FISH for MAML2 rearrangement

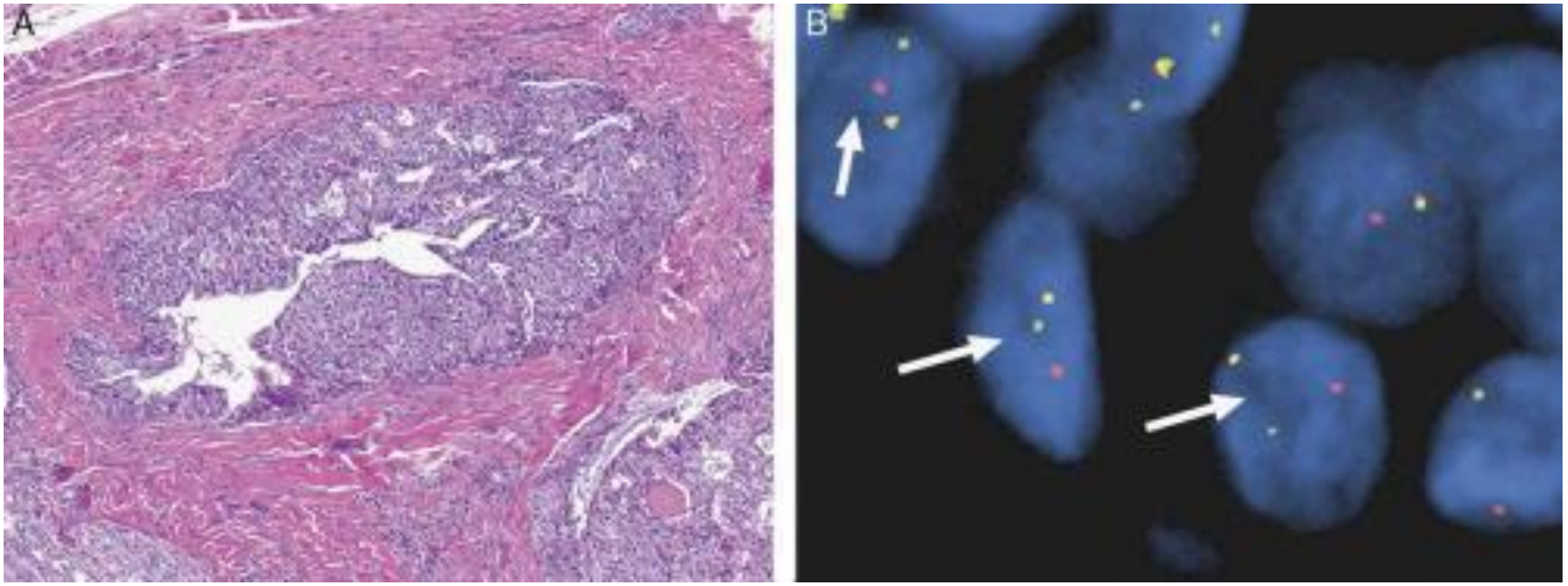


FIGURE 6 . FISH for MAML2 rearrangement detection using breakapart probes. A, Intermediate grade mucoepidermoid carcinoma (hematoxylin and eosin, 100x). B, By FISH, the cells (arrows) demonstrate 1 intact MAML2 copy indicated by juxtaposition of the fluoroisothiocyanate (green) and specrum orange (red)-labeled probes (yellow signal), and 1 split copy resulting in the separation of the red and green signals within the cell. FISH indicates fluorescence in-situ hybridization.

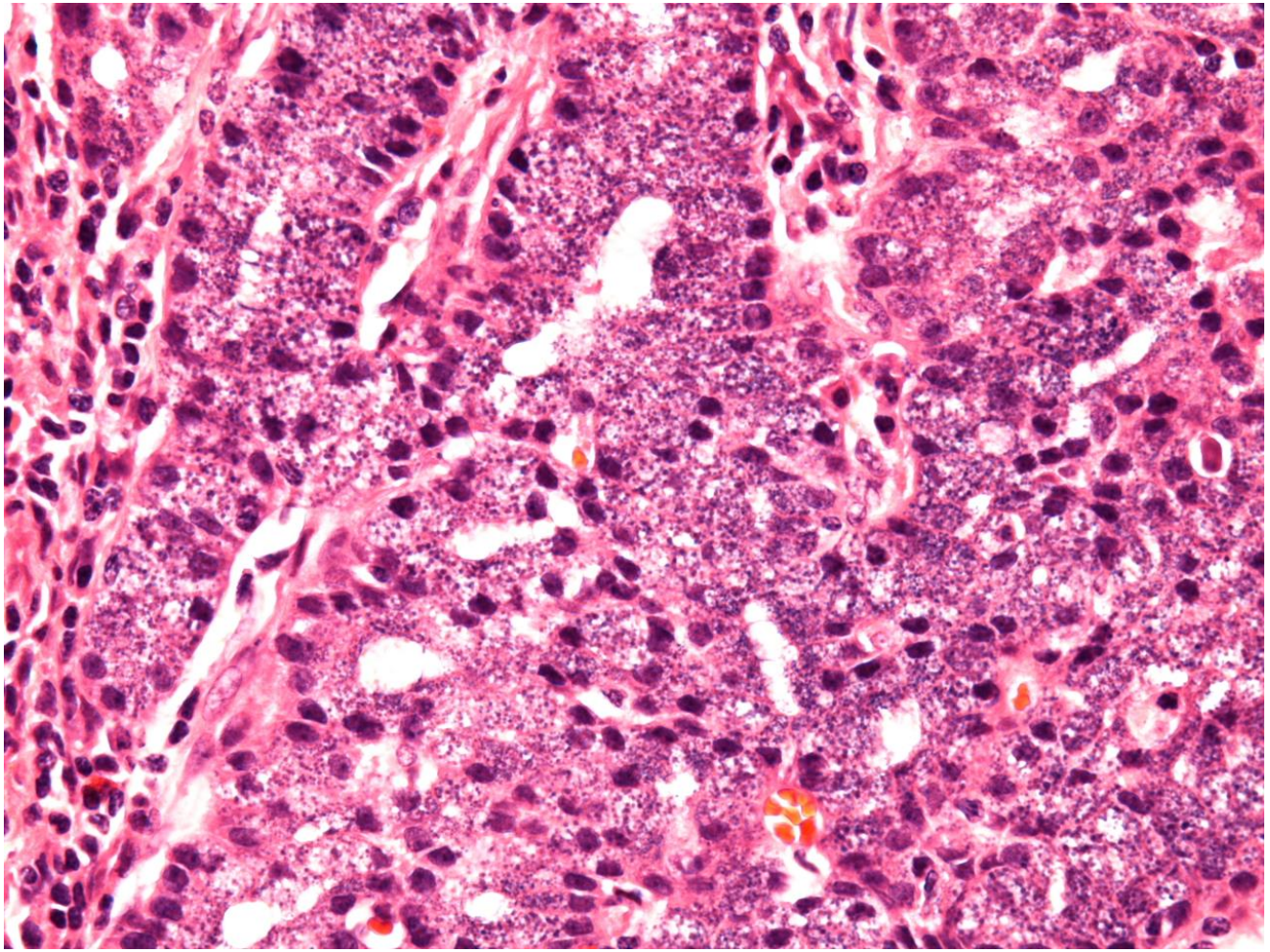
Seethala, R. Advances in Anatomic Pathology. 18(1):29-45, January 2011.

Acinic Cell Adenocarcinoma

- Characterized by basophilic, granular, acinar cell and intercalated duct differentiation (usually only a minority of the tumor)
- 80% in the parotid gland, may present with nerve pain, usually circumscribed but with adjacent parenchymal infiltration
- Low-grade carcinoma - best survival of the common malignant tumors
- Histopathologic patterns – solid, microcystic, papillary cystic, follicular

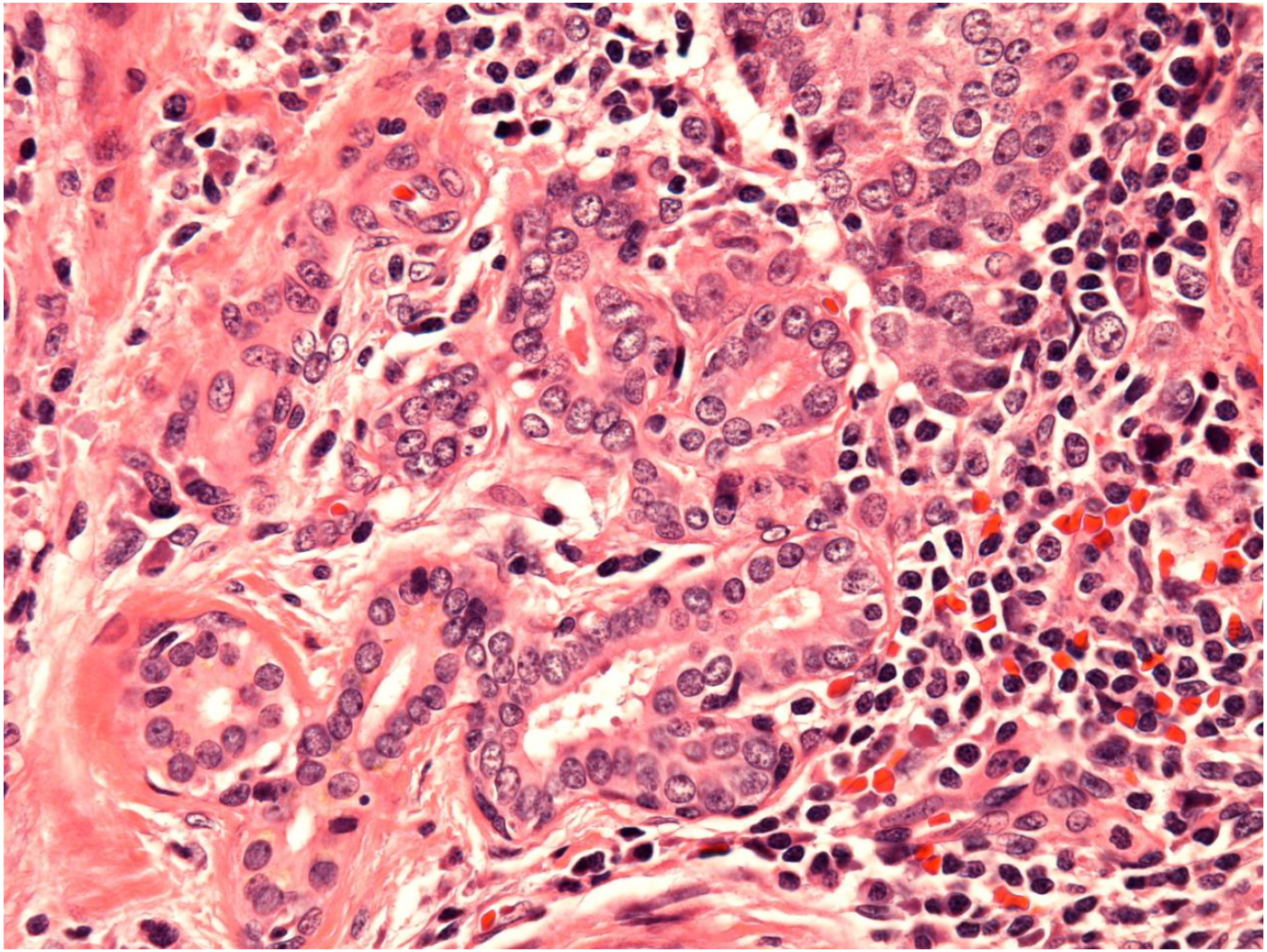
Acinic Cell Adenocarcinoma

- Acinar cell type



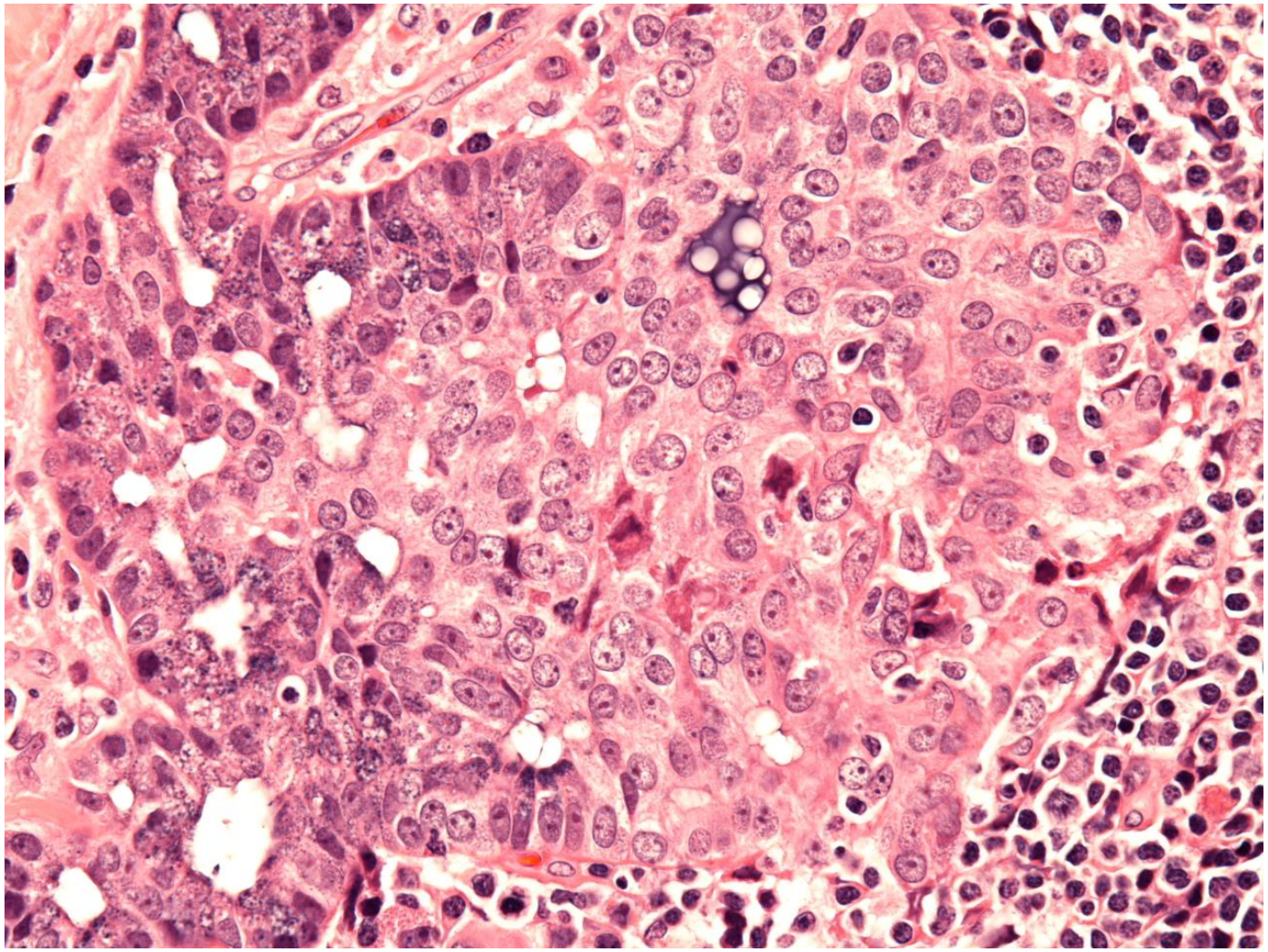
Acinic Cell Adenocarcinoma

- Ductal cell type



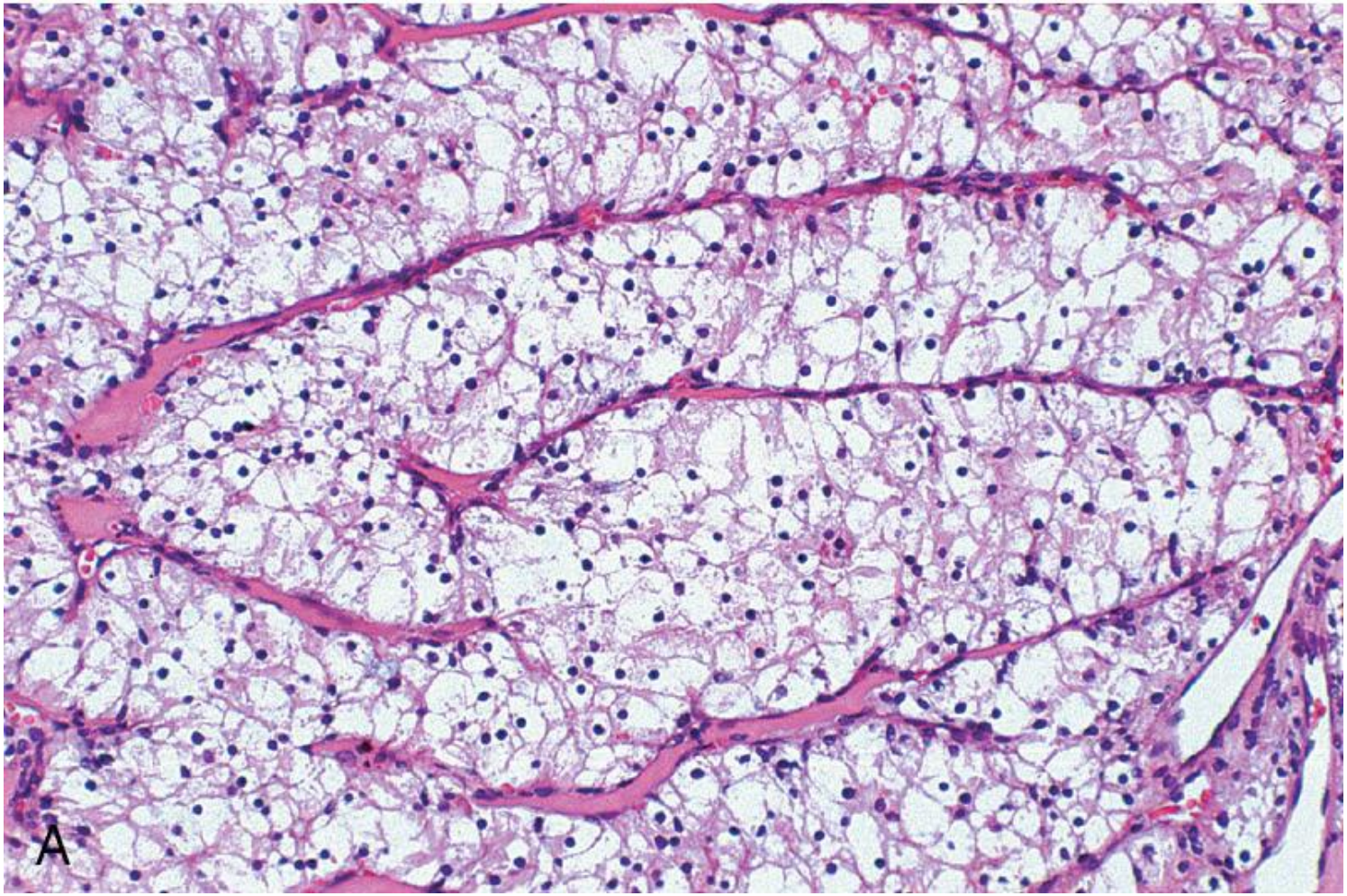
Acinic Cell Adenocarcinoma

- Acinar and non-specific glandular type cell



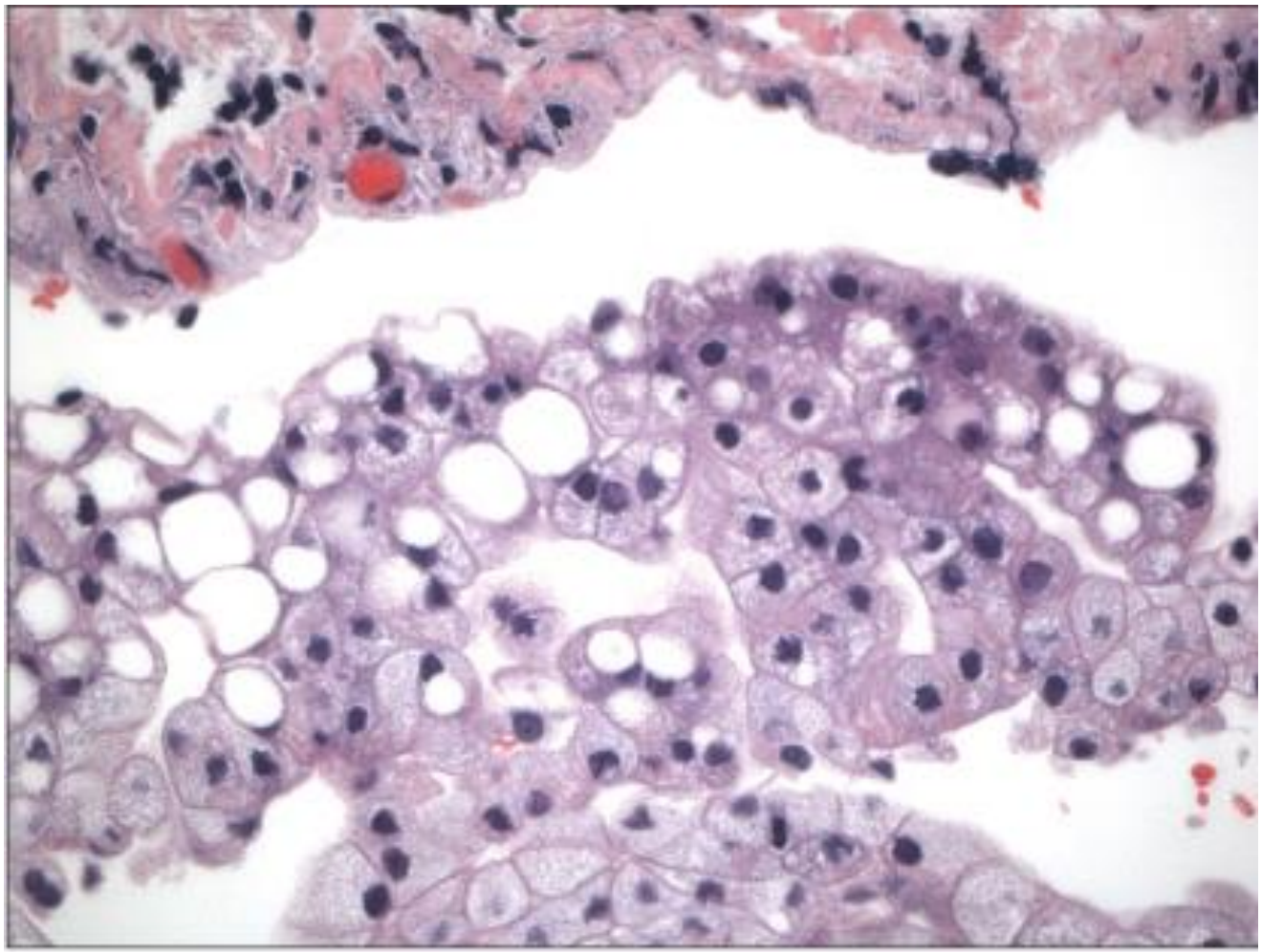
Acinic Cell Adenocarcinoma

- Clear Cells



Acinic Cell Adenocarcinoma

- Vacuolated cells



Acinic cell carcinoma
Histology and prognosis

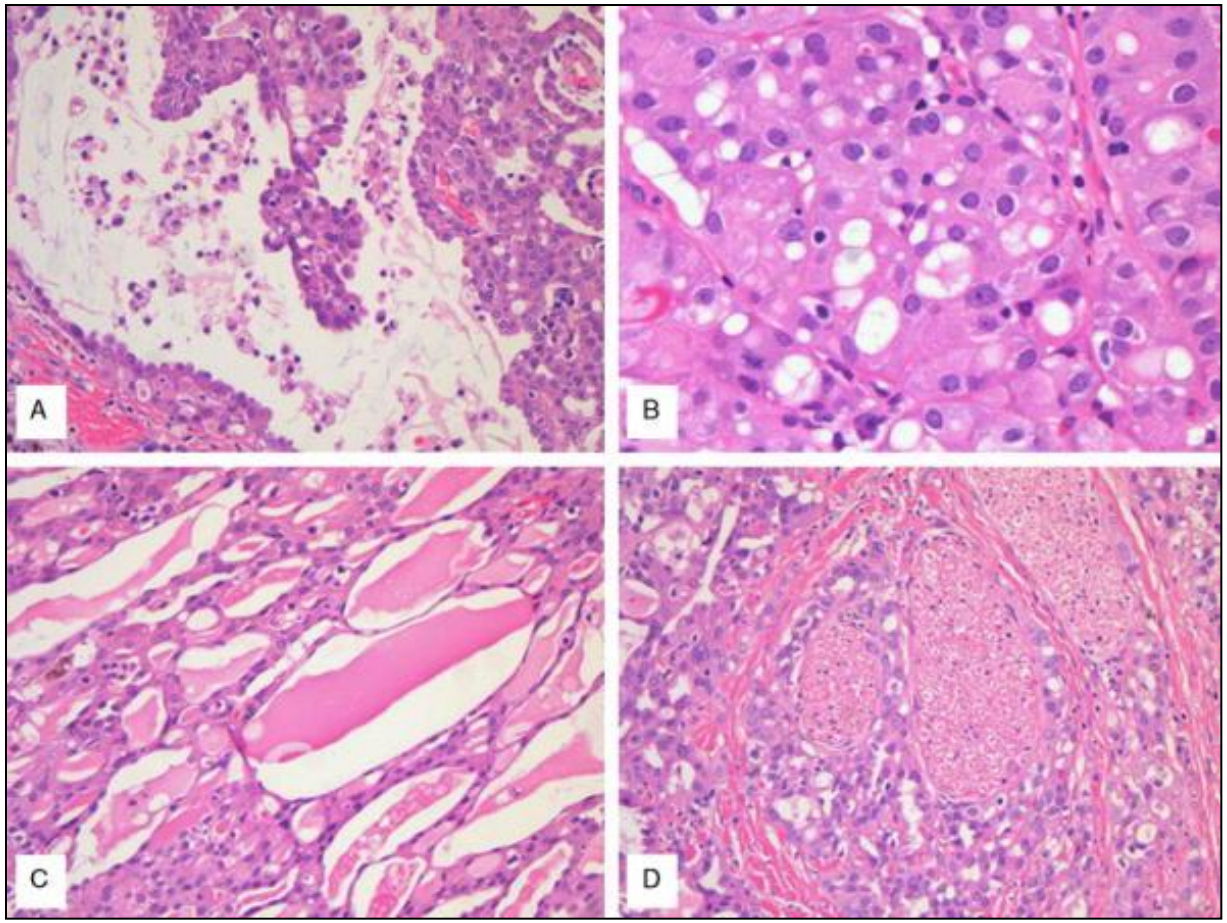
Favorable
- Well demarcated with microcystic growth pattern and lymphoid areas
- Numerous zymogen granules

Potentially adverse indicators
- Sclerotic stroma
- Necrosis
- “Hypogranular” and Cytologic atypia

(Mammary Analog) Secretory Ca

- Rare, relatively new entity
- Mean 45 yrs, males>females
- Mostly major salivary glands
- 25% with nodal mets
- Median 7-8 yr survival
- Major D/D
  - Acinic cell ca
  - ADC NOS
- Circumscribed
- Lobulated, fibrous septae
- Microcystic and tubular growth pattern with PAS+ bubbly secretions
- Monomorphous cells with low grade vesicular nuclei
- Resembles secretory Ca breast
- IHC CK7/8/18, S-100, Mammaglobin
- t(12;15) ETV6-NTRK3

FIGURE 2



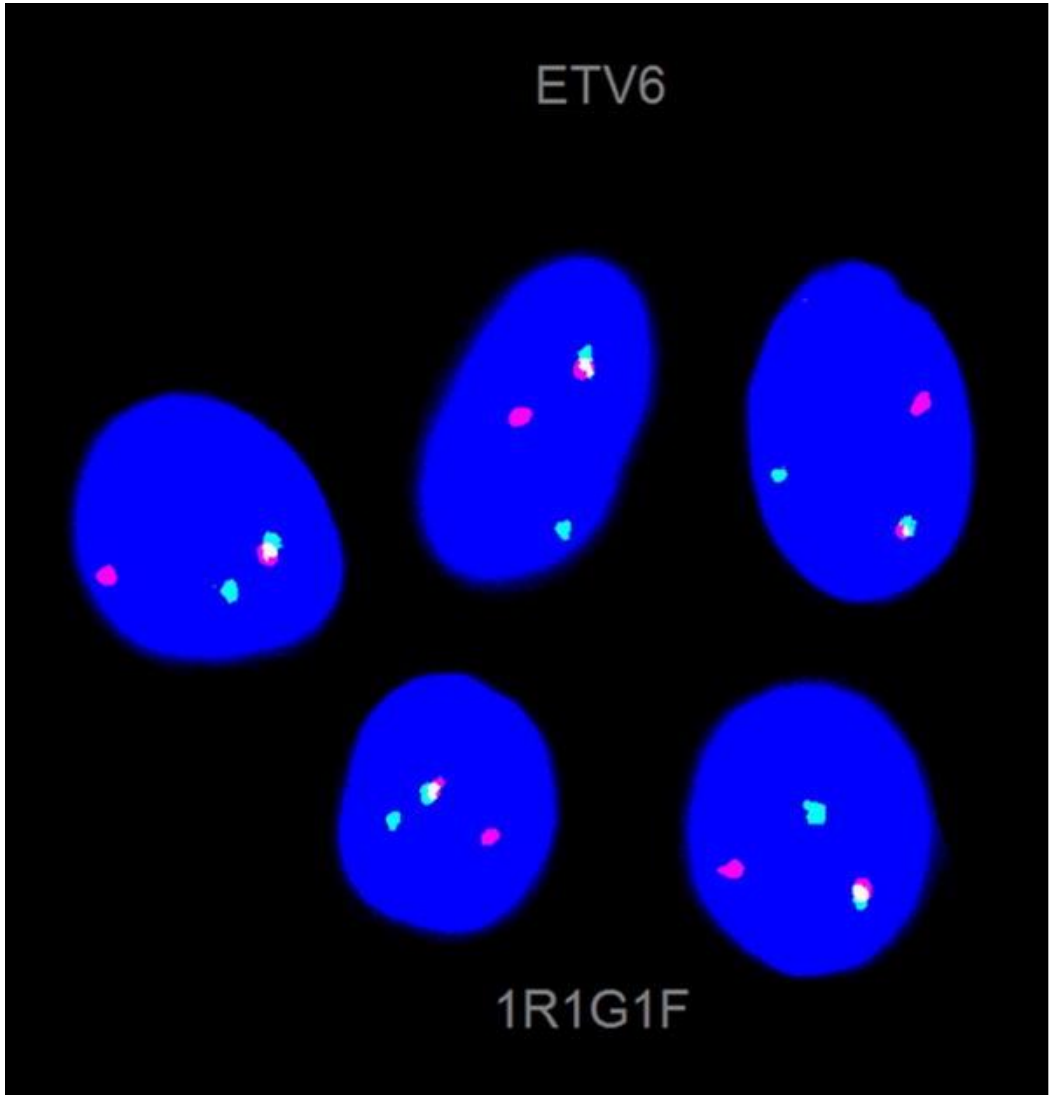
Mammary Analog Secretory Carcinoma of Salivary Gland Origin With the ETV6 Gene Rearrangement by FISH: Expanded Morphologic and Immunohistochemical Spectrum of a Recently Described Entity.

Connor, Ashton; Perez-Ordonez, Bayardo; Shago, Mary; Skalova, Alena; MD, PhD; Weinreb, Ilan

American Journal of Surgical Pathology. 36(1):27-34, January 2012.
DOI: 10.1097/PAS.0b013e318231542a

FIGURE 2 . A, Most MASC cases show some degree of cyst formation with micropapillary features and hobnailing of the cells [hematoxylin and eosin (H&E); x200)]. B, Typical MASCs show minimal pleomorphism and have granular eosinophilic cytoplasm with small microvacuoles (H&E; x400). C, One example of MASC showed a thyroid-like appearance with colloid-like secretions (H&E; x200). D, Perineural invasion was a common finding and was present in 3 of 7 cases (H&E; x200). \raster='rg1'

FIGURE 4



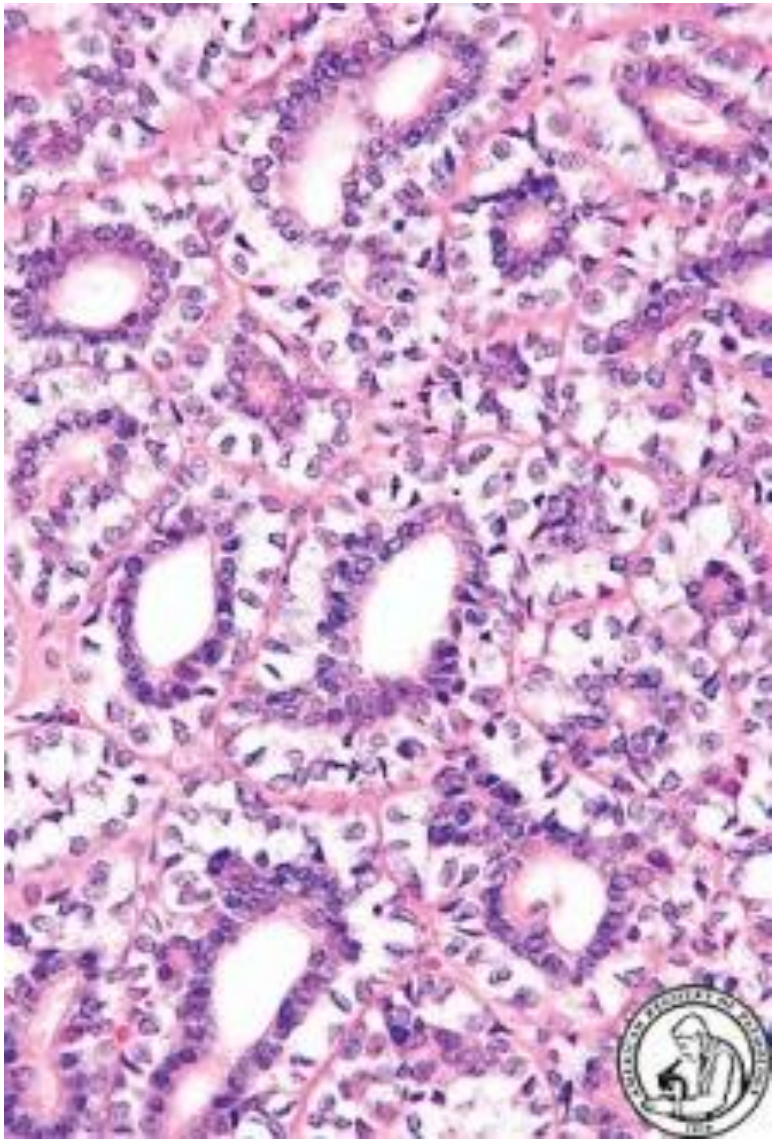
Mammary Analog Secretory Carcinoma of Salivary Gland Origin With the ETV6 Gene Rearrangement by FISH: Expanded Morphologic and Immunohistochemical Spectrum of a Recently Described Entity.

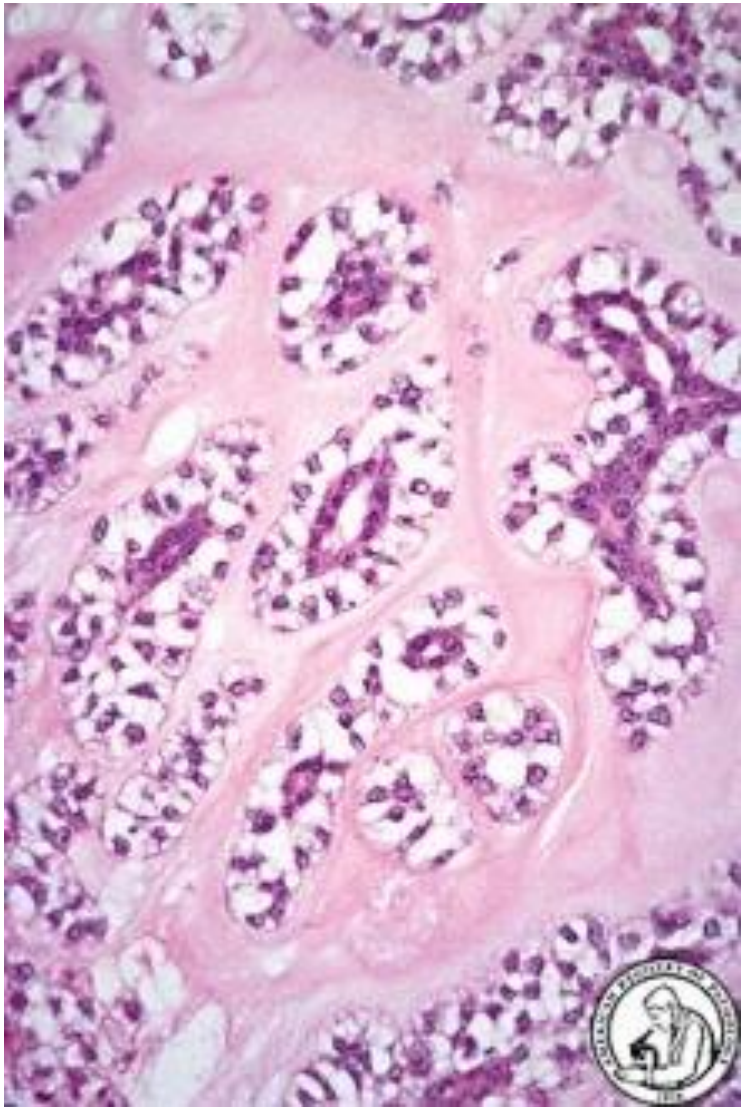
Connor, Ashton; Perez-Ordonez, Bayardo; Shago, Mary; Skalova, Alena; MD, PhD; Weinreb, Ilan

American Journal of Surgical Pathology. 36(1):27-34, January 2012.
DOI: 10.1097/PAS.0b013e318231542a

FIGURE 4 . FISH for the ETV6 gene was positive in all 7 cases. There is 1 fused yellow signal in each cell with a second set of separated spectrum green and orange signals representing the break-apart signal.

Epithelial – Myoepithelial Carcinoma





(Hyalinizing) Clear cell carcinoma

- Minor salivary gland
- Low grade malignancy (non-fatal)
- Cords and nests of clear cells in hyalinized stroma
- May have squamous features
- Infiltrative, perineural invasion common
- 40% have mucin
- t(12;22) EWSR1-ATS1 (clear cell ca and AFH also but different breakpoint)

LGCC

- “Low grade SDC”
- Excellent prognosis
- Smooth cysts with micropapillae, Roman arches
- Cytoplasmic microvacuoles and yellow refractile pigment
- Apocrine snouts
- Myoep cells retained
- IHC – Diffuse CK+ and S-100+, HER2 and AR negative

SDC

- Rare and aggressive tumor with mets at presentation
- Resembles breast carcinoma
  - Cribriform, solid and micropapillary
  - Comedo necrosis
  - Calcifications
- Stromal and perineural invasion
- IHC – AR+, HER2+, PSA occasionally +, ER/PR negative

Approach

Morphologic patterns

- Pleomorphic adenoma
- Solid tumors (basal cell adenoma, myoep, oncocytoma)
- Cystic tumors (Warthin, canalicular adenoma, cystadenoma, papilloma)
- Biphasic (ADCC, EMC, PA)

Site based

- Minor glands (PLGA, canalicular, ADCC, MEC)
- Parotid (Warthin, basal cell,others)

Clinical features suggesting malignancy

- Asymptomatic swelling is the most common presentation - benign or malignant
- Symptoms usually not impressive
  – Pain may not indicate malignancy
  – Growth rate not reliable
  – Paresthesia is a sign of malignancy
- Facial nerve paralysis 12-14% of parotid malignancies
  – Suggests poor prognosis
- Paresthesia – DDx = Adenoid cystic carcinoma
- Tumor fixation or ulceration, consider malignancy
- Benign intra-oral lesions often ulcerate

Prognosis
(Overall)

- Stage of tumor – The usual predominate factor
- Other factors for specific tumors
  - Age and gender
  - Facial nerve involvement (Parotid tumors)

Prognosis
Tumor Type

- Most carcinomas have only a single grade
  - Low grade
    - Acinic cell
    - Basal Cell
    - Polymorphous low grade adenocarcinoma
  - High Grade
    - Salivary duct carcinoma
    - Squamous cell carcinoma
    - Undifferentiated carcinoma

Prognosis
(Microscopic Grading)

Some tumors are graded microscopically

- Grading on cytology
  - Adenocarcinoma NOS
- Grading on predominate growth pattern
  - Adenoid cystic carcinoma
- Specific grading criteria
  - Mucoepidermoid carcinoma

Conclusions

- Cell types and architecture have extensive overlap
- Clear cell and oncocytic change is non-specific
- Cytogenetics is increasingly useful

- *MYB–NFIB* fusion specific for adenoid cystic carcinoma
- *CRTC1–MAML2* fusion typical of low/intermediate-grade mucoepidermoid carcinoma,
- *ETV6–NTRK3* fusion in mammary analogue secretory carcinoma.
- Similarly, gene fusions involving the *PLAG1* and *HMGA2*oncogenes are specific for benign pleomorphic adenomas.