

**Diagnosing Salivary Gland Tumors
by FNA:
How Far Can We Go?**

W.C. Faquin, M.D., Ph.D.
Director, Head and Neck Pathology
Massachusetts General Hospital
Massachusetts Eye and Ear Infirmary
Harvard Medical School
Boston, MA




HARVARD MEDICAL SCHOOL
DEPARTMENT OF CONTINUING EDUCATION

**CURRENT CONCEPTS IN HEAD AND NECK &
ENDOCRINE PATHOLOGY**
JUNE 3-6, 2015

Directed by:
W.C. Faquin, MD PhD, V. Noe, MD PhD, R.M. Sadow, MD PhD

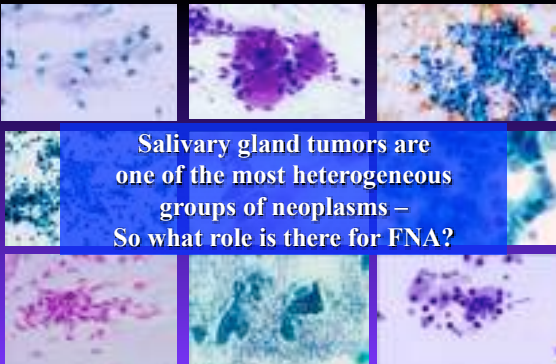
Guest Speakers: *Drs. Ricardo Lloyd & Bruce Wenig*

Held At:
The Fairmont Copley Plaza Hotel
Boston, MA, USA



What are some of the most important salivary gland tumors to recognize by FNA, what are the pitfalls, and what ancillary tests can we use?

Salivary gland tumors are one of the most heterogeneous groups of neoplasms – So what role is there for FNA?



SALIVARY GLAND FNA

Rationale for FNA:

- Guide the clinical management/pre-op strategy:
 - »Non-neoplastic
 - »Benign tumor or low-grade carcinoma
 - »High-grade carcinoma

WARNING!

While most salivary gland tumors can be readily diagnosed in surgical resection specimens, caution is warranted when interpreting small biopsies and FNAs!

SALIVARY GLAND FNA: How Far Can We Go?

Usually Specific Diagnosis	Sometimes Specific Diagnosis	Usually Descriptive Diagnosis
Pleomorphic adenoma	Adenoid cystic carcinoma	Basal cell adenoma, tubulotrabeular and solid types
Warthin tumor	LG mucosquamous carcinoma	HG mucosquamous carcinoma
Basal cell adenoma, Membranous type	Mucocyst	Polymorphous low grade adenocarcinoma
Acute and chronic sialadenitis	Carcinoma ex PA	Salivary duct carcinoma
Reactive lymph node	Small cell carcinoma	Basal cell adenocarcinoma
Lymphoma	Mucocele	Epithelial-myoepithelial carcinoma
	Oncocytoma	
	LESA	
	Acinic cell carcinoma	

Pitfall: Normal Salivary Gland FNA

Beware of aspirates containing only normal salivary gland elements – they are essentially non-diagnostic!

FNA OF THE NORMAL SALIVARY GLAND

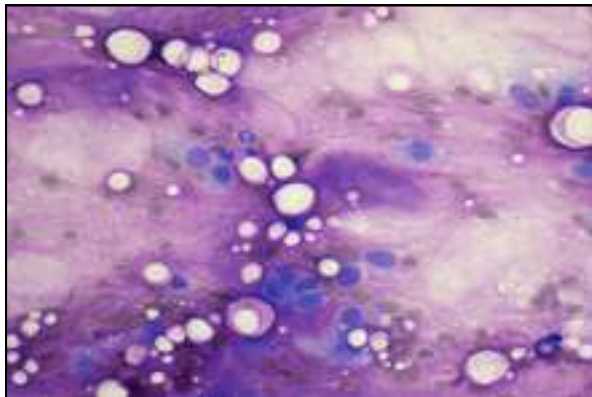
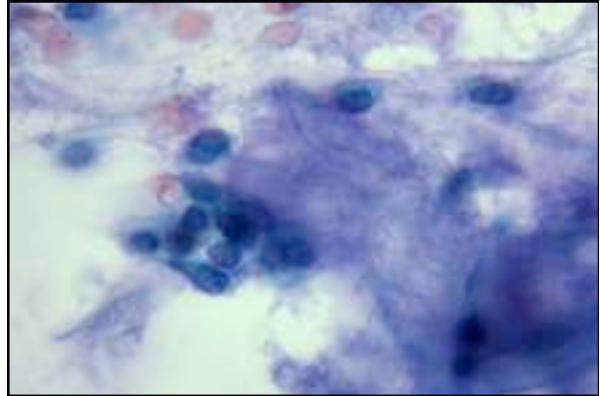
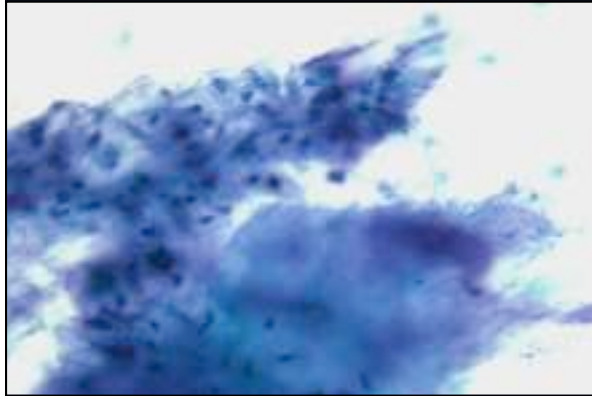


SELECTED CATEGORIES OF SALIVARY GLAND TUMORS

Matrix-Containing Salivary Gland Tumors

Case History:

A 36 year-old female presented with a 1.0 cm mass in the right cheek that had been slowly enlarging for one year. An FNA was performed.



CYTOLOGIC DIAGNOSIS:
Pleomorphic adenoma arising in accessory parotid tissue of cheek.

Pleomorphic Adenoma
(Benign Mixed Tumor)

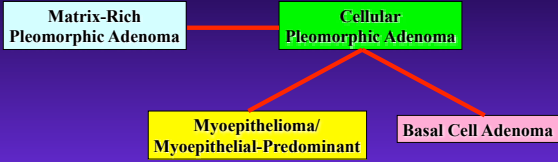
- Most common salivary gland tumor in both children and adults
- 75-80% of parotid tumors & 50% of all salivary tumors
- Superficial parotid gland...esp. the tail of the parotid at jaw angle
- 5-10% risk of malignant transformation
- PLAG1 gene rearrangement is most common molecular change

Pleomorphic Adenoma
Cytologic Features:

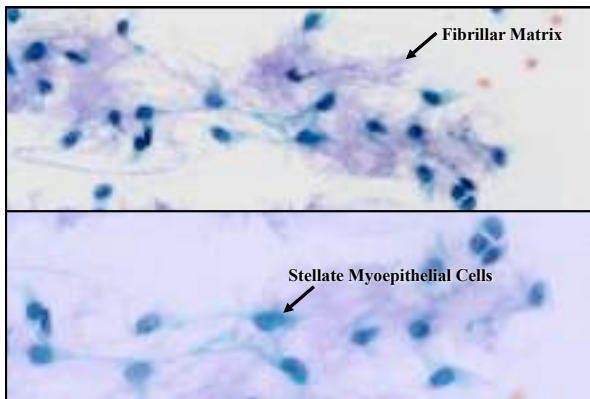
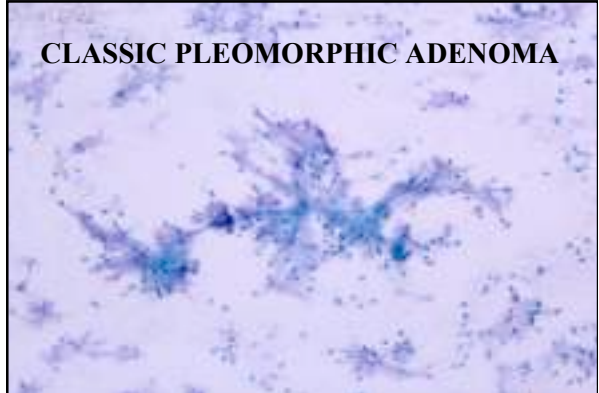
Cells:
Epithelial cells in cohesive, honeycomb groups
Myoepithelial cells singly and clusters:
plasmacytoid, epithelioid, spindled, or clear

Matrix:
Fibrillar with frayed, indistinct margins, embedded cells, metachromatic

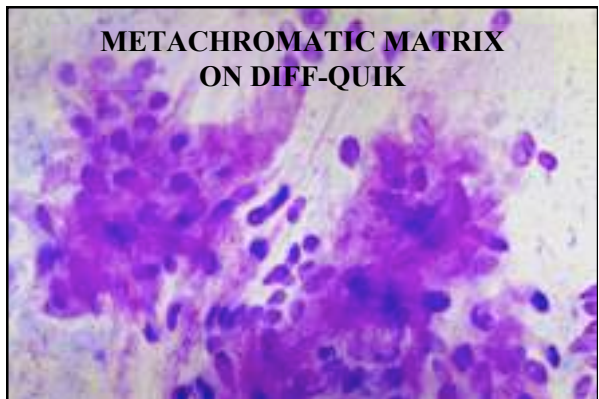
Spectrum of Pleomorphic Adenoma



CLASSIC PLEOMORPHIC ADENOMA



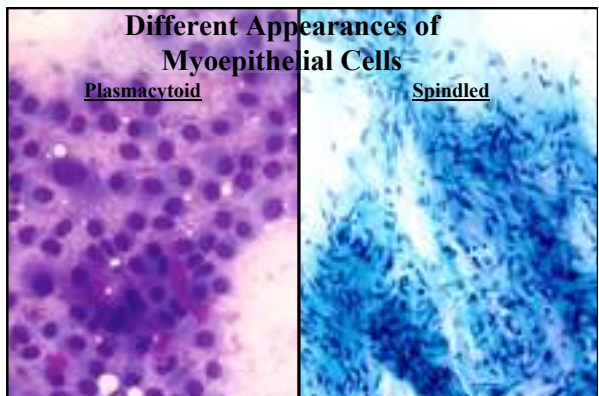
METACHROMATIC MATRIX ON DIFF-QUIK



Cluster of Ductal Cells

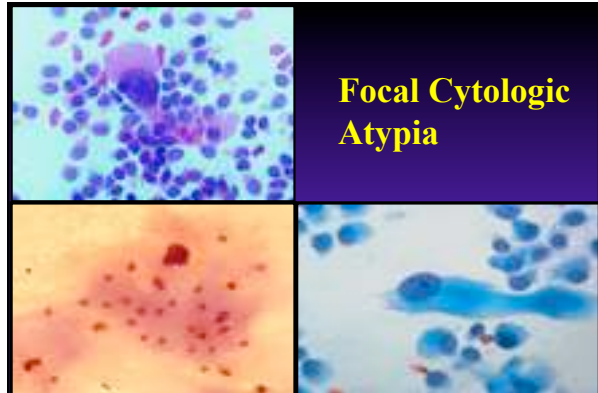


Different Appearances of Myoepithelial Cells



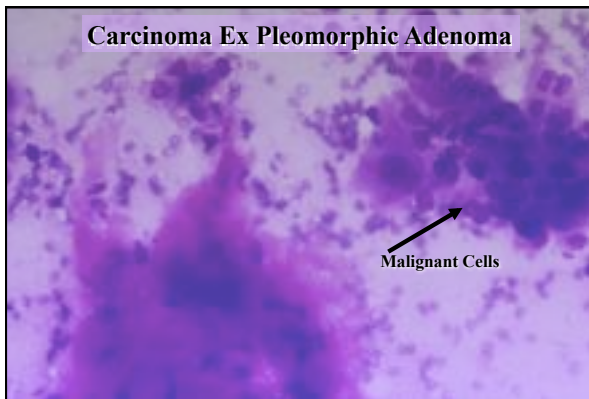
VARIANTS OF PLEOMORPHIC ADENOMA

- Cellular PA with sparse matrix
- Focal adenoid cystic-like areas
- Cytologic atypia
- Metaplasia
 - Squamous
 - Mucinous
 - Sebaceous
 - Oncocytic

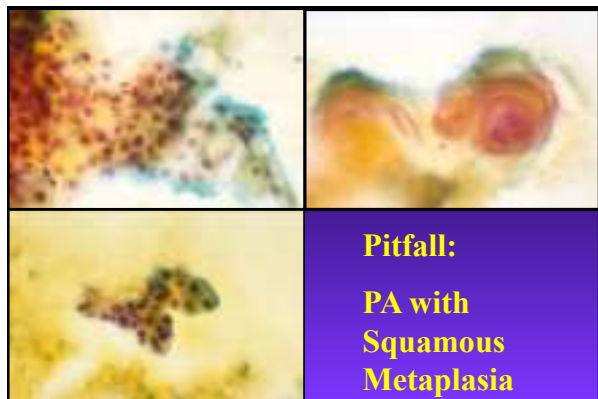


Focal Cytologic Atypia

Carcinoma Ex Pleomorphic Adenoma



Malignant Cells



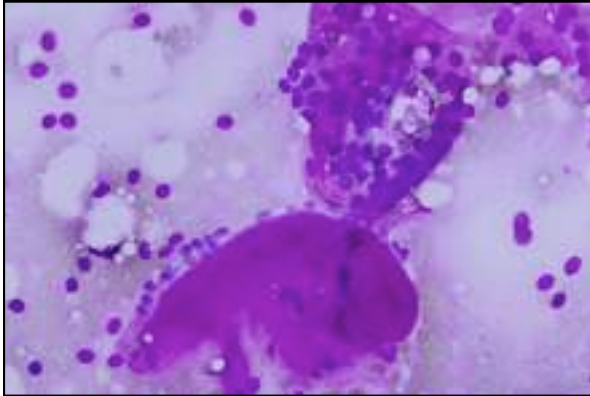
Pitfall:
PA with Squamous Metaplasia

Differential Diagnosis of Matrix-Containing Tumors

- Pleomorphic adenoma
- Adenoid cystic carcinoma
- Basal cell adenoma/adenocarcinoma
- Myoepithelioma
- Epithelial-myoepithelial carcinoma
- Polymorphous low grade adenocarcinoma
- Carcinoma ex pleomorphic adenoma

CASE

History: A 63 yo man with a painful 1.5 cm parotid mass. An FNA was performed.



Ancillary Studies on FNA Cell Block:
The tumor is positive by IHC for CD117 and MYB.

CYTOLOGIC DIAGNOSIS:
ADENOID CYSTIC CARCINOMA.

Adenoid Cystic Carcinoma

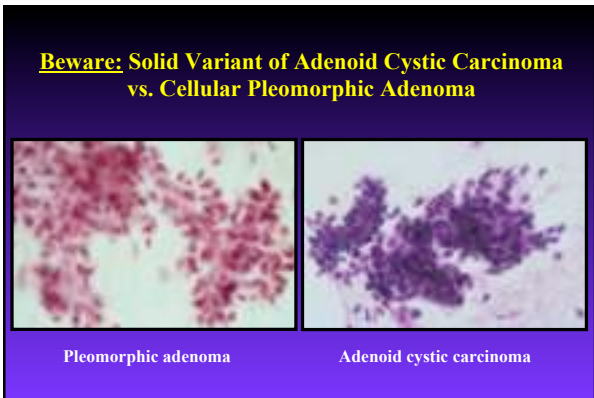
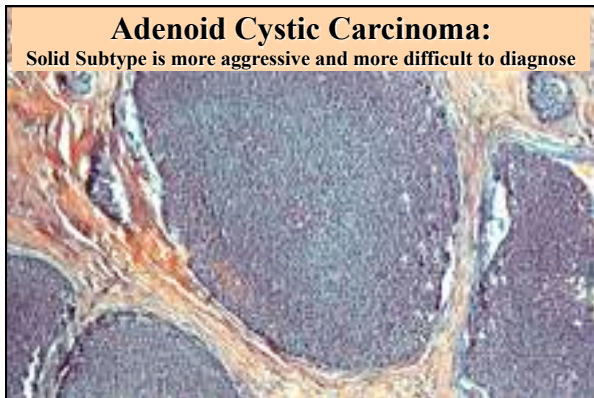
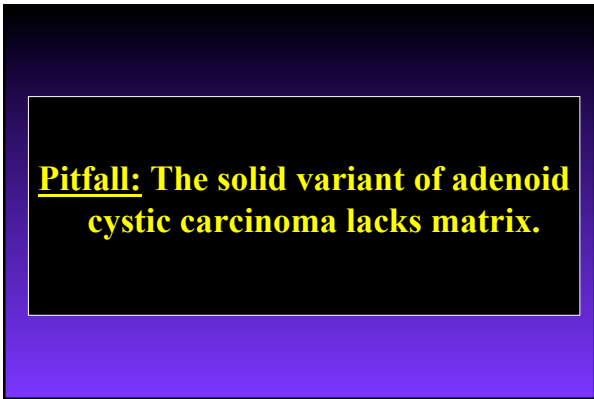
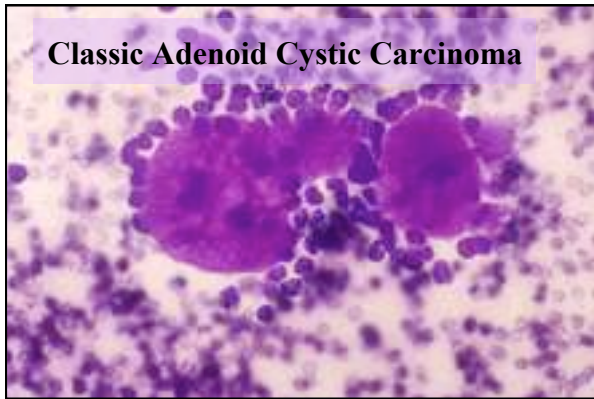
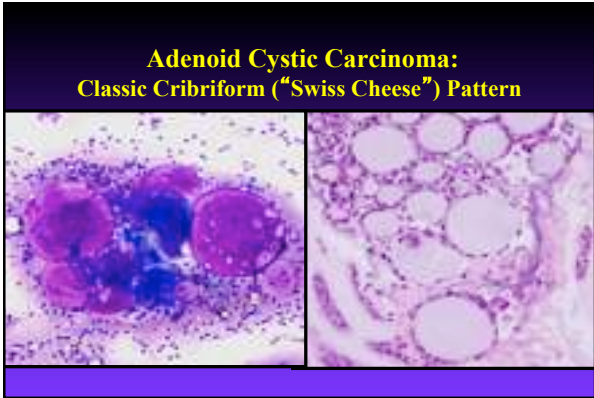
- 4-10% of all salivary gland neoplasms
- Indolent behavior but very poor long-term survival (<20% survival at 10 years)
- Submandibular gland, palate, and parotid
- FNAB is often reported as **painful!**

Adenoid Cystic Carcinoma **Cytologic Features:**

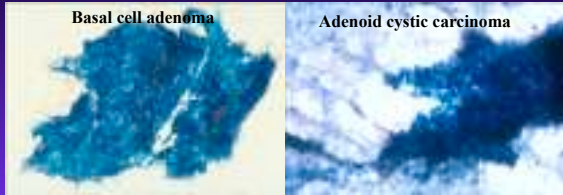
- Cells:**
 Basaloid cells with dark angulated nuclei
 Variable atypia
- Matrix:**
 3-D spheres and branching tubules
 Acellular
 Metachromatic with sharp borders

FNA of Adenoid Cystic Carcinoma

- 3 Subtypes:**
- **Cribriform** – Most easily recognized
 - Cylindromatous pattern of pseudocystic spaces
 - **Tubular**
 - Ducts and tubules with central lumens
 - **Solid** – Difficult to recognize
 - Lacks matrix
 - More atypical with mitotic activity



Overlapping Features:
Solid Basal Cell Adenoma vs
Solid Adenoid Cystic Carcinoma



BASALOID TUMORS

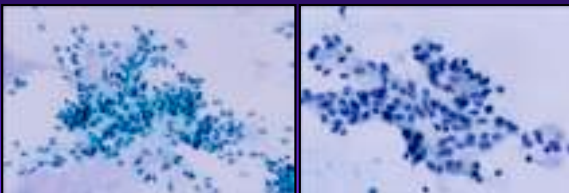
*Because of significant cytologic overlap,
most basaloid cases will receive a
descriptive diagnosis and DDX.*

How do we distinguish AdCC from PA?

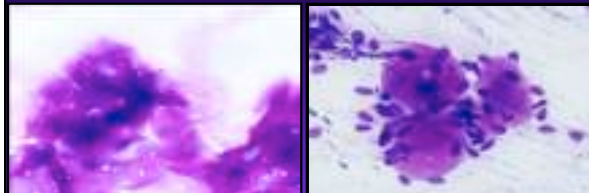
Pitfall: FNA Sample Preparation

Both **alcohol-fixed** and **air-dried**
preparations are essential in the
evaluation of matrix-containing
tumors!

Pitfall: Adenoid Cystic Carcinoma
vs. Pleomorphic Adenoma?



Pitfall: Adenoid Cystic Carcinoma
vs. Pleomorphic Adenoma?



Pleomorphic adenoma

Adenoid cystic carcinoma

Pleomorphic adenoma

Adenoid cystic carcinoma

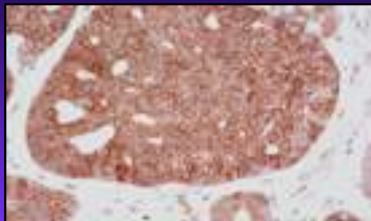
Which ancillary markers can help us with this ddx?

Adenoid Cystic Carcinoma

Immunohistochemistry:

- Over 90% are strongly positive for CD117 (KIT)
- Useful for all variants including solid forms
- IHC can be performed on cytologic and histologic samples

Immunoreactivity for CD117 (KIT): Overexpressed but no mutations in KIT



Adenoid Cystic Carcinoma: Recent Advance – MYB Translocation

Cytogenetics:

- t(6;9) MYB oncogene-NFIB transcription factor
 - 86% MYB-NFIB fusion transcripts
 - Detected by FISH
- MYB Immunohistochemistry:
- 82% AdCC (+)
 - 14% non-AdCC tumors tested (+)



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

MYB immunostaining is a useful ancillary test for distinguishing adenoid cystic carcinoma from pleomorphic adenoma in FNAB specimens

Pusztaszeri M, Sadow M, Faquin W. Cancer Cytopath 2014



FNA

BIOPSY



Classic Pleomorphic Adenoma vs Classic Adenoid Cystic Carcinoma

Pleomorphic Adenoma

- predominance of myoepithelial cells
- minimal atypia
- matrix: fibrillar with ragged edges and embedded myoepithelial cells
- PLG1 rearrangement

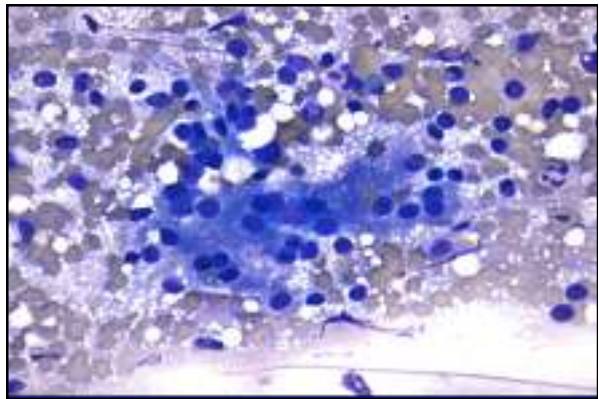
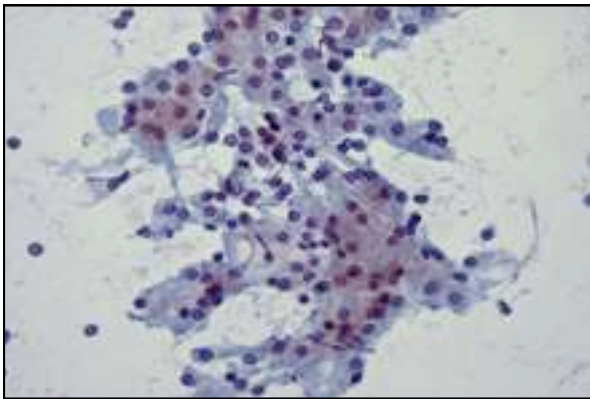
Adenoid Cystic Ca

- Basaloid cells
- variable atypia
- matrix: acellular, smooth edges, homogeneous
- Myb+, CD117+

**Oncocytic-Appearing
Salivary Gland Tumors**

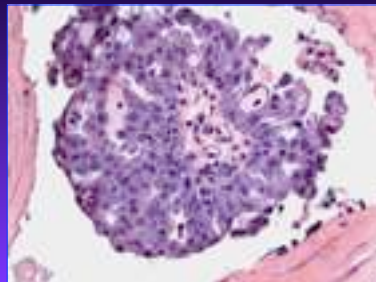
Case History:

A 50 year old woman with a 1.5 cm right non-tender parotid mass that was partially cystic on CT scan. An FNA was performed.



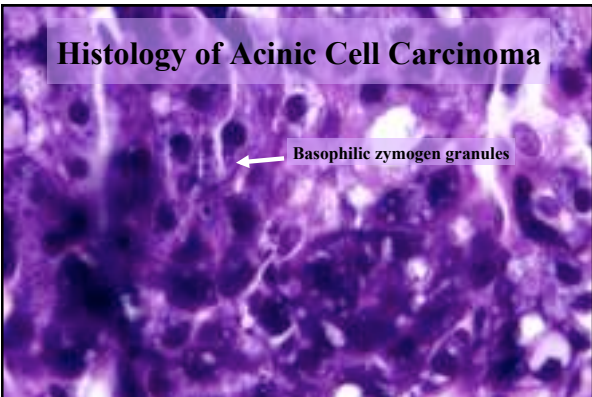
CYTOLOGIC DIAGNOSIS:
Suspicious for Acinic Cell Carcinoma.

**Clinical Management: Superficial parotidectomy
Papillary-Cystic Acinic Cell Carcinoma**



Acinic Cell Carcinoma

- Second most common salivary gland malignancy
- 2-6% of all salivary gland neoplasms
- Low-grade malignancy :
Recapitulates growth of normal acinar cells
F>M, 90% parotid
- PAS/D+, a-Chymotrypsin+, Dog1+, p63-

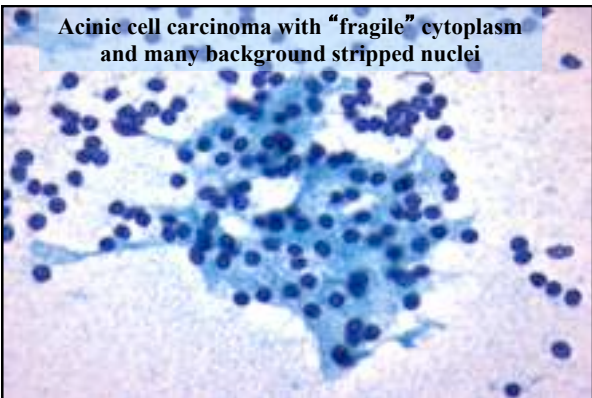
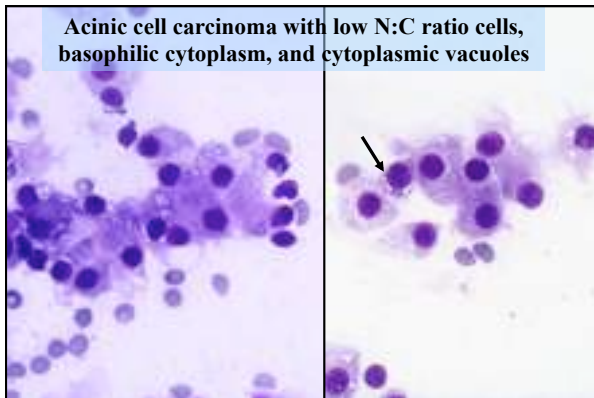
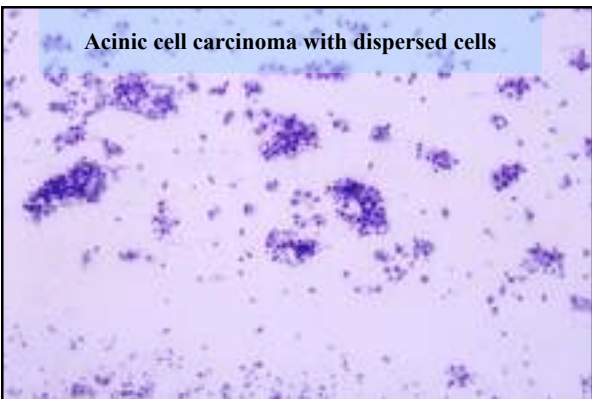


Acinic Cell Carcinoma

Cytologic Features:

Cells (high cellularity):
Serous-type acinar cells (low N/C ratio)

Background:
Stripped nuclei ± lymphocytes
“Clean” may be “cystic”
Capillary meshwork
Psammoma bodies



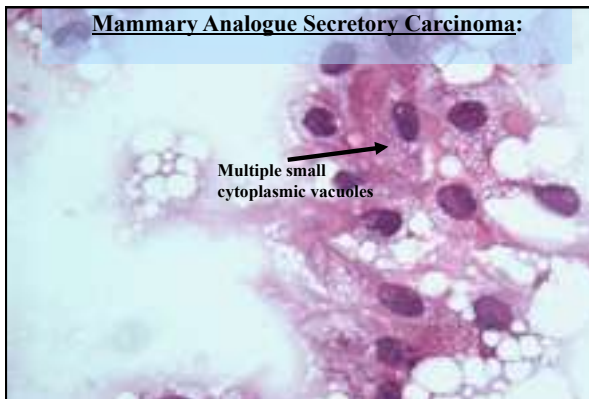
DDX of Oncocytic Tumors

Acinic cell carcinoma
Mammary analogue secretory carcinoma
Oncocytoma
Warthin tumor
Mucoepidermoid carcinoma (oncocytic variant)
Oncocytic carcinoma
Metastatic renal cell carcinoma

Mammary Analogue Secretory Carcinoma

- First described by Skalova et al in 2010
- Similar to secretory carcinoma of breast
- Previously classified as acinic cell carcinoma or adenocarcinoma, NOS
- Absence of true serous-type acinar differentiation
- Parotid gland most common
- T(12;15)(p13;q25) ETV6-NTRK3 translocation

Mammary Analogue Secretory Carcinoma:



FNA of Mammary Analogue Secretory Carcinoma

Dispersed population of low N/C cells

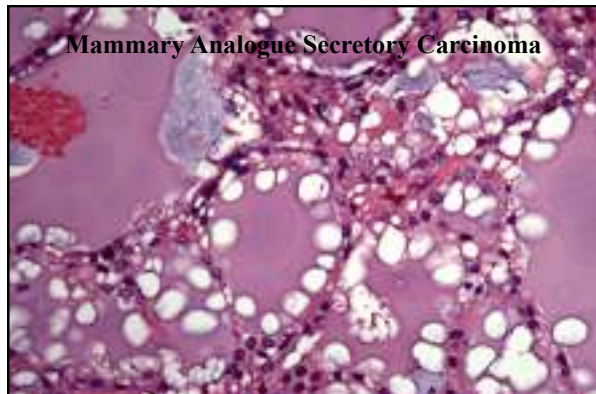


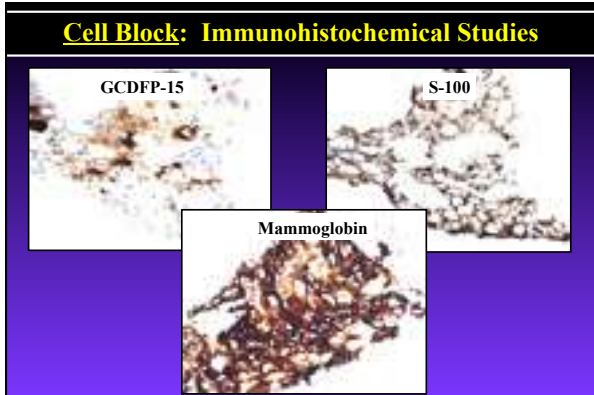
FNA of Mammary Analogue Secretory Carcinoma:

Round eccentric nucleus with small distinct nucleolus

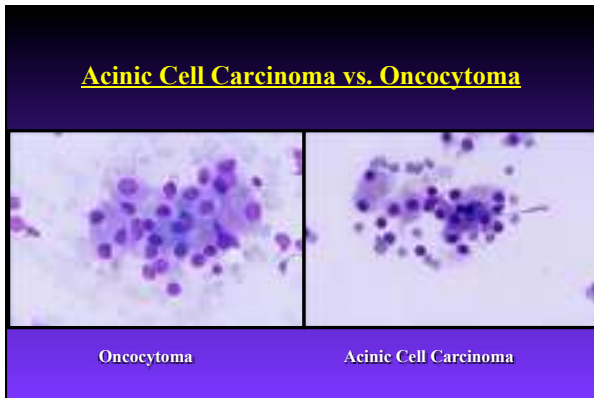
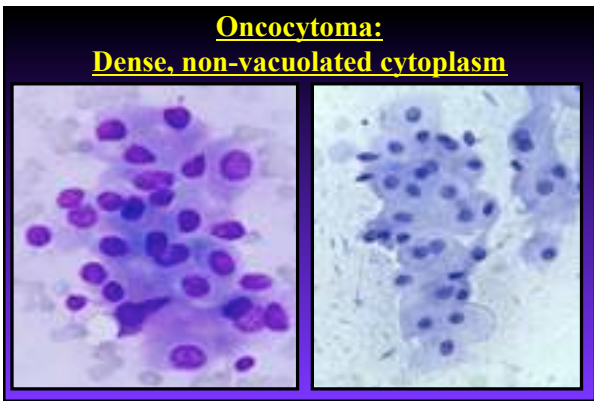
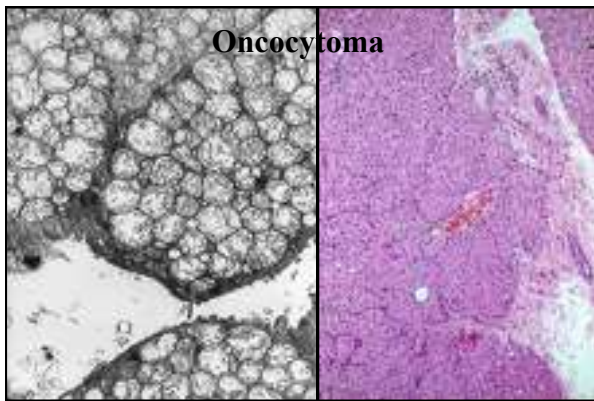


Mammary Analogue Secretory Carcinoma





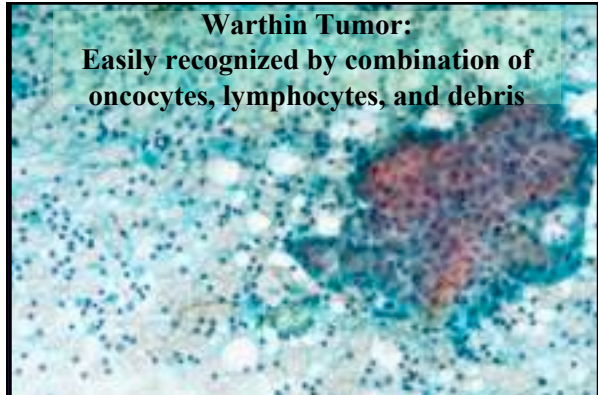
Problem: How is oncocytoma distinguished from acinic cell carcinoma?



<u>Acinic Cell Carcinoma</u>	<u>Oncocytoma</u>
- Vacuolated cytoplasm	No cytoplasmic vacuoles
- Delicate, slightly basophilic cytoplasm	Dense, granular eosinophilic cytoplasm
- PAS + D granules	No PAS + D granules
- PTAH weak/negative	PTAH strongly positive
- DOG-1 +, P63-	P63+

What about Warthin Tumor?

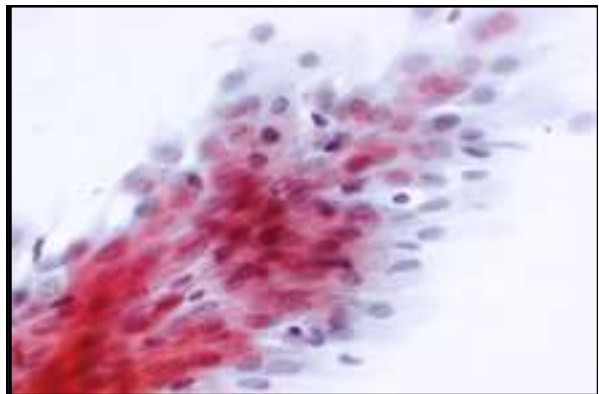
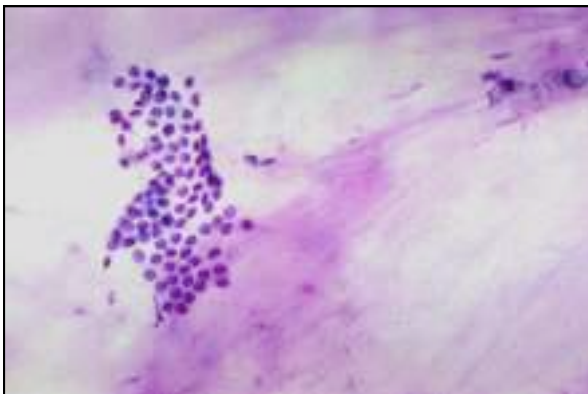
Warthin Tumor:
Easily recognized by combination of oncocytes, lymphocytes, and debris



Cystic and Mucinous Salivary Gland Tumors

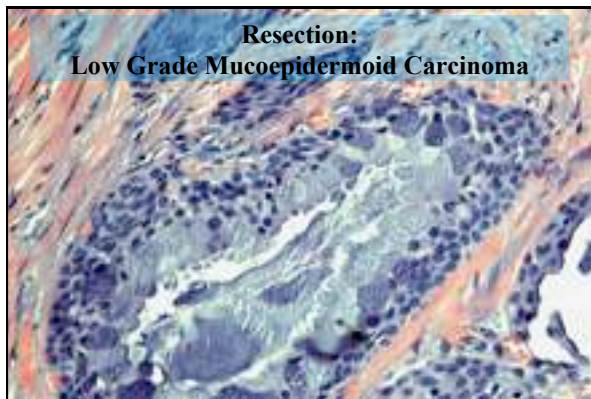
CASE

History: A 58 year old man with a 2.0 cm palate mass. An FNA was performed.



CYTOLOGIC DIAGNOSIS:
Mucinous neoplasm highly suspicious for mucoepidermoid carcinoma.

Molecular Analysis:
Revealed a t(11:19) rearrangement, supporting the diagnosis of mucoepidermoid carcinoma.

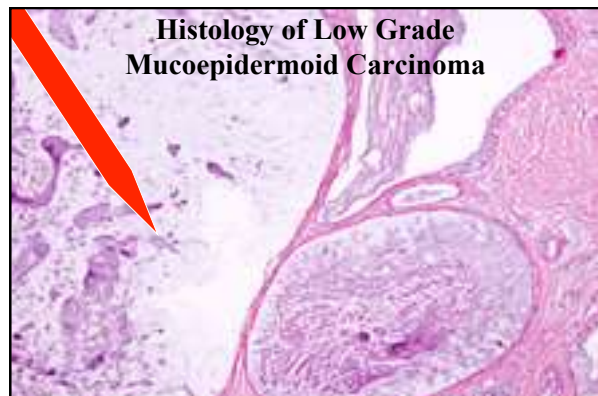


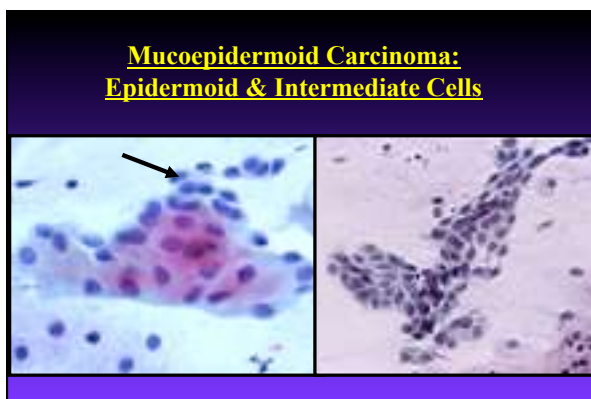
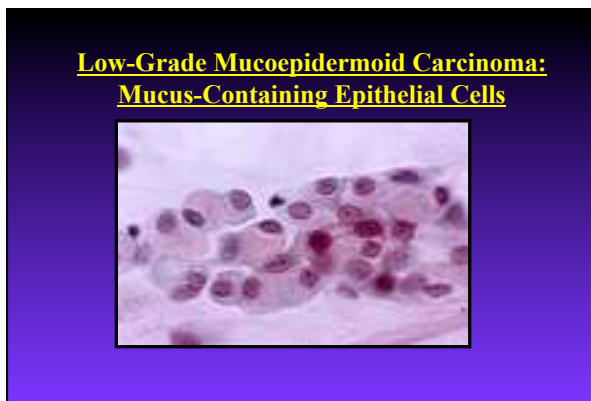
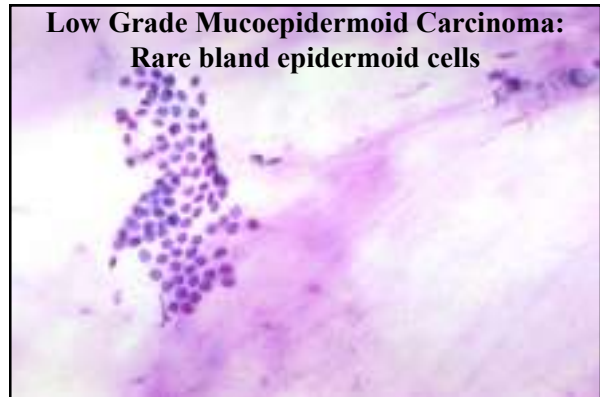
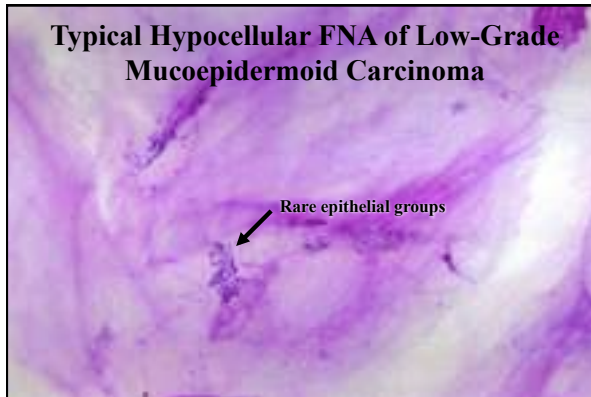
Low Grade Mucoepidermoid Carcinoma

- Most common salivary gland cancer in children and adults
- Usually slow growing and painless
- Residual mass post-aspiration
- Often a good clinical prognosis

Mucoepidermoid Carcinoma

- Cytologic Features:**
- 3 Cell Types: Mucus, epidermoid, and intermediate
 - Other variations: Columnar, clear, oncocytic
 - Keratinization is absent
 - P63+ but negative for myoepithelial cells





Pitfall: Low-Grade Mucoepidermoid Carcinoma

Low grade mucoepidermoid carcinoma is the most common cause of false negative salivary gland diagnoses:

- Hypocellularity due to cystic nature
- Bland cytology of cells
- Mucinous cells resemble foamy histiocytes

Mucoepidermoid carcinoma can easily be confused with a mucocele.

Mucocele

Cytologic Features:

- Hypocellular
- Scant to absent epithelium
- Foamy macrophages and inflammation

Pitfall: Low-Grade Mucoepidermoid Carcinoma vs. Mucocele

A cell block is diagnostically useful to stain for keratin, p63, CD68, and mucin.

LG Mucoepidermoid Ca

Mucocele

Mucoepidermoid Carcinoma and Ancillary Markers

Immunoprofile:

- P63 +
- Negative for myoepithelial markers
- Special stains:
 - Mucicarmine +

Mucoepidermoid Carcinoma and Ancillary Markers

Cytogenetics:

- t(11:19) translocation
- MECT1/MAML2
- More common in low grade
- Seethala et al Am J Surg Pathol (2010)
 - 60% overall
 - LG 74%, IG 63%, HG 32%

Key Point:

Low grade mucoepidermoid carcinoma should be considered in the differential diagnosis of any salivary gland FNA with significant amounts of background mucin.

High-Grade Salivary Gland Tumors

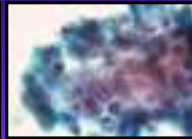
Differential Diagnosis of High-Grade Salivary Gland Carcinoma

Salivary Duct Carcinoma
High Grade Mucoepidermoid Carcinoma
Carcinoma *Ex* Pleomorphic Adenoma
Squamous Cell Carcinoma
Metastasis

High-grade carcinomas:
Can be difficult to distinguish, but
clinical management is usually similar



Salivary duct ca



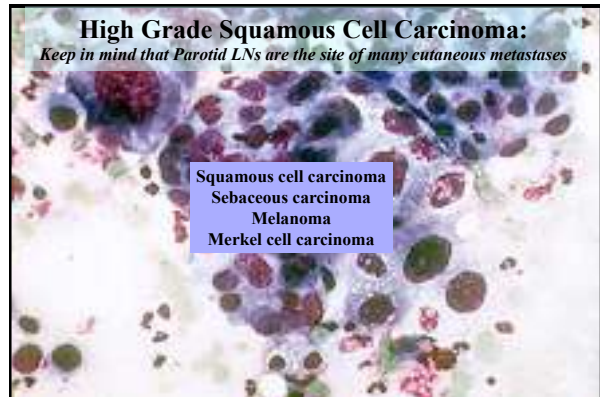
High-grade MEC



Ca Ex PA

High Grade Squamous Cell Carcinoma:

Keep in mind that Parotid LNs are the site of many cutaneous metastases



Squamous cell carcinoma
Sebaceous carcinoma
Melanoma
Merkel cell carcinoma

SUMMARY: Advance in Salivary Gland Diagnosis- Increasing Availability of Molecular Markers

- Mammary analogue secretory carcinoma:
 - ETV6-NKRT Translocation
- Pleomorphic adenoma:
 - PLAG1 gene rearrangements
- Clear cell carcinoma:
 - T(12;22) EWSR1-ATF1 fusion transcript
- Mucoepidermoid carcinoma:
 - t(11;19) MECT1/MAML2
 - 74% of LG cases
- Adenoid cystic carcinoma:
 - T(6;9) MYB-NFIB transcription factor
 - Present in 50-80%

Thank you!