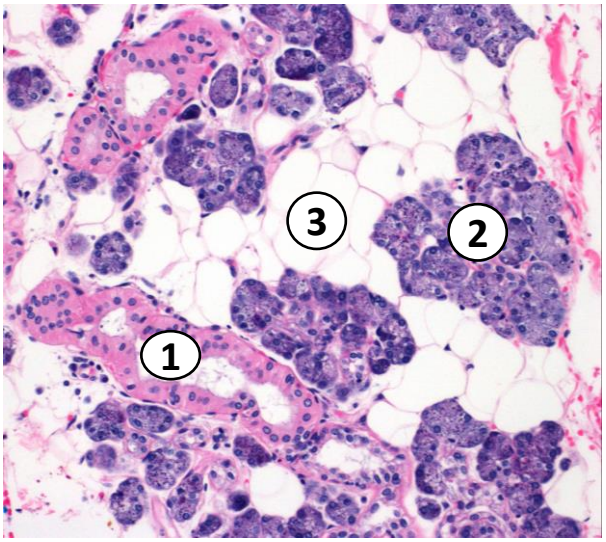
Salivary Gland

Normal Salivary Gland



Normal components:
1) **Ducts**: Interlobar, to intercalated, and striated. Cuboidal to columnar epithelium. Surrounded by myoepithelial cells.

2) **Acini**: Serous (esp. in parotid, with zymogen granules) to mucous (esp. sublingual), surrounded by myoepithelial cells. Looks like grapes on cytology.

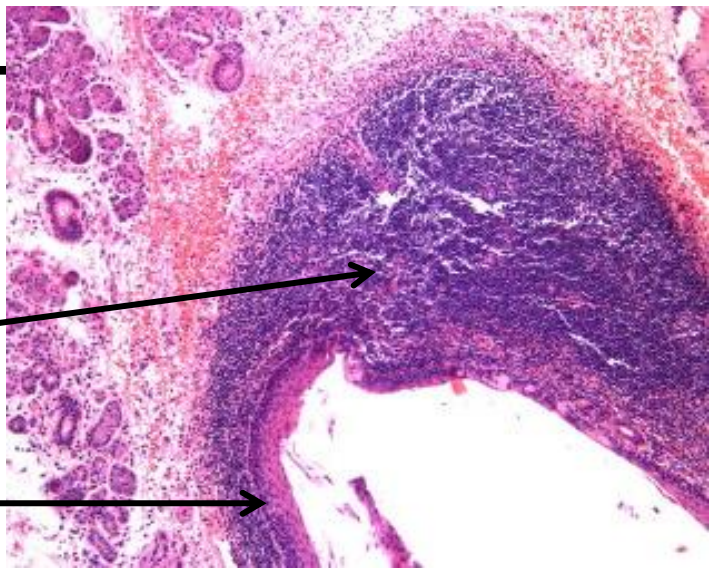
3) **Fat** (esp. in parotid)

Also: **lymph nodes** (esp. in parotid, where benign salivary gland can be within lymph nodes).

If have symmetric enlargement of salivary glands with no discrete mass, consider **sialadenosis**, a benign condition associated with systemic disorders like diabetes, malnutrition, and cirrhosis.

Inflammatory

HIV-Salivary Gland Disease

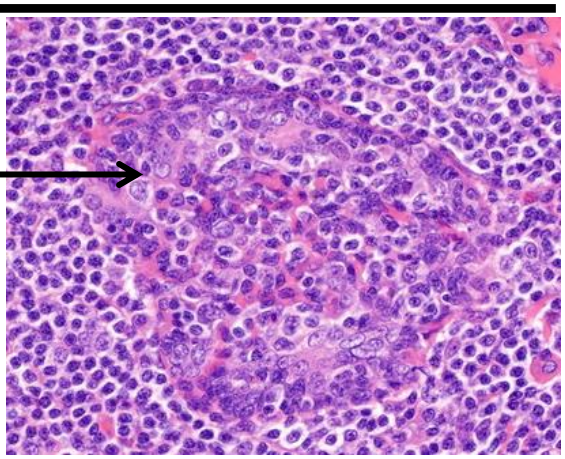


Seen with Human Immunodeficiency Virus (HIV)
Mostly younger men.
Painless swelling, Xerostomia,

Florid follicular hyperplasia, attenuated to absent mantle lymphocytes, disruption of the germinal centers (follicle lysis), and the presence of multinucleated giant cells

Multiple squamous epithelial-lined cysts and lymphoepithelial lesions

Lymphoepithelial Sialadentitis (LESA)



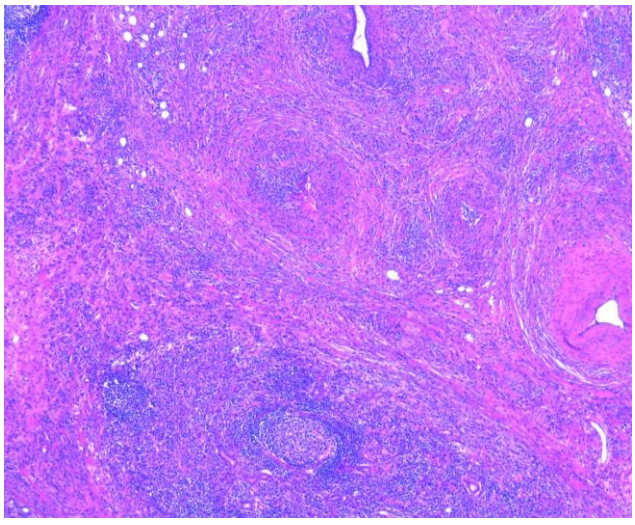
Chronic, systemic, lymphocytic, autoimmune inflammation

Hallmark finding: *Lymphepithelial lesions*
Follicular lymphoid hyperplasia surrounding and infiltrating salivary ducts with **atrophy**

Usually women in the parotid.
Histologic finding for Sjogren's syndrome (but can be seen in other disorders or incidentally)
Can develop into MALT lymphoma→ so consider doing IHC to confirm polyclonal inflammatory infiltrate.

IgG4-related sialadenitis

aka "Küttner tumor"

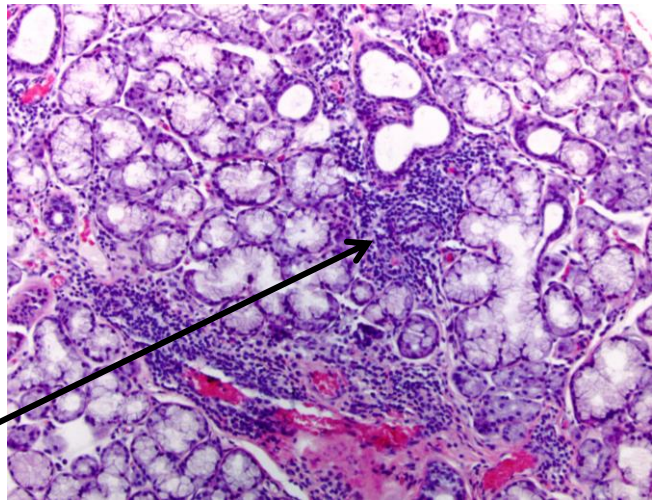


Multiorgan autoimmune disorder that can form **tumefactive lesions**.
Defined throughout the body by:
1) Dense lymphoplasmacytic infiltrate
2) Storiform pattern of fibrosis
3) Obliterative phlebitis

Increased numbers of IgG4+ plasma cells
(Supposed to see >100 per single HPF!!)
Often increased serum IgG4

Preserved lobular architecture with extensive fibrosis, chronic inflammation, and atrophy.
Florid lymphoid hyperplasia with germinal centers.

Sjögren syndrome



Chronic autoimmune disease characterized by lymphocytic infiltration of multiple exocrine glands
Lacrimal glands→ **dry eyes** (keratoconjunctivitis sicca)
Salivary gland→ **dry mouth** (xerostomia)

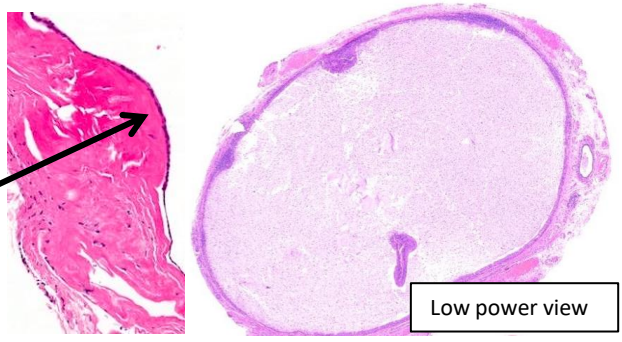
<u>Usually older women.</u>

Serology: autoantibodies against **Ro/SSA** and **La/SSB**

Often diagnosed <u>*clinically*</u> (no tissue biopsy)

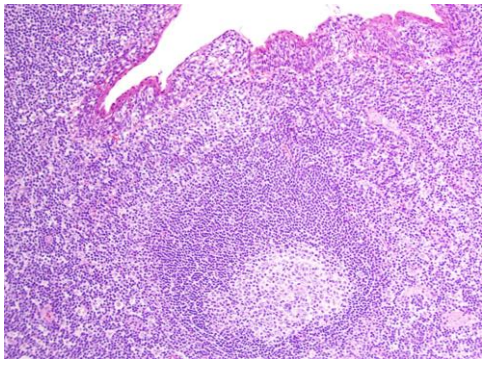
<u>*Labial biopsy findings (sometimes used):*</u>
"Focus Score:" foci containing ≥50 lymphocytes
Focus scores greater than 1 focus/4 mm2 support Dx

Salivary duct cyst



Acquired cyst due to **post-obstructive duct dilation.**
Most common salivary gland cyst.
Wall contains fibrous tissue.
Lined by cuboidal, columnar, or squamous epithelium, +/- goblet cells and oncocytes.
Can have associated inflammation, secretions, etc..

Lymphoepithelial cyst



Uncommon acquired **parotid** cyst.
Usually unilocular.
Fibrous capsule. Lined by a variety of epithelial types (squamous, cuboidal, etc..)
Abundant lymphoid tissue with <u>prominent germinal centers.</u>
<u>*Unrelated*</u> to HIV

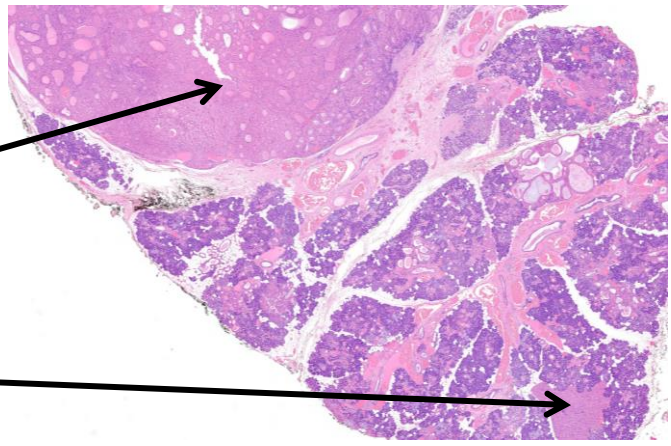
Oncocytic

Pink cells, often because they contain abundant mitochondria. Often big, polygonal, with well-defined borders, granular cytoplasm, with large round nuclei with prominent nucleoli.

Oncocytic hyperplasia

Oncocytic metaplasia:
Non-mass forming transformation of glandular epithelium to oncocytes

Nodular oncocytic hyperplasia:
Non-neoplastic, mass-forming, circumscribed proliferation of oncocytes, which can be focal or diffuse. Unencapsulated. Often multifocal, admixed with normal salivary tissue (aka *Oncocytosis*). Usually in parotid. Clear cell change can be seen too.



Oncocytoma

Benign

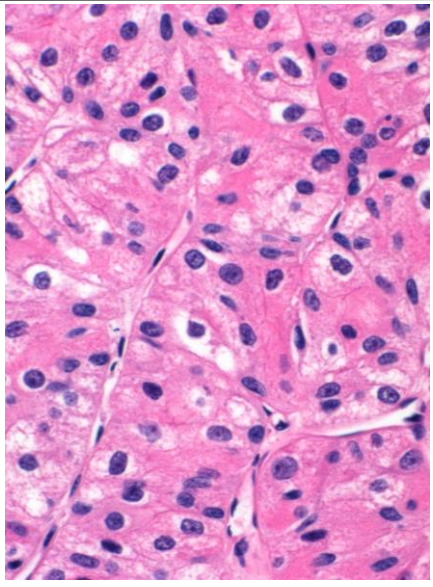
Circumscribed to encapsulated proliferation of oncocytes.
Unifocal.

Actually **Biphasic**
1. Inner oncocytes,
2. Outer myoepithelial cells

Usually in parotid.

No significant: pleomorphism, mitotic activity, or invasive growth.

Usually negative for S100 and SOX10.



Oncocytic Carcinoma

Malignant.

Oncocytic lesion with pleomorphism, mitoses, and/or invasion.

Super **rare** and not well-defined → Not actually in the current WHO → so would likely fall under "Salivary gland carcinoma, NOS"

May or may not be encapsulated.

Warthin Tumor

Old name: *Papillary cystadenoma lyphomatosum*

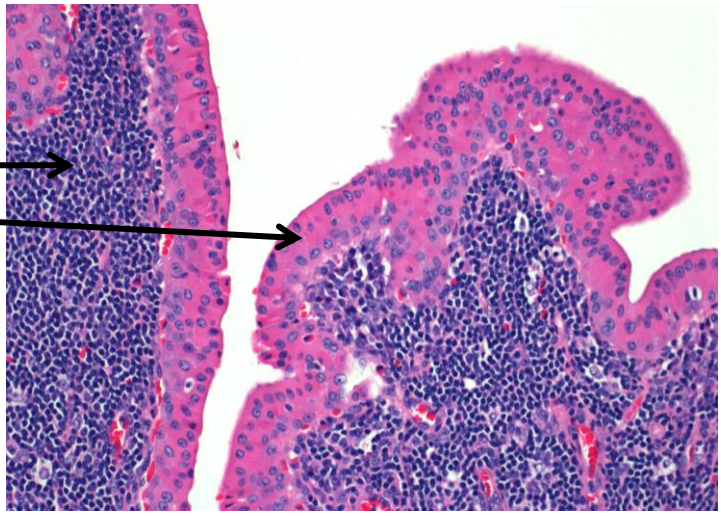
Benign

Key elements:
1) Mature lymphoid tissue, surrounding
2) Bilayerd oncocytic epithelium, with
3) Cystic to papillary growth

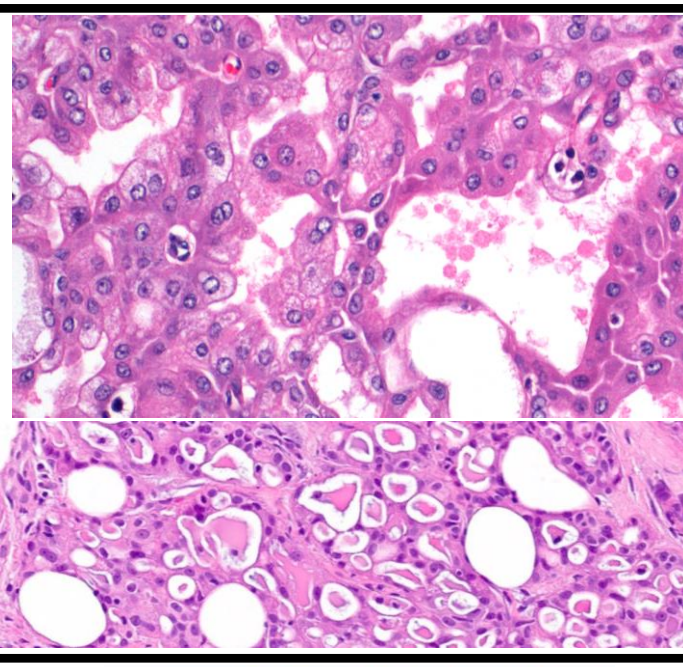
Strongly linked to smoking, can be bilateral

Likely develops from transformation of salivary gland tissue entrapped in a lymph node.

Almost exclusively in parotid, usually at angle of jaw. Aspirated fluid often thick, dark "motor oil."



Secretory Carcinoma



Formerly: *"Mammary Analogue Secretory Carcinoma"*

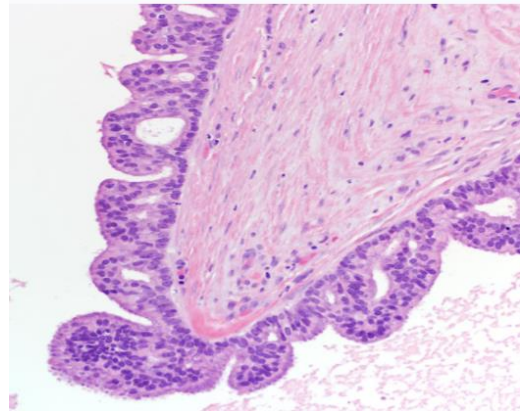
Malignant, but relatively indolent.

Monophasic: Eosinophilic, granular, bubbly, to vacuolated cytoplasm
Tubular, papillary and cystic growth.
Sometimes has distinctive eosinophilic secretions in lumina.
No zymogens present.

Molecular: **ETV6**-NTRK3 (most common) or ETV6-RET gene fusions.

IHC: (+) **S100, mammaglobin, GATA3**, PanTRK
(-) p63/p40, DOG1

Intraductal Carcinoma



Non-invasive carcinoma with retained myoepithelial cells.
Think of as similar to DCIS of the breast.
Rounded lobules/ducts.

Can be papillary, cribriform, or solid.
Several subtypes (see below) and can be mixed.

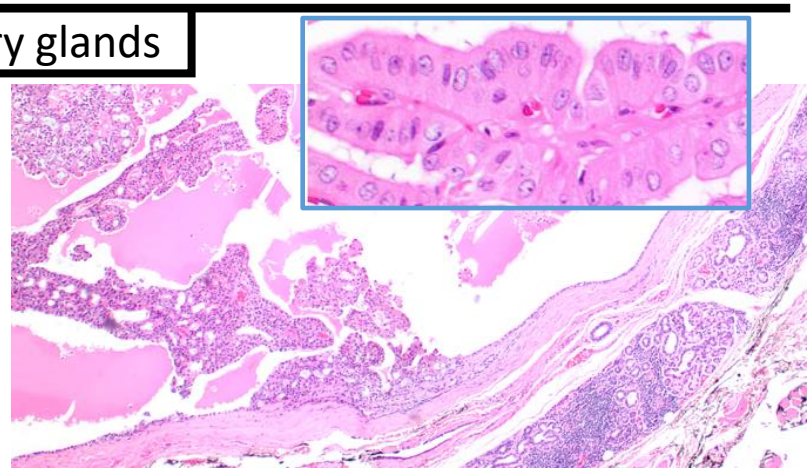
Can highlight myoepithelial cells with p63.
If totally non-invasive→ Excellent prognosis!

Usually in Parotid.

Subtype	Grade	S100/ Sox10	AR	Mammaglobin	Genetics	Associated Invasion
Intercalated	Low	++	-	+	NCOA4::RET fusions	Rare
Apocrine	Low or High	-	++	-	Complex. No fusions	Common
Oncocytic	Low	++	-	+	TRIM33::RET fusions BRAF V600E	Unknown

Modified from: WHO Classification of Tumors of the Head and Neck. 5th Edition

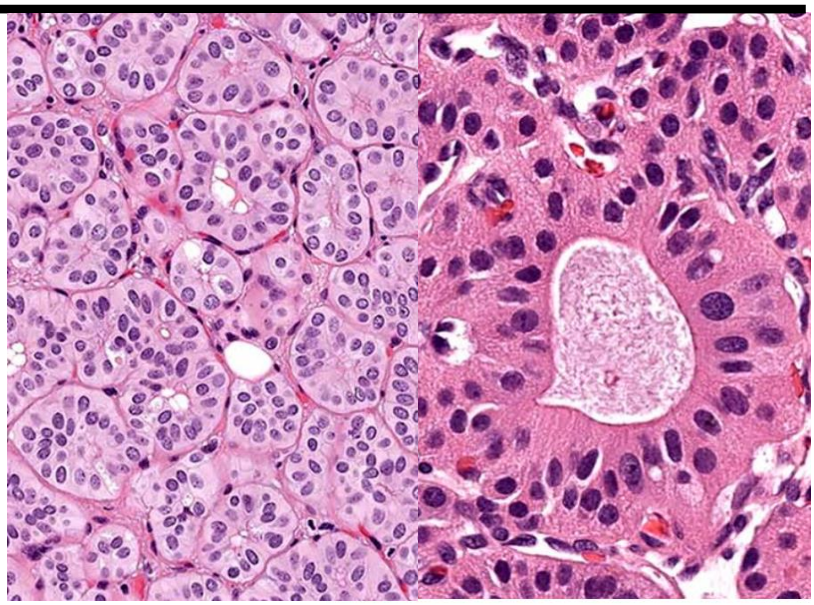
Cystadenoma of the salivary glands



Benign

Unicystic or multicystic non-invasive bland neoplasm with an oncocytic or mixed epithelial lining.
No lymphoid stroma (vs Warthin)
Intact basal cell layer.
Variable papillary component.

Striated duct adenoma



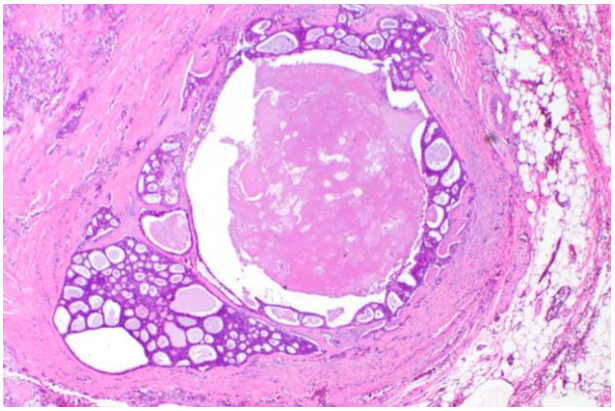
Benign. Rare.

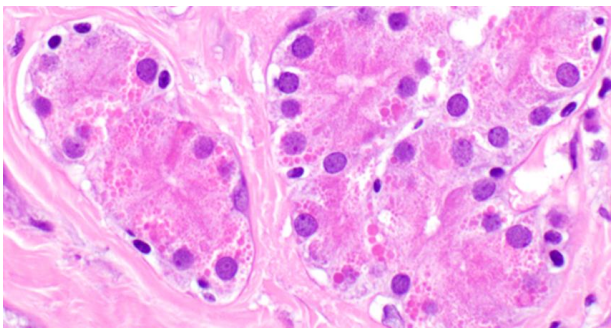
Well-circumscribed and encapsulated.
Closely spaced ducts and cysts
Single layer of eosinophilic luminal cells
Minimal intervening stroma lined

IHC: (+) CK, S100
(-) p63, SMA, calponin, (no myoeps present, unlike oncocytoma)

Molecular: IDH2 p.R172 mutations

Sclerosing Polycystic Adenoma





Benign (can recur, and rarely transform)
Previously thought to be reactive ("Adenosis"), but actually a neoplasm.

Well-circumscribed. Usually in parotid.
Often Cystic-appearing and/or multilobular.
Acinar cells containing large hypereosinophilic cytoplasmic granules, with mixtures of ductal and myoepithelial cells.

Apocrine metaplasia and intraductal proliferation creating a resemblance to low-grade ductal carcinoma in situ.

Molecular: PI3K pathway genes, most frequently PTEN
IHC: Loss of PTEN

Other

Hyalinizing clear cell carcinoma
Acinic cell carcinoma
Mucoepidermoid carcinoma
Sebaceous lesions

Basaloid

Looks very cellular and blue at low-power

Basal Cell Adenoma *"BCA"*

Benign, well-circumscribed and/or encapsulated.
Usually Parotid.

Peripheral palisading on outside of nests
Solid, trabecular, membranous, or tubular growth
Two cell population. Vesicular nuclei.
Basement membrane material, but not much "stroma."

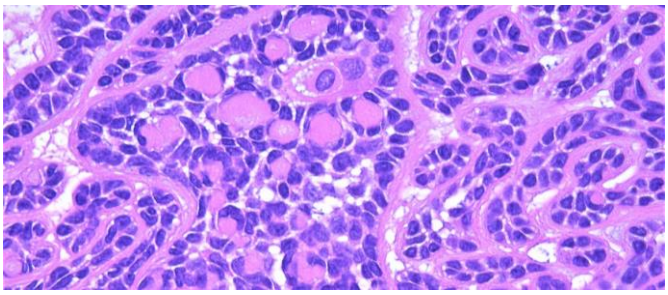
IHC: Nuclear β-catenin.
Molecular: CTNNB1 and CYLD1 alterations

(Unlike PA, there is a lack of blending with associated myoepithelial-type stroma)

Basal Cell Adenocarcinoma

Malignant

Like a basal cell adenoma, but with **invasion**, necrosis, and numerous mitotic figures



Adenoid Cystic Carcinoma

Malignant. Relatively common.
Major and minor salivary glands.

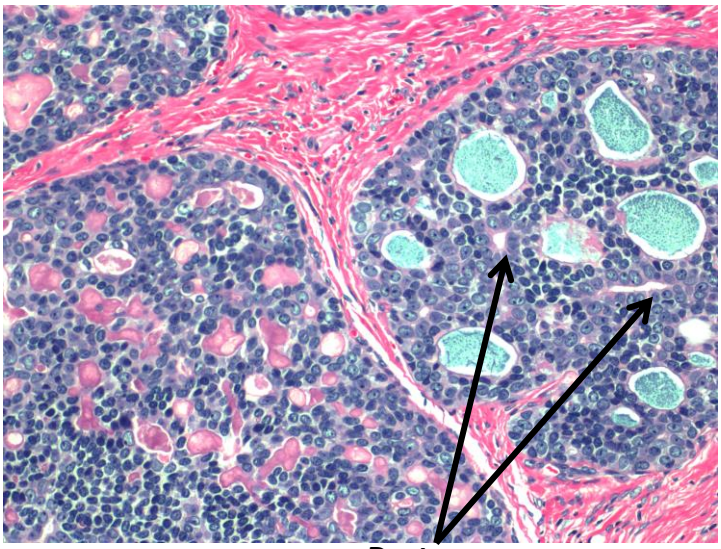
Cribriform, tubular or solid growth

2 cell types: 1) Myoepithelial and 2) Ducts

Low-grade: Mostly **myoepithelial** (small cells with oval to angulated nuclei), (+)p40 and SMA

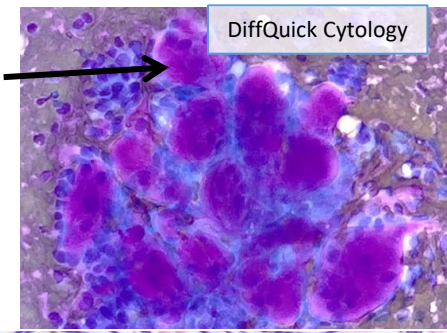
High-grade: Mostly **ductal cells** (larger cells with more vesicular chromatin), (+) CD117 and CK

Ducts can be inconspicuous in low-grade
(See image →)



Grading: give % Solid component (>30% is bad).

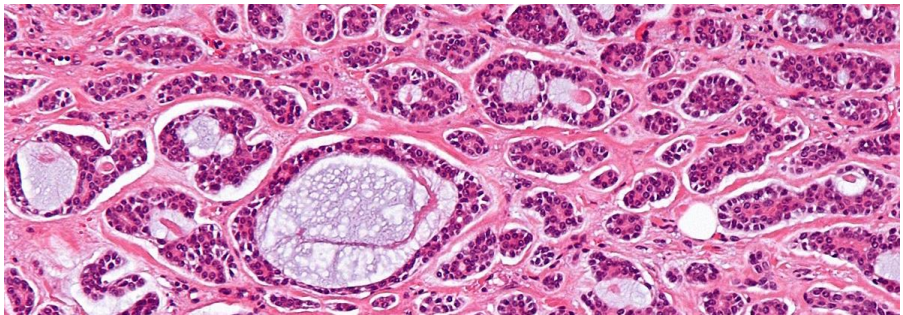
Myoepithelial cells form microcysts that contain hyaline or blue mucoid (which are visible on FNA, with "stromal exclusion" of myoepithelial cells)

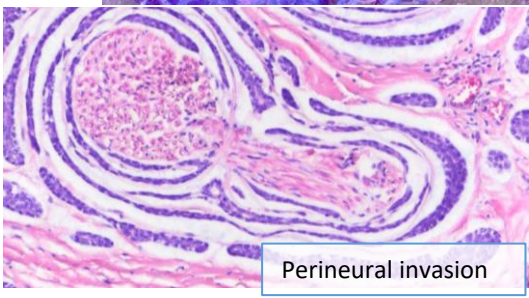


Cytogenetics: Fusions of MYB (~60%), MYBL1, or NFIB

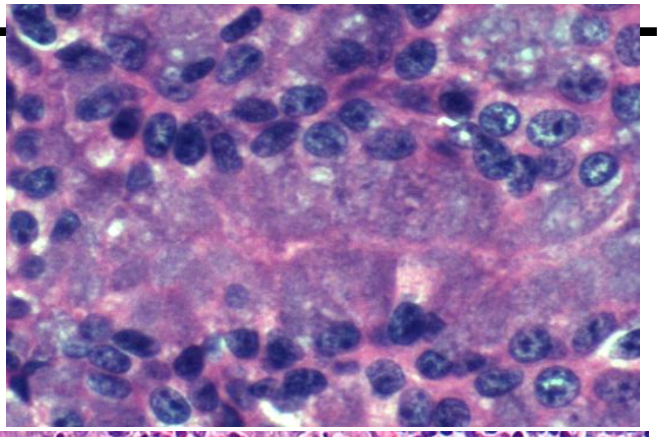
Infiltrative → **Extensive PNI** → Pain → Paralysis
Lymph node metastases relatively rare unless high-grade.

Persistent local spread. OK 5yr survival, but poor long-term survival.





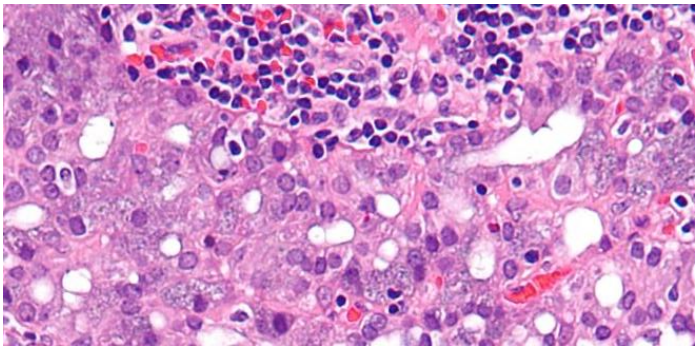
Acinic Cell Carcinoma



Malignant, but generally not aggressive

Composed of **<u>acinar cells</u>** with variable cytoplasm (vacuolated, clear, oncocytic, to hobnailed) and architecture (solid to cystic or follicular).

Classically, has cells that are large, polygonal with basophilic **<u>granular cytoplasm</u>** (contains **<u>zymogens</u>**→ highlighted by PASD).



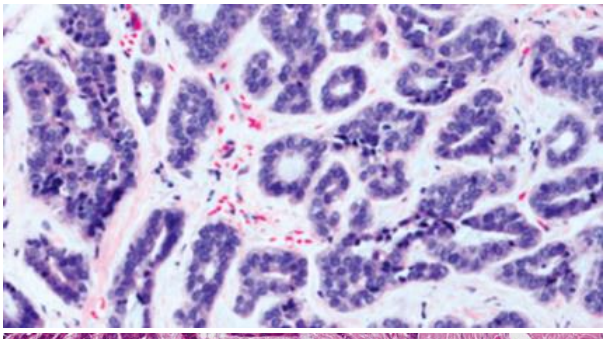
No mucinous differentiation.
Sometimes prominent lymphoid infiltrate

Usually in parotid. Can see in kids.

Molecular: **NR4A3 Translocations** common

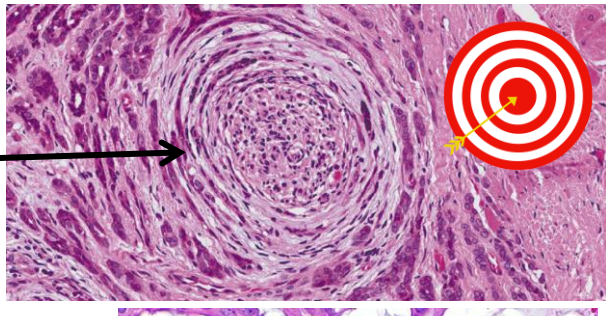
IHC: (+)**DOG-1** (membranous, canalicular, or cytoplasmic), SOX-10 and NR4A3 or NR4A2.
(-)p40, Mammoglobin

Polymorphous adenocarcinoma



Formerly, "Polymorphous Low-Grade Adenocarcinoma" → "PLGA"
Malignant, but low-grade, indolent neoplasms

Conventional Polymorphus Carcinoma *(PmA)*
<u>Cytologically</u> **<u>uniform</u>** <u>cells</u> **(monophasic)**
Bland, round to spindled cells with moderate amounts of cytoplasm. Oval nuclei with vesicular chromatin.



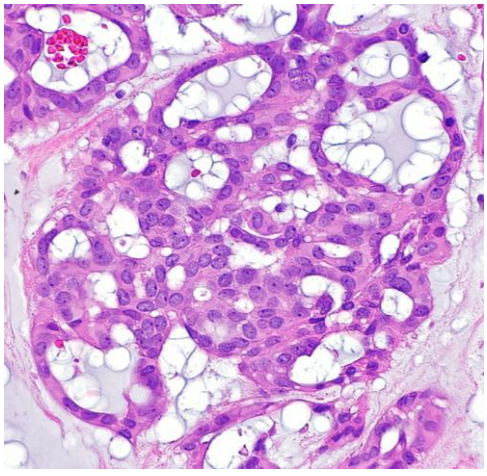
<u>Varied *architecture*</u> (hence the "polymorphous")
Concentric layering, "whorled," Tubules to single file

<u>Infiltrative</u> with significant <u>PNI</u> (sometimes "Targetoid") →

Molecular: PRKD fusions/mutations
IHC: Strong, diffuse staining with S100. p63+ but p40 -

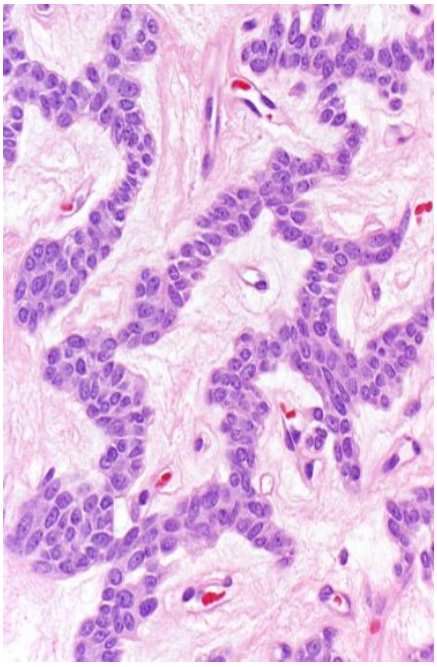
Always in <u>MINOR salivary glands</u>, often palate

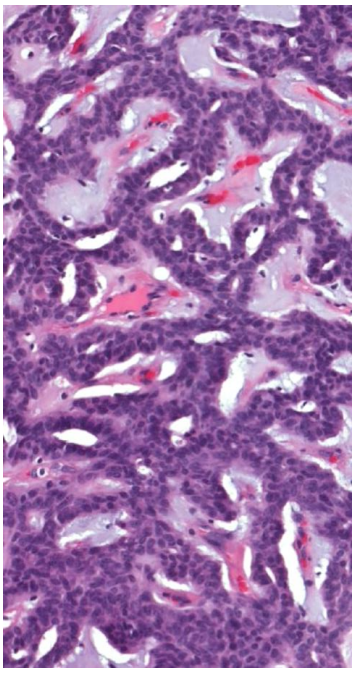
Cribriform Polymorphous Adenocarcinoma →



(also called Cribriform Adenocarcinoma of Salivary Gland or Tongue; CASG or CAT)
(Considered a separate entity by some authors)
Predominant papillary and glomeruloid growth.
Multinodular, separated by fibrous septae
Clear nuclei.
Worse prognosis.

Canalicular Adenoma





Benign.

Very often upper lip.
(Sometimes other minor salivary gland sites)

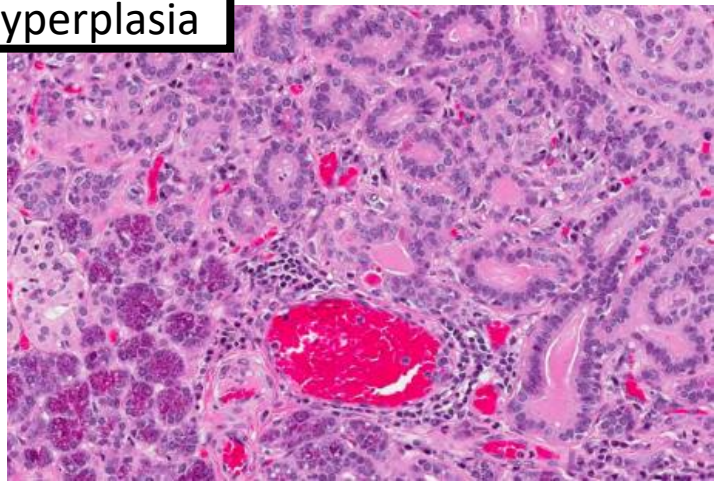
Encapsulated. **Monophasic**

Monotonous, isomorphic syncytium of cuboidal to columnar cells anastomosing/interconnecting in a lattice of cords, ribbons, and canaliculi.
No basal/myoepithelial layer.
Sometimes papillary projection into cystic spaces.

Cords separated by loose fibrillar stroma.

IHC: Peripheral GFP only. (+)CK, S100, CD117.
(-)SMA, p63

Intercalated duct adenoma and hyperplasia



Monotonous proliferation resembling bilayered (epithelial and myoepithelial) intercalated ducts.

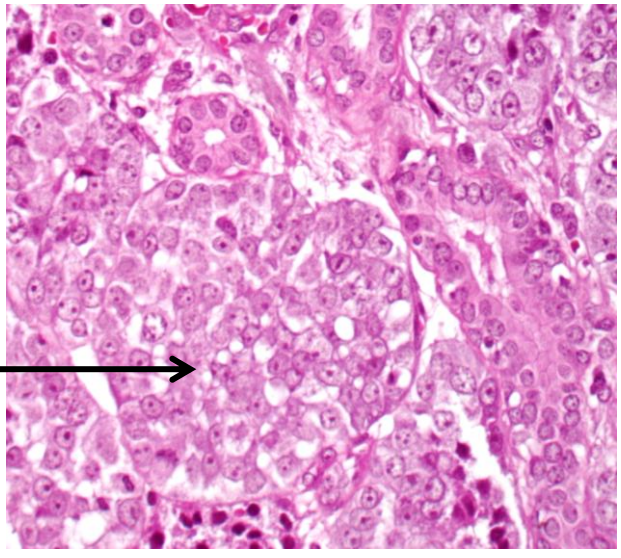
Small→ Often incidental (adjacent to other lesions)

Well circumscribed or encapsulated?→ adenoma
Intermixed with acini?→ hyperplasia

Additional Basaloid tumors

Small cell neuroendocrine carcinoma: Like in the lung! Be sure to exclude a met from the lung (or Merkel cell from the skin)!

Sialoblastoma: Usually present at birth—anlage neoplasm. Solid, organoid nests of primitive basaloid cells, separated by dense fibrous stroma. Indistinct cell borders. High N:C ratio. Vesicular chromatin. Low-grade malignant.



Prominent Spindled Cells and/or Stroma

Pleomorphic Adenoma *"PA"*

Benign, but can recur if not completely excised.
(aka Benign Mixed Tumor)

Most common tumor of salivary glands. Usu. **Parotid**

Three components, encapsulated, well-circumscribed:
1) **Ductular structures** with surrounding myoepithelial cells
2) **Myoepithelial cells** (can be spindled, epithelioid, plasmacytoid, etc…) intimately admixed with stroma
3) Mesenchymal-like tissue (often **myxoid stroma**, but can be chondroid, fibrous, mucoid, osseos, etc…)

Architecturally and cellulary pleomorphic (lots of ***variation***), but cytologically bland!
Can have occasional bizarre tumor cells ("ancient change")

Well delineated and/or encapsulated, but can be multinodular or have "pseudopodia" or satellite nodules.

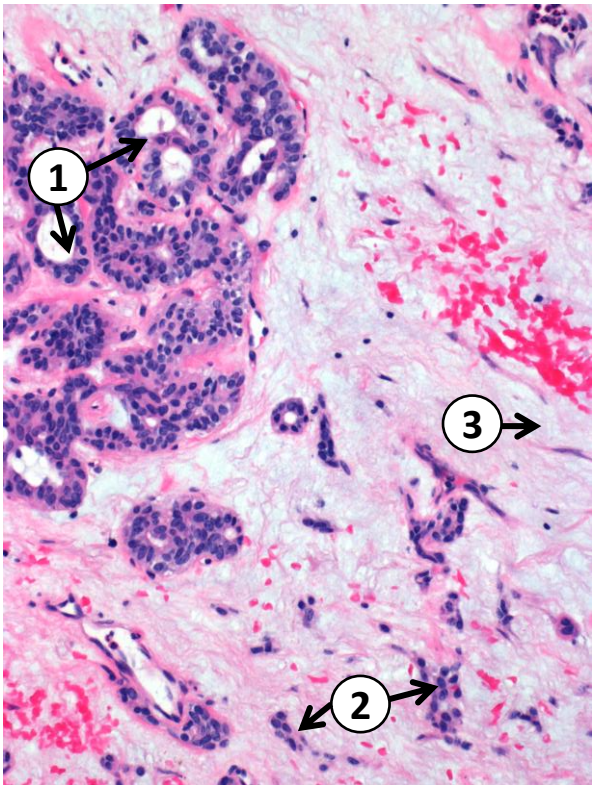
Capsule may be absent in minor salivary gland and chondromyxoid-predominant tumors.

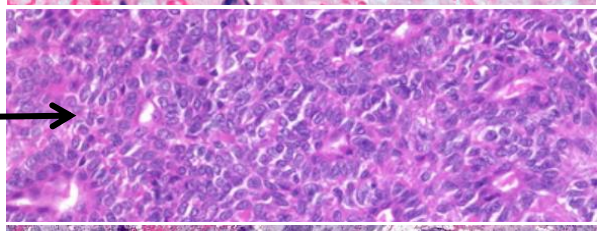
One component can dominate. If ducts and/or myoepithelial cells dominate (with little stroma), can use the term "cellular" PA

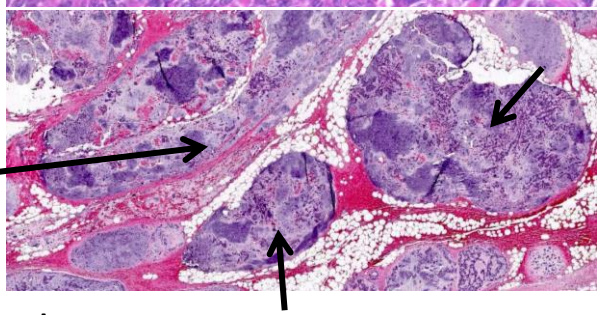
Can also see: tyrosine crystals, squamous metaplasia, cystic degeneration.

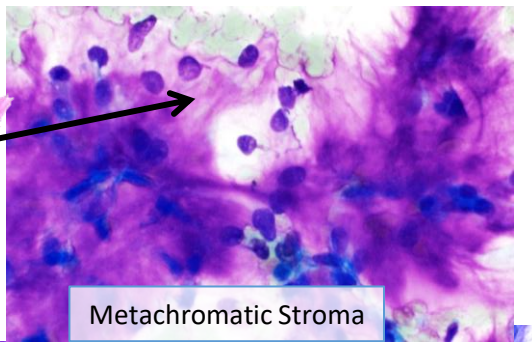
Cytogenetics: **PLAG1 or HMGA2 fusions** very common

"Recurrent" PA's (ones that come back after prior excision) contain multiple nodules with chondromyxoid morphology.





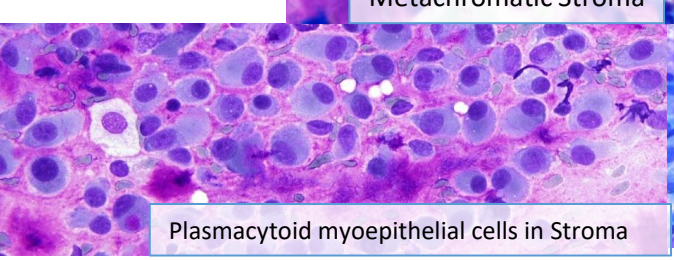




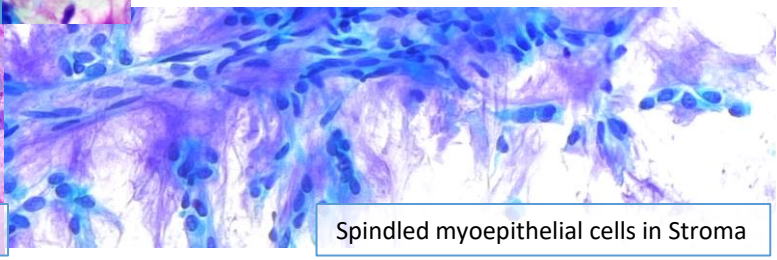
Metachromatic Stroma

Cytology:
Prominent fibrillar, metachromatic stroma that on a Diff-quick stain looks like ***"Troll Hair."***

Also visible ductal cells and myoepithelial cells intimately admixed with the stroma



Plasmacytoid myoepithelial cells in Stroma



Spindled myoepithelial cells in Stroma

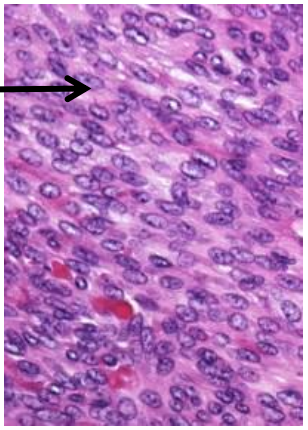
Myoepithelioma

Benign

Composed almost **exclusively myoepithelial cells** and the stroma they produce.
Monomorphic-appearing
Typically spindled to plasmacytoid.
Well circumscribed/encapsulated.

Although may see some collagen, chondroid/myxochondroid stroma is absent.

Vs PA: Monomorphic without ducts.
Vs BCA: Not basaloid. Less stroma.

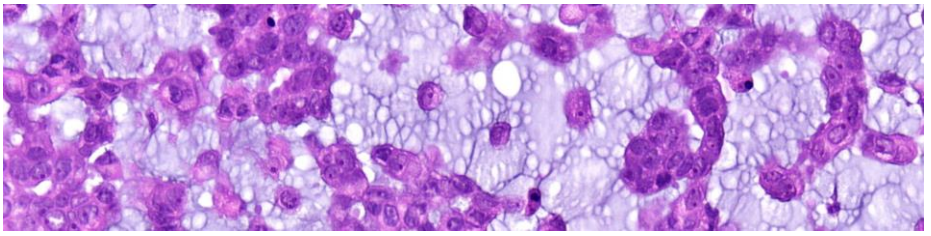


Myoepithelial Carcinoma

Malignant

Composed of almost entirely **myoepithelial cells**

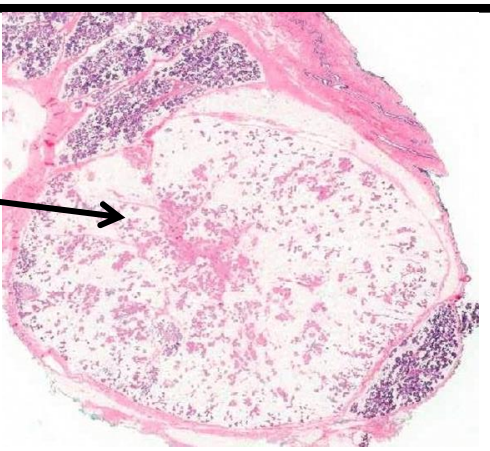
Presence of necrosis, atypical mitotic figures, **invasion** to surrounding parenchyma



Sialolipoma

Benign

Lipoma *with* benign salivary epithelial components.



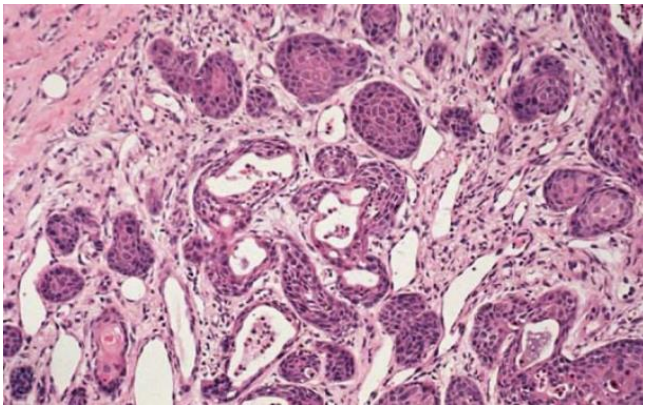
Also Consider

Carcinosarcoma
Canalicular adenoma
Epithelial-myoepithelial carcinoma

A mesenchymal (non-salivary) tumor!

Squamoid

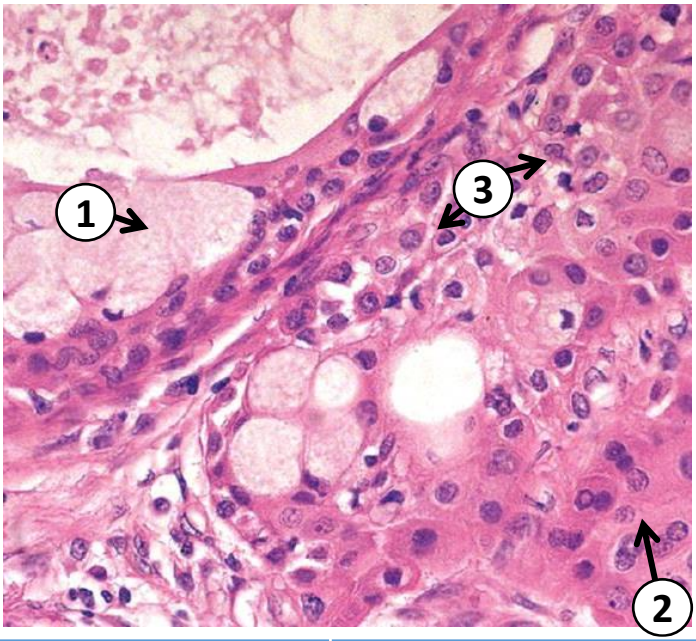
Squamous metaplasia



Can see in normal salivary glands or tumors (e.g., PA)
Classic Mimic of SCC!

In minor salivary gland often called:
"Necrotizing Sialometaplasia"
Lobular architecture is maintained
Smooth, rounded contours
Often associated inflammation and reactive changes
Acinar coagulative necrosis

Mucoepidermoid carcinoma



Malignant. Most common salivary cancer in US.

Three components:
1) Mucinous cells (stain with PASD/mucicarmine)
2) Squamoid cells
3) "Intermediate cells" (neither squamous nor mucinous, with scanter cytoplasm)

Oncocytic variant exists, but is rare.
Can be solid or cystic.

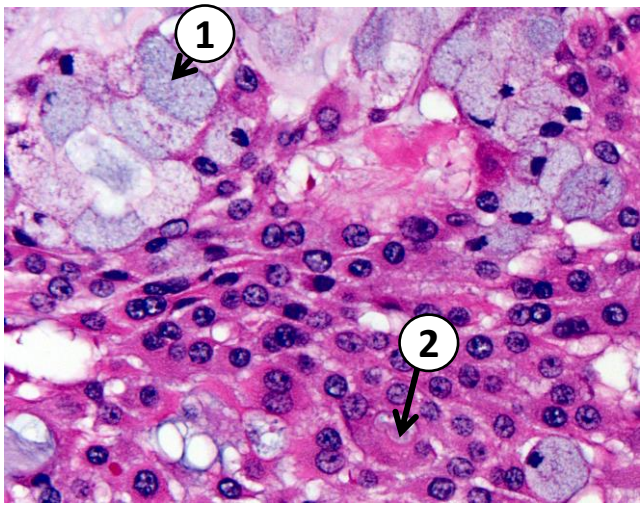
Often in parotid, but can get anywhere.
Broad age range, including kids

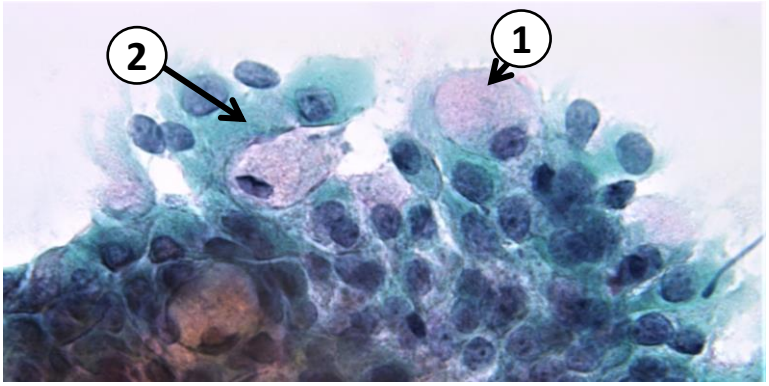
Cytogenetics: **MAML2 gene fusions** almost definitional now

Must grade. Several systems, but often graded intuitively (see table)

IHC: (+)p63, p40, (-) S100, SOX10

Low-Grade	High-Grade
Mostly cystic	More solid
Well-circumscribed	Infiltrative
More mucinous cells	More squamous cells
Cytologically bland	More atypical cytologically
Low mitotic count	High mitotic count, Necrosis





Squamous Cell Carcinoma

If it is entirely squamous (with no mucinous cells or intermediate cells, and esp. when there are keratin pearls), a **metastasis** needs to be excluded clinically

→ Often actually a metastasis from a Head or Neck squamous cell carcinoma (e.g., to an intra parotid lymph node). Also consider extensive SCC differentiation of another salivary gland carcinoma.

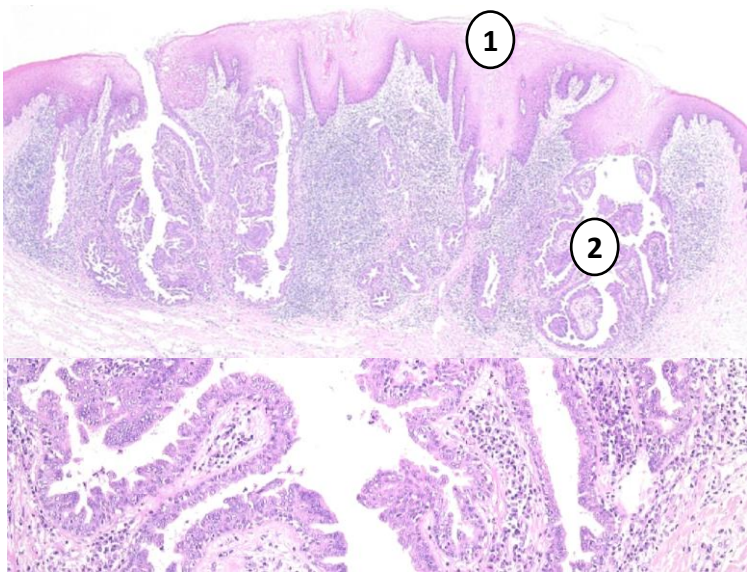
Of note, higher grade Mucoep's often are more squamous, so make sure the tumor is well-sampled. If it has lots of dense keratinization, it's likely a metastasis. Mucoep's are squamoid, not squamous. Consider HPVish to exclude a cystic HPV-positive SCC metastasis.

Sialadenoma papilliferum

Benign. Rare.

Has two components:
1) Surface exophytic mucosal squamous proliferation, with contiguous
2) Submucosal salivary gland ductal epithelium that shows endophytic papillary infoldings and cystic-like spaces.
Common associated lymphoid infiltrate.
Usually hard palate.

Molecular: BRAF p.V600E mutations

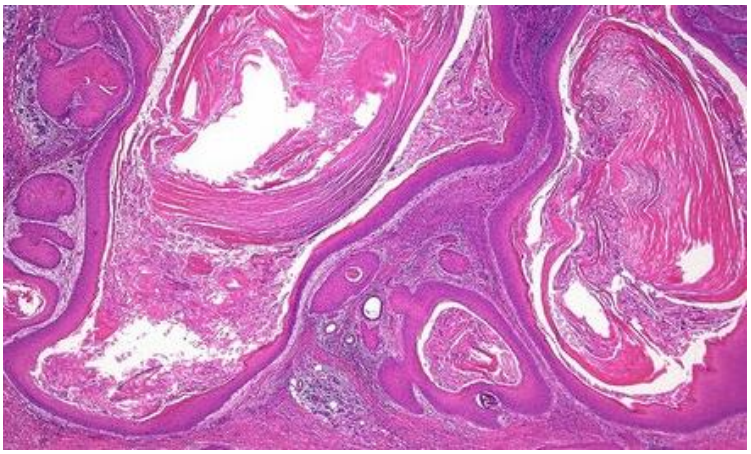


Keratocystoma

Benign

Multicystic spaces lined by squamous epithelium without a granular layer
Keratinized lamellae
Sharply defined squamous cell islands

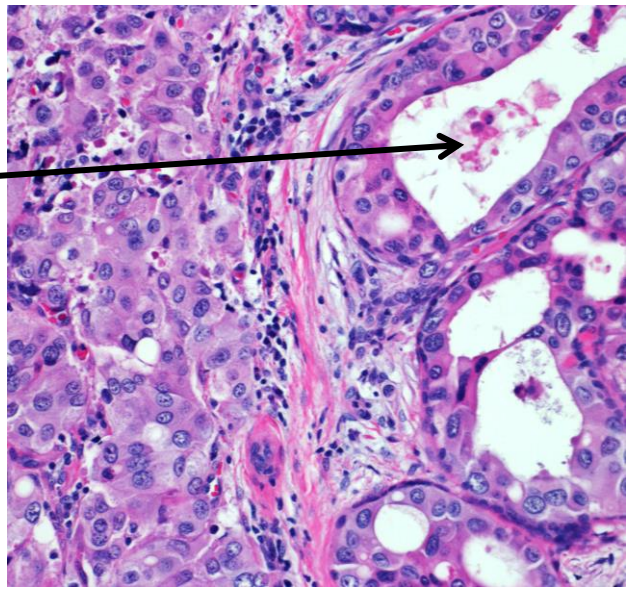
Molecular: RUNX2 rearrangements



DDX: Malignancy with squamous differentiation (e.g., metastatic SCC). The absence of necrosis, invasion, and cytologic atypia argues against malignancy.

High-Grade

Salivary Duct Carcinoma



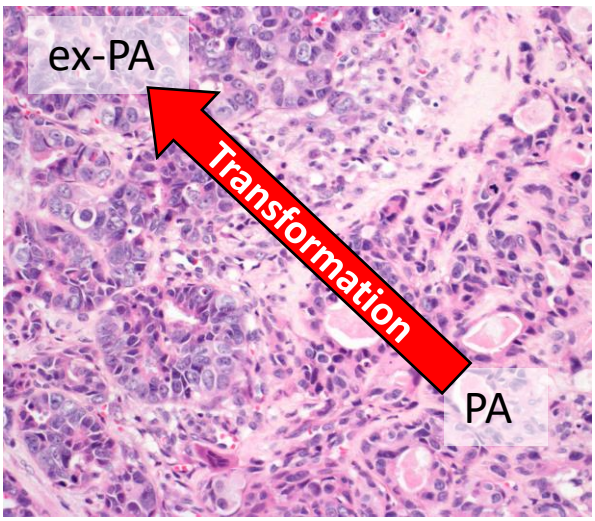
Resembles breast ductal carcinoma
(both invasive and in situ components)
Large ducts with comedonecrosis (like DCIS!)
Often **apocrine**/oncocytic with abundant eosinophilic cytoplasm. Cytologically high-grade.

IHC: (+) CK7. (-) S100 and SOX10
Androgen receptor (AR) positive in 90%
HER2 positive in about 1/3

Often in parotid, sometimes arising from a pleomorphic adenoma (see below)

Very **Aggressive**.

Carcinoma ex-pleomorphic adenoma



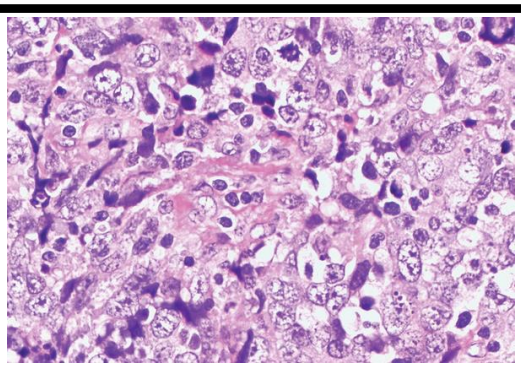
Carcinoma *arising* from a **Pleomorphic Adenoma**
May be a specific type of epithelial or myoepithelial carcinoma→ most often Salivary Duct Carcinoma

Very pleomorphic, with lots of mitoses, necrosis and destructive growth.

Molecular: PLAG1 or HMGA1 rearrangements (from pre-existing PA) and TP53 (in carcinoma)

Usually older (time to de-differentiate) in parotid
Often long history of mass (i.e., a PA), now with rapid enlargement.

Lymphoepithelial Carcinoma



Sheets and cords of polygonal large syncytial cells with eosinophilic cytoplasm and vesicular nucleoli. Also, scattered spindled cells.

Abundant lymphoplasmacytic infiltrate

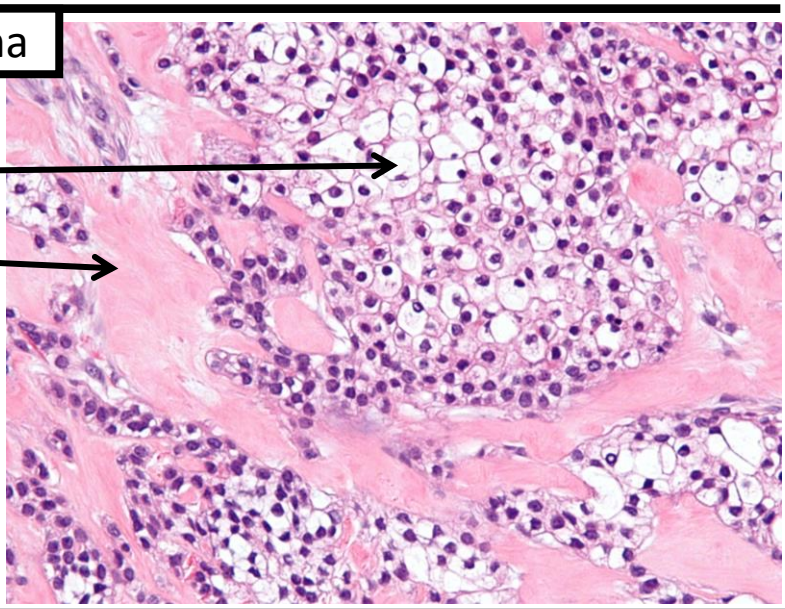
Often EBV positive (like nasopharyngeal carcinoma, must consider metastases!); Also stains with CK

Other High-grade

Carcinosarcoma→ Malignant epithelium *and* mesenchymal components
Metastases
Any other de-differentiated tumors

Clear Cell

Hyalinizing Clear Cell Carcinoma



Malignant, but indolent.

Sheets and tests of **polygonal clear** and eosinophilic cells

Hyalinized/sclerotic stroma

Can have squamous and/or mucinous areas

Molecular: EWSR1-ATF1 fusion

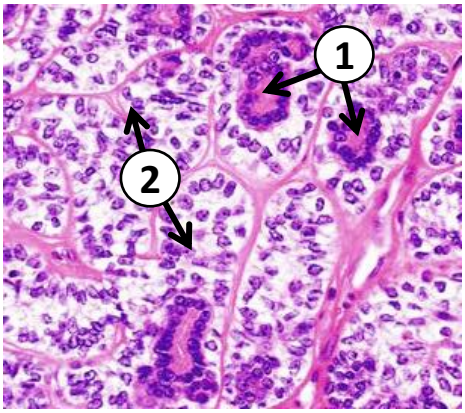
Unencapsulated, infiltrative

Usually intraoral minor salivary glands

"Clear" b/c full of glycogen→ stains with PAS
IHC: (+) CK and p63. (-)S100, SMA, calponin

Epithelial-Myoepithelial Carcinoma

"EMC"



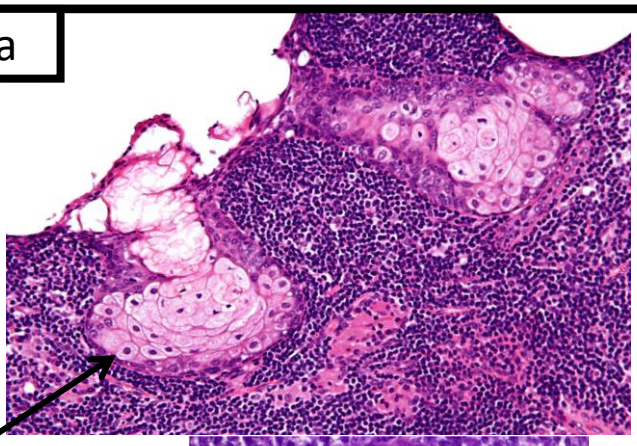
Malignant, but good prognosis.

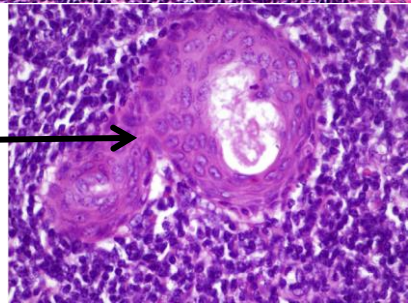
Multinodular invasive growth.

Biphasic:
1) Inner luminal ductal cells, with eosinophilic cytoplasm
2) Outer myoepithelial cells, with clear cytoplasm

Usually in parotid

Sebaceous adenoma/lymphadenoma





Benign. Rare.
Well-circumscribed.
Irregularly sized and shaped nests of sebaceous cells.
Frequent cystic and/or squamous change.
No cytologic atypia.

Sebocytes stain for p63, EMA, adipophilin, and perilipin

If sebaceous cells, but *no* lymphoid tissue→ *sebaceous adenoma*.

If sebaceous cells with prominent benign reactive germinal centers→ *sebaceous lymphadenoma*

If *non*-sebaceous ducts with prominent germinal centers→ *lymphadenoma*

If invasive/malignant→ *Sebaceous adenocarcinoma*

Miscellaneous/Other Tumors

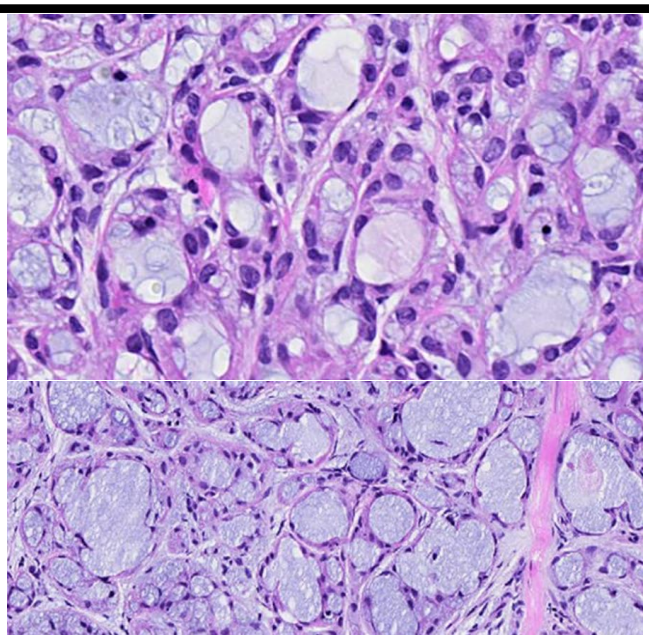
That don't fit well into my scheme! ;-)

Ductal papillomas

Benign epithelial neoplasms arising from the main excretory salivary ducts.
Often near oral mucosa opening. Often intermixed mucoid cells.

"Intraductal papilloma"—exophytic papillary projections into a cystic space. Columnar cells.
"Inverted papilloma"—endophytic growth. Squamoid cells.

Microsecretory adenocarcinoma



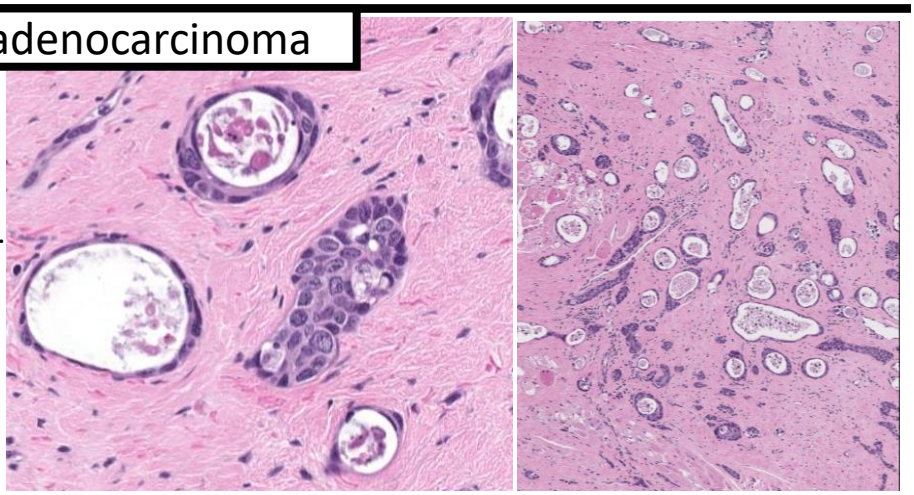
Malignant, but usually indolent.

Microcystic-predominant growth.
Uniform incalated duct-like tumor cells with **attenuated** eosinophilic to clear cytoplasm.
Small, hyperchromatic nuclei.
Bluish secretions.
Fibromyxoid stroma.
Rounded borders with subtle infiltration.

Molecular: **MEF2C-SS18 fusion**
(Dx with SS18 FISH or PCR, same as Synovial Sarcoma)

IHC: (+)S100, SOX10, p63;
(-)p40, mammoglobin, calponon.

Sclerosing microcystic adenocarcinoma



Malignant, but indolent.

<u>Infiltrative</u>.
Low-grade with bland cytology.
Embedded in **dense sclerotic stroma**.
Biphasic cell population with attenuated myoepithelial cells.

Arises in minor salivary glands.
Frequent PNI.

Looks like cutaneous syringoma or microcystic adnexal carcinoma.

Other

<u>Mucinous Adenocarcinoma</u>: Primary salivary gland carcinoma with prominent intracellular and/or extracellular mucin (that doesn't fit into other groups). Recurrent ATK1 mutations. IHC: (+) CK7, (-) CK20.

ABC's

Try Building a DDX from the ABC's

A: Architecture

How are the nests of tumor arranged?

Encapsulated (Benign, usually)
Pleomorphic adenoma
Basal cell adenoma
Myoepithelioma
Oncocytoma
Warthin tumor
Epithelial-Myoepithelial carcinoma

Note: *All minor salivary gland tumors are unencapsulated*

Circumscribed
Pretty much anything
(Benign or Malignant)

Infiltrative (Malignant, usually)
Adenoid cystic
Acinic cell carcinoma
Basal cell adenocarcinoma
Mucoepidermoid carcinoma
Oncocytic carcinoma
Intraductal carcinoma
Clear cell carcinoma
Epithelial-myoepithelial carcinoma
Carcinosarcoma
Carcinoma ex-PA
Myoepithelial carcinoma
Secretory carcinoma
Lymphoepithelial carcinoma

B: Bi-Phasic (Phases)

How many different types of cells are present?

Monophasic
Myoepithelioma
Myoepithelial carcinoma
Clear cell carcinoma
Polymorphous adenocarcinoma
Small cell neuroendocrine carcinoma
Salivary duct carcinoma
Canalicular adenoma
Secretory carcinoma

Biphasic
Adenoid cystic
Basal cell adenoma/CA
Epithelial-Myoepithelial CA
Warthin tumor
Oncocytoma/CA
Intraductal carcinoma
Lymphoepithelial carcinoma

Triphasic (or More!)
Pleomorphic adenoma
Mucoepidermoid carcinoma
Acinic cell carcinoma
Carcinosarcoma
Carcinoma ex-PA

C: Cytology

Which types of cells are present?

Acinar cells
Acinic cell carcinoma

Basal cells
Basal cell adenoma
Basal cell carcinoma
Oncocytoma
Oncocytic carcinoma

Tumor-Associated Lymphoid Proliferations
Mucoepidermoid carcinoma
Acinic cell carcinoma
Lymphoepithelial carcinoma
Lymphadenoma

Clear cells
Clear cell carcinoma
Acinic cell carcinoma
Secretory carcinoma

Myoepithelial cells
PA
Adenoid cystic
Myoepithelioma/CA
Basal cell adenoma/CA
Epithelial-myoepithelial carcinoma
Intraductal carcinoma
Carcinoma ex-PA

Ductal cells
PA
Adenoid cystic
Basal cell adenoma/CA
Canalicular adenoma
Epithelial-myoepithelial carcinoma
Salivary Duct carcinoma
Polymorphous Adenocarcinoma
Secretory carcinoma
Carcinoma ex-PA
Acinic cell carcinoma

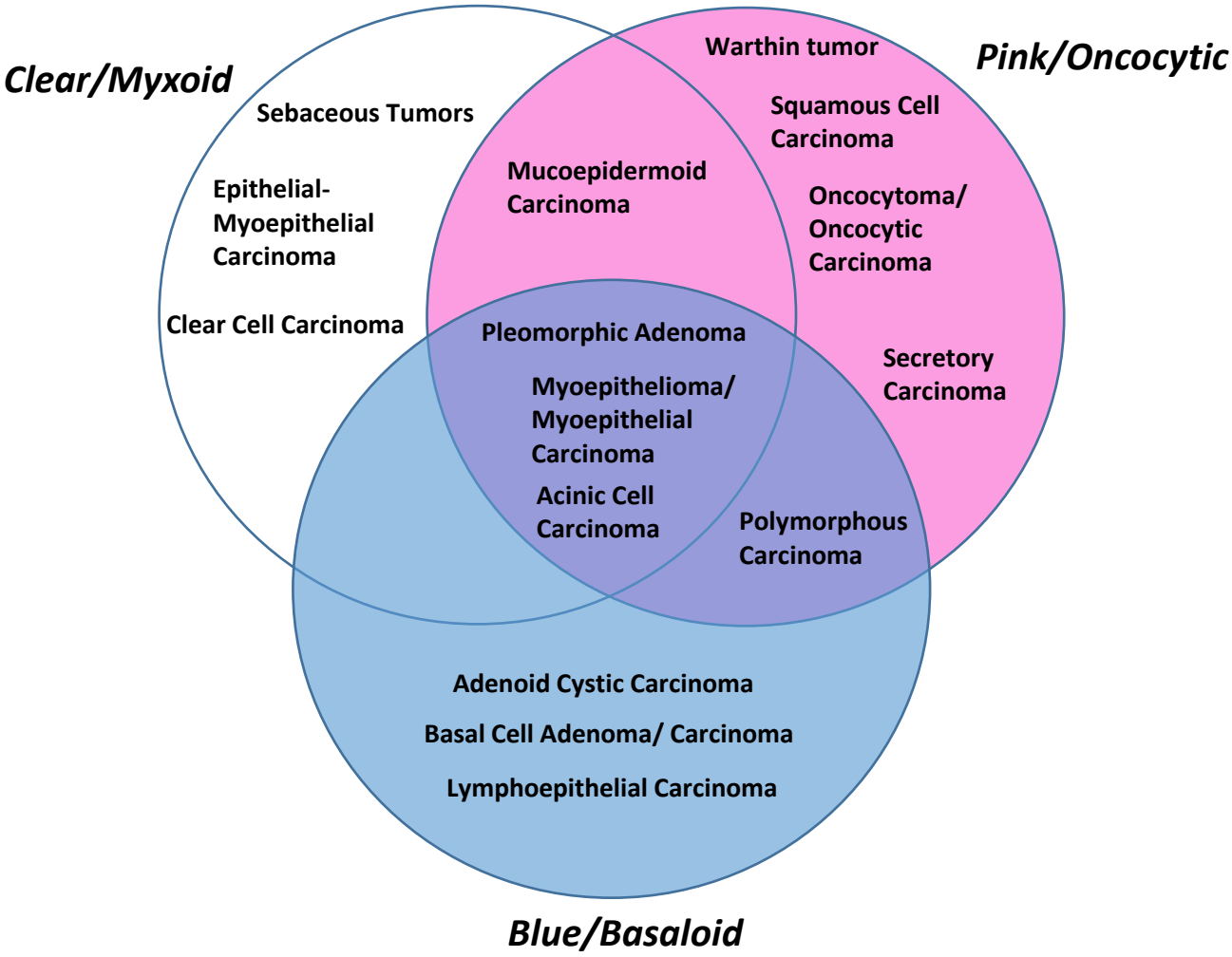
Mucous cells
Mucoepidermoid carcinoma

Oncocytes
Oncocytoma/CA
Clear cell carcinoma
Secretory carcinoma
Warthin tumor

Note: Modified from a presentation by Joaquín J. García MD, Division of Anatomic Pathology, Mayo Clinic Rochester

ABC's

Try Building a DDX from the ABC's



Note: Modified from: Seethala. Modern Pathology (2017) 30, S84–S95

Stains/Studies

Warning: Morphology is still King!

Note: Many salivary gland tumors have at least *some* myoepithelial component

Myoepithelial markers: p63, p40, Calponin, SMA, GFAP, S100, SOX10
(but somewhat unpredictable—tumors don't always obey the usual "rules"!)

High-grade Salivary Tumors

	p63/p40	SMA, Calponin	CK8/18	CK5/6	Mucin	AR	Synaptophysin
Mucoepidermoid, High-grade	+	-	Focal	+	+	-	-
Squamous cell carcinoma	+	-	-	+	-	-	-
Salivary Duct Carcinoma	-	-	+	-	-	+	-
Poorly-differentiated neuroendocrine carcinoma	-/+	-	Dot-like	-	-	-	+

Basaloid Salivary Tumors

	p63	p40	SMA/ Calponin	S100	CD117	LEF-1	PLAG1	MYB
Pleomorphic adenoma	+	+	+	+	+/-	+/-	+	-
Basal cell adenoma/carcinoma	+	+	+	-/+	+/-	+	-	-
Adenoid cystic carcinoma	+/-	+/-	+	+	+	-	-	+
Myoepithelioma/carcinoma	+	+	+	+	-	-	-/+	-
EMEC	+	+	+	+	-/+	-	-	-
PLGA	+	-	-	+	+/-	-	+/-	-

Myoepithelial markers in "Abluminal" (outside) cells

Clear Cell Salivary Tumors

	p63/p40	S100	Sox10	DOG1
Myoepithelioma/carcinoma	+	+	-	-
EMEC	+	+	-	-
Acinic cell carcinoma	-	-	+	+
Mucoepidermoid carcinoma	+	-	-/+	-/+

Oncocytic Salivary Tumors

	p63	p40	S100	Mammaglobin	Sox10	DOG1	GATA3	AR
Warthin & Oncocytoma	+	-	-	-	-	-	-	-
Acinic cell carcinoma	-	-	-	-	+	+	-	-
Secretory carcinoma	-	-	+	+	+	-	+	-
Mucoepidermoid carcinoma	+	+	-	-	-/+	-/+	-	-
Salivary duct carcinoma	-	-	-	-/+	-	-	+	+

Most common molecular alterations

Tumor	Most common molecular alteration
Adenoid cystic carcinoma	MYB, MYBL1 fusions, NOTCH mutations
Clear cell carcinoma	EWSR1-ATF1 Fusion
Intraductal carcinoma	RET fusions; PIK3CA or HRAS mutations
Mucoepidermoid carcinoma	MAML2 fusions
Pleomorphic adenoma	PLAG1, HMGA2 fusions/amplifications
Polymorphous low-grade adenocarcinoma	PRKD fusions/mutations
Secretory carcinoma	ETV6 Fusions
Acinic cell carcinoma	NR4A3 fustion/activation
Epithelial-Myoepithelial Carcinoma	HRAS mutations
Myoepithelial Carcinoma	PLAG1 or EWSR1 fusions
Basal cell adenoma/adenocarcinoma	CTNNB1 or CYLD mutations
Sialadenoma papilliferum	BRAF V600E mutation
Striated duct adenoma	IDH2 mutations
Intercalated duct adenoma/hyperplasia	CTNNB1 or HRAS mutations
Sclerosing polycystic adenoma	PIK3CA, PIK3R1, PTEN mutations
Keratocystoma	RUNX2 fusions
Microsecretory adenocarcinoma	MEF2C::SS18 fusion
Salivary duct carcinoma	HER2 amplification, TP53 mutation, AR copy gain
Mucinous adenocarcinoma	AKT1 p.E17K mutations

Grading Salivary Gland Tumors

Some tumors have "intrinsic" grade. Others have a variable grade and must be specifically graded. Intrinsically graded tumors can still be up/down-graded (usually up) based on atypia, etc…

Low-grade (Treated surgically like benign tumors)	Intermediate (Treated variably)	High-grade (Treated aggressively)	Variable grade
Acinic Cell Carcinoma Polymorphous Adenocarcinoma Basal Cell Adenocarcinoma Epithelial-Myoepithelial Carcinoma Secretory carcinoma Clear Cell Carcinoma	Myoepithelial Carcinoma	Salivary Duct Carcinoma Neuroendocrine carcinomas Lymphoepithelial carcinoma Primary squamous cell carcinoma	Mucoepidermoid Carcinoma Adenoid Cystic Carcinoma Adenocarcinoma, NOS Intraductal Carcinoma Carcinoma-ex Pleomorphic Adenoma

High-grade Transformation

Low/intermediate grade tumors can undergo "High-grade Transformation" (i.e., De-differentiation)

- Lose recognizable conventional histomorphology, with increased mitotic activity and pleomorphism
- Transformed component usually high-grade carcinoma NOS or squamous cell carcinoma
- Tends to occur in patients older than the median age for individual neoplasms
    - (Time for tumors to de-differentiate)
- More aggressive behavior→ Worse prognosis

Adapted from a presentation from Justin A. Bishop, MD Chief of Anatomic Pathology UT Southwestern Medical Center

Milan System

On FNA's, try to use the Milan system to guide clinical management and whenever possible subtype the tumor and, if malignant, give a grade (high vs low).

Category	Explanation	Risk of Malignancy	Clinical Management
1. Non-diagnostic	Insufficient material for Dx	25%	Clinical and radiologic correlation/repeat FNA
2. Non-Neoplastic	Inflammatory/reactive changes (e.g., reactive lymph node, infection)	10%	Clinical follow-up and radiologic correlation
3. Atypia of Undetermined Significance	Indefinite for neoplasm (often inadequately sampled neoplasm) (e.g., rare atypical cells, abundant mucin)	20%	FNA or surgery
4. Neoplasm: Benign	E.g., Pleomorphic adenoma, Warthin Tumor	<5%	Surgery or follow-up
4. Neoplasm: Uncertain Malignant Potential	E.g., "Basaloid neoplasm" (Favor Monomorphic adenoma, cannot rule out adenoid cystic)	35%	Surgery
5. Suspicious for Malignancy	Features suspicious for malignancy but not unequivocal	60%	Surgery
6. Malignant	Clearly malignant (e.g., Mucoep, Adenoid cystic, etc…). Try to subtype and grade if possible.	90%	Surgery