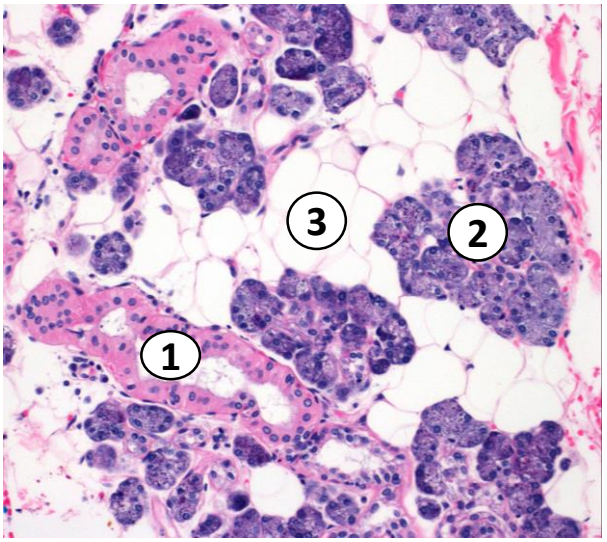
Prepared by Kurt Schaberg

Salivary Gland Tumors

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 salivary gland can be within benign lymph nodes).

If have symmetric enlargement of salivary glands with no discrete mass, consider **sialadenosis.**

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

Oncocytic hyperplasia (aka *Oncocytosis*): Non-neoplastic, mass-forming proliferation of oncocytes, which can be focal or diffuse. Unencapsulated. Often multifocal, admixed with normal salivary tissue.

Oncocytoma

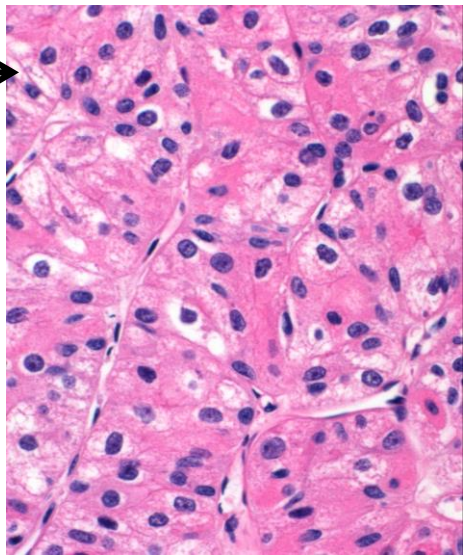
Benign

Circumscribed to encapsulated proliferation of oncocytes.

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

Usually in parotid

No significant: pleomorphism, mitotic activity, or invasive growth



Oncocytic Carcinoma

Malignant

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

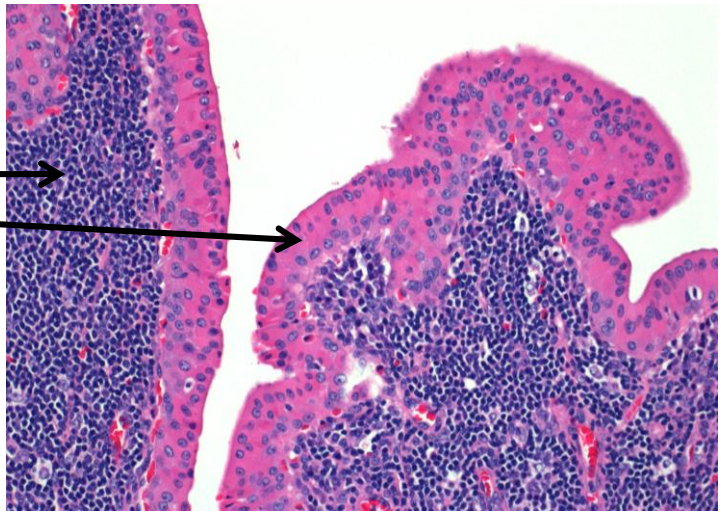
May or may not be encapsulated.

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



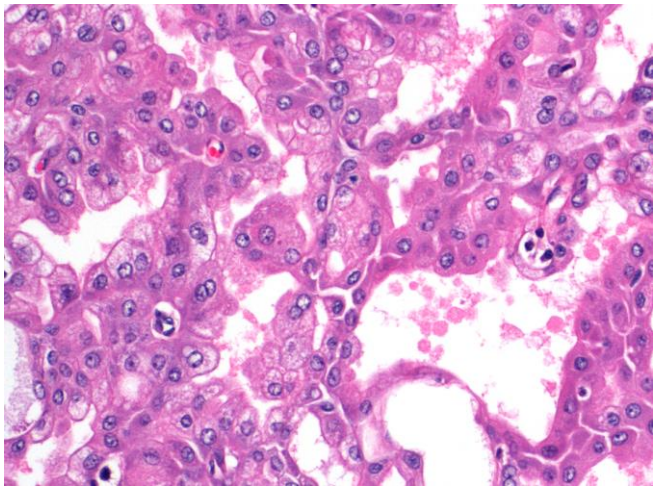
Strongly linked to smoking, can be bilateral

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"*



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

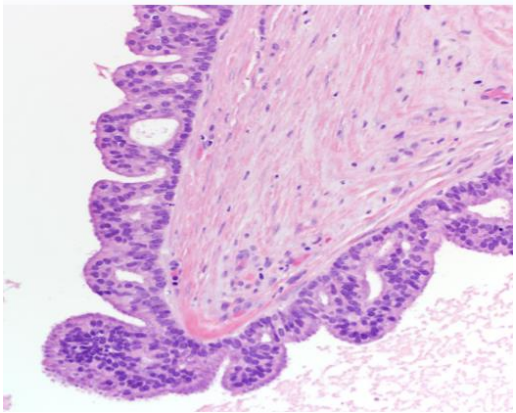
ETV6-NTRK3 gene fusions.

Stains: Positive for **S100** and **mammaglobin.**

Malignant, but relatively indolent.

Intraductal Carcinoma

Non-invasive carcinoma with retained myoepithelial cells. Think of as like DCIS of the breast.
- Can highlight myoepithelial cells with p63.
- If totally non-invasive→ Excellent prognosis!



Usually in Parotid.

Intercalated duct type	Apocrine type
Always low-grade S100+, mammaglobin+ Most have RET fusion (with NCOA4 or TRIM27) Only rarely associated with invasion	Variable grade AR+, GCDFP15+, S100 –, mammaglobin – Salivary duct carcinoma-like genetics Often associated with invasion

Basaloid

Looks very cellular and blue at low-power

Basal Cell Adenoma / Monomorphic Adenoma

Benign, well-circumscribed, Usually Parotid

Solid, trabecular, or tubular growth
Perpendicular basal cells on outside of nests
Epithelial cells on inside of nests

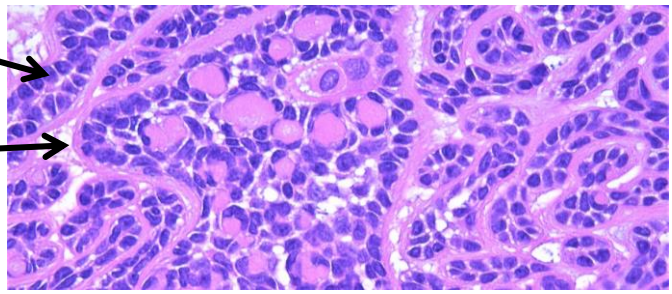
No significant stroma, aside from possibly a "membrane" surrounding a nest

(Think of *pleomorphic adenoma without the stroma* – hence the name *monomorphic* adenoma)

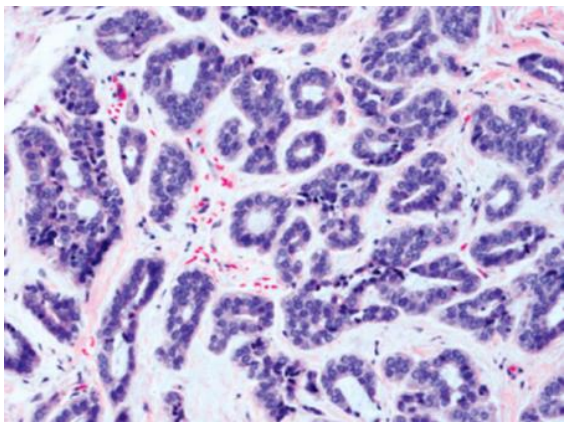
Basal Cell Adenocarcinoma

Malignant

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



Polymorphous Carcinoma



Cytologically **uniform** cells **(monophasic)**
Bland, round to spindled cells with moderate amounts of cytoplasm. Oval nuclei with vesicular chromatin.
Strong, diffuse staining with S100. p63+ but p40 -

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

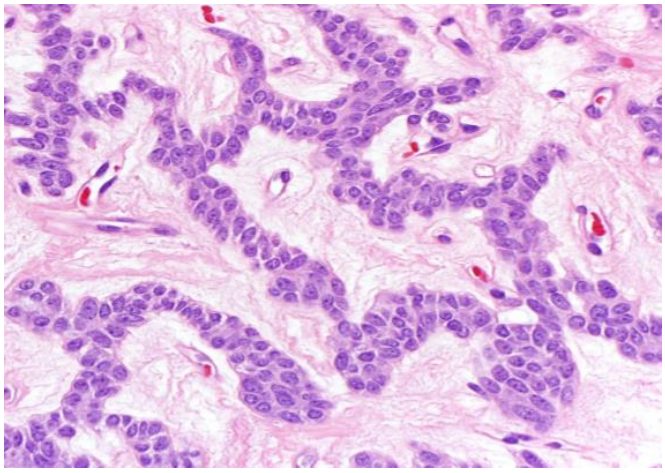
Infiltrative with significant PNI

PRKD fusions/mutations

Always in MINOR salivary glands, often palate

Formerly called "Polymorphous Low-Grade Adenocarcinoma" → "PLGA"

Canalicular Adenoma



Almost always upper lip

Encapsulated

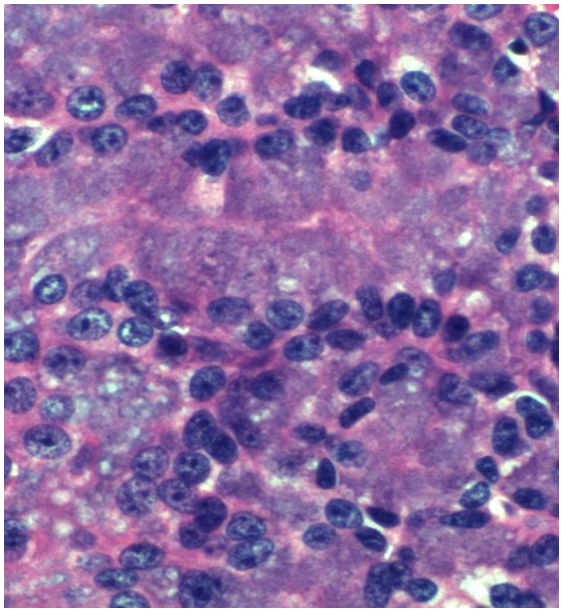
Monophasic

Characteristic "canalicular" pattern of **cords and ribbons** of basaloid tumor cells with occasional **interconnecting**.

Cords separated by loose fibrillar stroma

Benign

Acinic Cell Carcinoma



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

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

Sometimes prominent lymphoid infiltrate

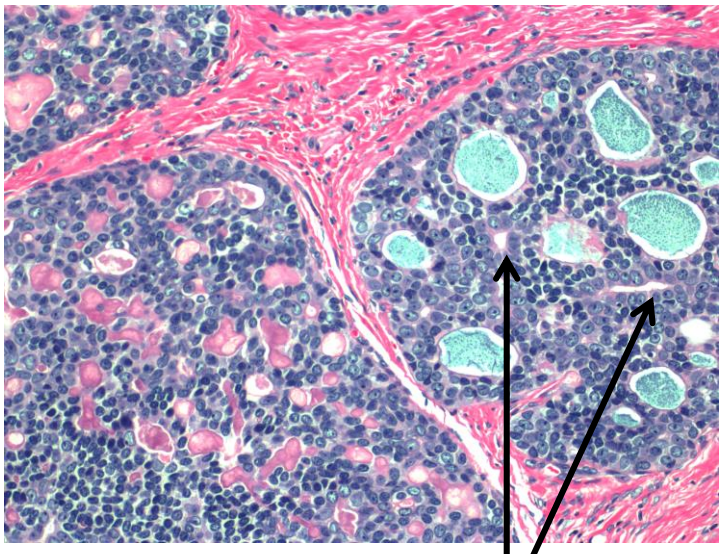
Usually in parotid. Can see in kids.

NR4A3 Translocations common

Stains: Positive for **DOG-1** and SOX-10

Malignant, but generally not aggressive

Adenoid Cystic Carcinoma



Ducts
(Most of the cells are myoepithelial in this case!)

Cribriform, tubular or solid growth

2 cell types: 1) Myoepithelial and 2) Ducts

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

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

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

Grading: give % Solid (ductal) component

Myoepithelial cells form pseudocysts that contain blue glycosaminoglycans or pink basement membrane material (which are visible on FNA, with "stromal exclusion" of myoepithelial cells)

Cytogenetics: Fusions of MYB or MYBL1 to NFIB

Infiltrative→ Extensive PNI→ Pain → Paralysis

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

Additional Basaloid tumors

Lymphadenoma: Encapsulated tumor with anastomosing cords of basaloid cells with abundant tumor-associated lymphoid tissue.
Small cell neuroendocrine carcinoma: Like in the lung!
Sialoblastoma: Primitive-appearing basaloid cells. Seen in kids.

Prominent Spindled Cells

Pleomorphic Adenoma

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

Most common tumor of salivary glands

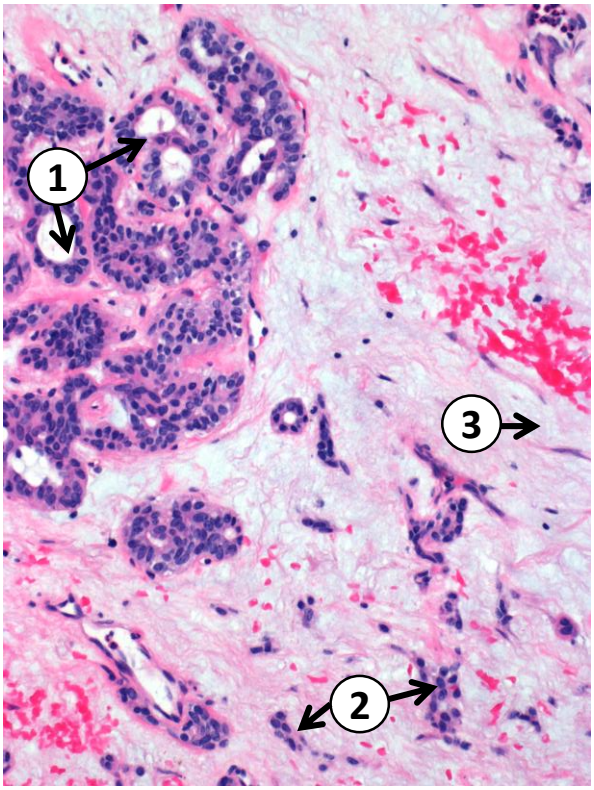
Three components, encapsulated, well-circumscribed:
1) **Ductular structures**
2) **Myoepithelial cells** (can be spindled, epithelioid, plasmacytoid, etc…), intimately admixed with stroma
3) Mesenchymal-like tissue (often **myxoid stroma**, but can be chondroid, etc…)

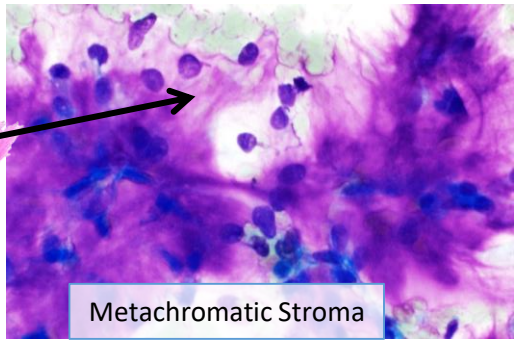
Architecturally pleomorphic (cytologically bland!)

If ducts or myoepithelial cells dominate (but some component is classic), can use the term "cellular" PA

Can see: tyrosine crystals, squamous metaplasia, cystic degeneration

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





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

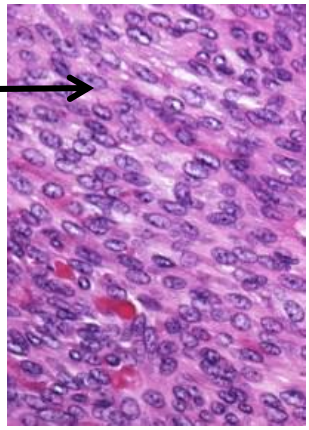
Also visible ductal cells and myoepithelial cells intimately admixed with the stroma

Myoepithelioma

Benign

Composed of entirely **myoepithelial cells**
Typically spindled to plasmacytoid

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



Myoepithelial Carcinoma

Malignant

Composed of entirely **myoepithelial cells**

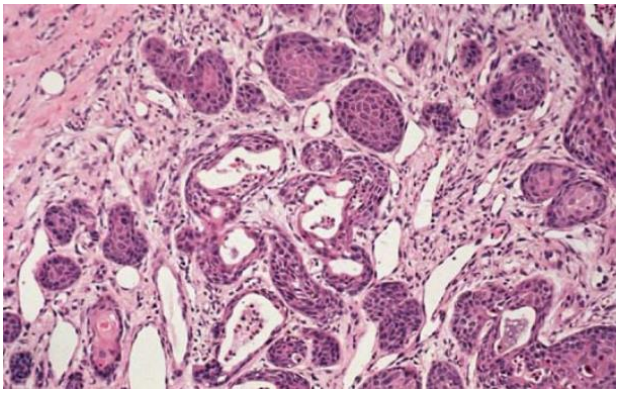
Presence of necrosis, atypical mitotic figures, invasion to surrounding parenchyma

Also Consider

Carcinosarcoma
Adenoid cystic carcinoma
Epithelial-myoepithelial carcinoma

Squamoid

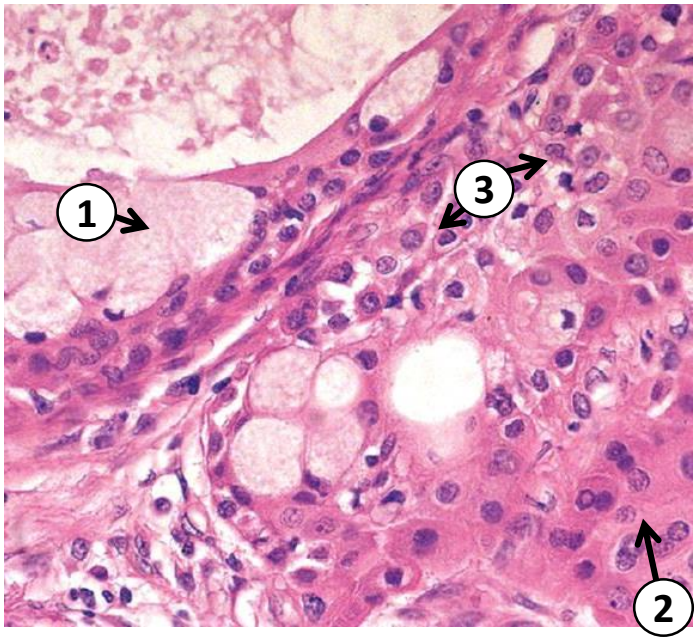
Squamous metaplasia



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



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

Oncocytic variant exists, but is rare.

Most common malignant salivary cancer.
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)

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

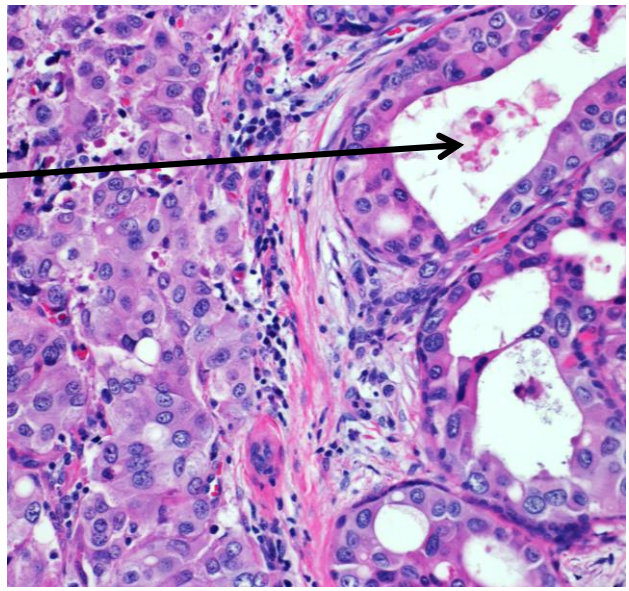
Squamous Cell Carcinoma

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.

High-Grade

Salivary Duct Carcinoma



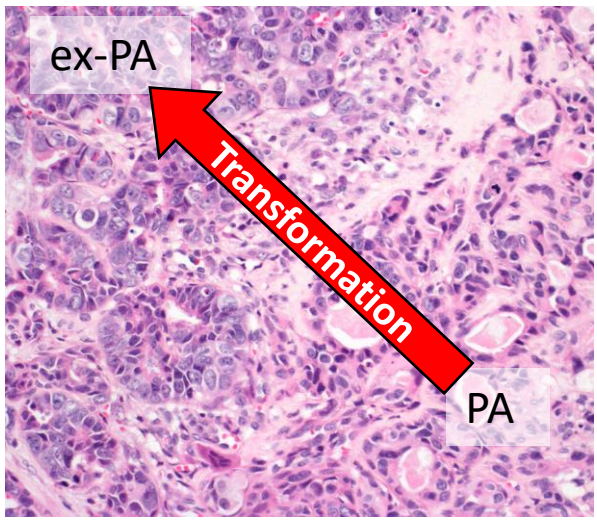
Resembles breast ductal carcinoma
(both invasive and in situ components)
Large ducts with comedonecrosis (like DCIS!)
Often apocrine/oncocytic

Stains: Androgen receptor (AR) and HER2 positive

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

Very Aggressive

Carcinoma ex-pleomorphic adenoma



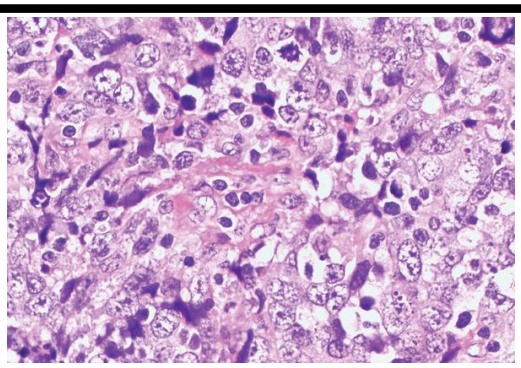
Carcinoma *arising* from a **Pleomorphic Adenoma**
May be a specific type of epithelial or myoepithelial carcinoma→ most often Salivary Duct Carcinoma

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

Cytogenetics: PLAG1-HMGA1 (in 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

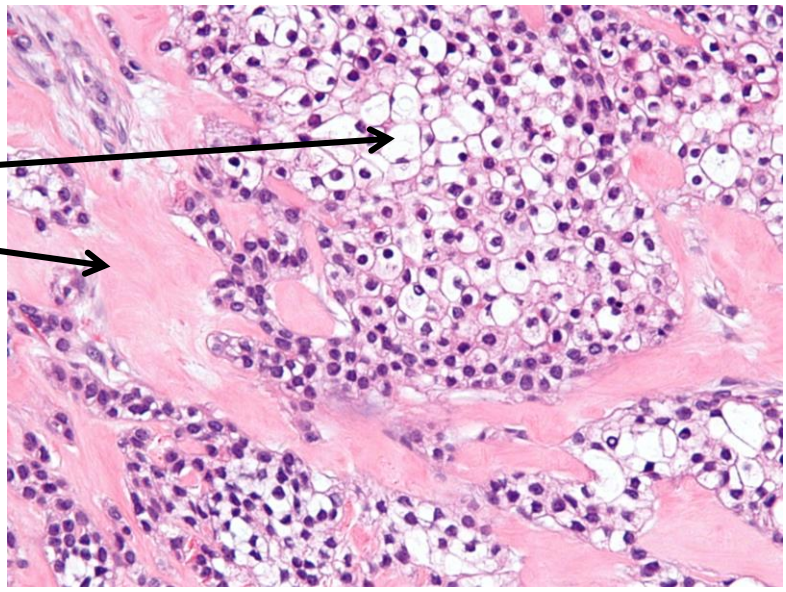
Often EBV positive (like nasopharyngeal carcinoma, must consider metastases!); Also stains with CK

Other High-grade

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

Clear Cell

Clear Cell Carcinoma



Aka: *Hyalinizing* clear cell carcinoma

Sheets and tests of **polygonal clear cells**
Hyalinized/sclerotic stroma

EWSR1-ATF1 fusion

Unencapsulated, infiltrative

Usually intraoral salivary glands

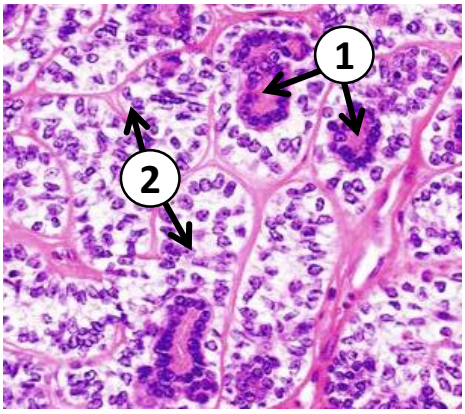
"Clear" b/c full of glycogen→ stains with PAS
Stains: CK and p63 positive, Neg. myoep markers

Epithelial-Myoepithelial Carcinoma

"EMC"

Malignant

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



Usually in parotid gland and indolent

Other Clear Cell

Acinic Cell Carcinoma
Secretory Carcinoma
Mucoepidermoid carcinoma

Pleomorphic adenoma

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

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

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
Secretory carcinoma

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

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!)

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

Stains/Studies

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	-	-	-	-/+	-	-	+	+

Molecular testing

Tumor	Most common molecular alteration
Adenoid cystic carcinoma	MYB fusions
Clear cell carcinoma	EWSR1-ATF1 Fusion
Intraductal carcinoma	NCOA4-RET fusions
Mucoepidermoid carcinoma	MAML2 fusions
Pleomorphic adenoma	PLAG1-HMGA2 fusions
Polymorphous low-grade adenocarcinoma	PRKD fusions/mutations
Secretory carcinoma	ETV6 Fusions
Acinic cell carcinoma	NR4A3 translocations
Epithelial-Myoepithelial Carcinoma	PLAG1/HMGA2 translocations or HRAS mutations
Myoepithelial Carcinoma	PLAG1/HMGA2 translocations or EWSR1 translocations
Basal cell adenoma/adenocarcinoma	CTNNB1 or CYLD mutations

Tables Adapted from:
The Milan System for Reporting Salivary Gland Cytopathology. Faquin and Rossi. 2018.
Quick Reference Handbook for Surgical Pathologists. Rekhtman et al. 2019.

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