Salivary Gland Cytology and The Milan System for Reporting

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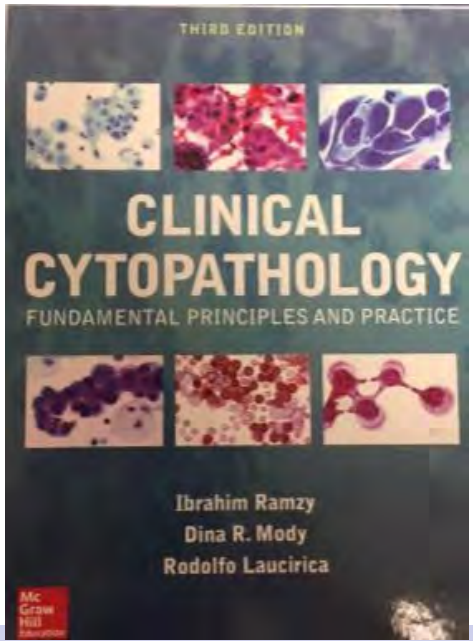
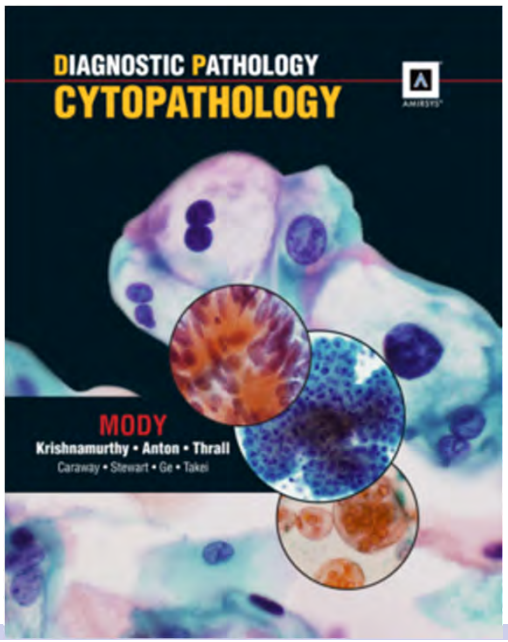
HOUSTON Methodist LEADING MEDICINE

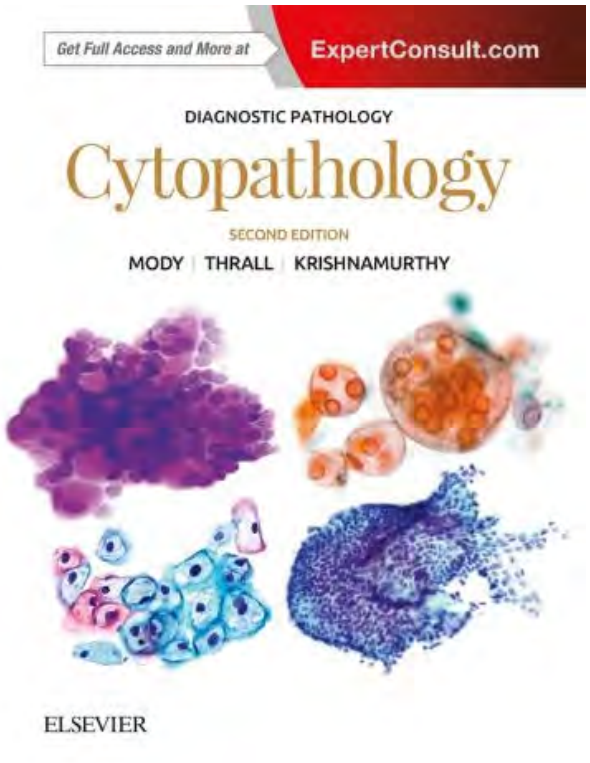
Weill Cornell Medical College

Conflict of Interest

- None with vendors of cytology equipment or HPV testing
- Amirsys (now Elsevier) and McGraw Hill
  - (Book publishers/Royalties)







Conflict of Interest

- Journal of The American Society of Cytopathology (Editor in Chief)

Conditions Affecting Salivary Glands

- Stones
- Cysts
- Infections/Inflammatory
- Sialadenosis
- Neoplasms
  - Benign
  - Low grade
  - High grade
- Others like intra or adjacent to salivary Lymph nodes

Salivary Gland FNA Diagnosis

- Based on cystic or solid
- Neoplastic or non neoplastic
  - Neoplasms divided into matrix producing or not
  - Basaloid
  - Oncocytic
  - Clear cell
  - Spindle cell cystic and mucinous
- Lymphocytic or not…lymph node/lymphoepithelial cyst
- Other characteristics

Salivary Gland Aspiration Patterns

- **Cystic Lesions**
  - Acellular clear fluid
    - Sialocoele
    - Lymphoepithelial cysts
  - Cloudy/mucoid fluid+/- cells
    - Lymphoepithelial cyst
    - Abscess
    - Mucocoele
    - Warthin's tumor
    - Low Grade Mucoepidermoid ca
    - Acinic cell ca(rare)
    - Cystic degeneration in any neoplasm
- **Inflammatory cells**
  - Abscess
  - Chronic sialadenitis
  - Lymphoepithelial sialadenitis
  - Warthin's
  - Lymph node
  - Lymphoma(monotonous)
- **Granulomas**
  - Sarcoid
  - TB
  - Fungal

Salivary Gland Aspiration Patterns

- **Oncocytic cell Pattern**
  - Nodular Oncocytic hyperplasia
  - Oncocytoma
  - Warthin's
  - Oncocytic carcinoma
  - Mucoepidermoid ca, oncocytic variant
  - Acinic cell carcinoma
  - Salivary duct carcinoma
  - MASC
- **Lymphocytic Cell pattern**
  - Chronic sialadenitis
  - Lymphoepithelial sialadenitis
  - Lymphoepithelial cyst
  - Lymph node
  - Lymphoma
  - Warthin's tumor
  - Acinic cell carcinoma
  - Mucoepidermoid carcinoma

Salivary Gland Aspiration Patterns

- **Basaloid cell Pattern**
  - Basal cell(monomorphic) adenoma/carcinoma
  - Cellular Pleomorphic adenoma
  - Adenoid cystic carcinoma
  - Myoepithelial carcinoma
  - Polymorphous low grade adenoca
  - Small cell carcinoma, prim/met
  - Cutaneous basal cell ca
  - Sialoblastoma
- **Clear cell Pattern**
  - Normal salivary gland
  - Lipoma
  - Acinic cell carcinoma
  - Mucoepidermoid carcinoma
  - Clear cell myoepithelioma/ca
  - Epithelial/myoepithelial carcinoma
  - Sebaceous lymphadenoma/ca
  - Metastatic clear cell ca/renal/Sq

Salivary Gland Aspiration Patterns

- **Neoplasms with stromal pattern**
  - Pleomorphic Adenoma: Fibrillary stroma
  - Adenoid Cystic ca: discrete, defined globules
  - Basal cell adenoma/ca: dense membrane like stroma
  - Polymorphous low grade adenoca
  - Myoepithelioma/ca
  - Nodular fasciitis: loose myxoid

- **High grade malignant neoplasms**
  - High grade Mucoepidermoid ca(MEC)
  - Carcinoma ex Pleomorphic Adenoma
  - Adenocarcinoma NOS
  - Salivary duct ca
  - Mammary Analogue Salivary Carcinoma (MASC)
  - Squamous cell ca
  - Merkel cell ca
  - Melanoma
  - Angiosarcoma
  - Other mets

Salivary Gland Aspiration Patterns

- **Mucinous**
  - Normal submandibular or sub lingual glands
  - Florid adenomatoid hyperplasia
  - Mucocoele
  - Low grade Mucoepidermoid ca
- **Spindle cells**
  - Schwannoma/NF
  - Myoepithelioma
  - PA with predominance of myoep
  - Angiosarcoma
  - Other mets
- **Crystals**
  - Tyrosine: Daisy petals in Pleomorphic adenoma (PA)
  - Amylase: elongated hexagons in chronic sialadenitis/cysts
  - Cholesterol: clear and colorless in Warthin's and various cysts
  - Asteroid bodies and calcium oxalate in sarcoidosis
  - Calcium crystals: Purple on pap, colorless on DQ: retained products of saliva
  - Psammoma bodies: normal or inflamed salivary gland and neoplasms, Benign and malignant

Problem with old way of reporting…

- No consistency
- Salivary gland neoplasms are the most heterogenous group, and hence also the most challenging, even more so on cytology and minute Core needle biopsies
  - Matrix containing tumors
  - Basaloid tumors
  - Oncocytic lesions/tumors
  - Cystic and mucinous lesions/tumors
  - High grade carcinomas
  - Clear cell tumors
  - Spindle cell lesions/neoplasms

Problem with old way of reporting…continued…

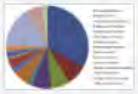
- Surgical pathology terminology often used
- Too many DIDGO's (describe it to death and let it go)…not helpful at all! Clinicians confused

- Agreement for need of defined diagnostic categories
- Clarity of communication
- Exchange of information across institutions
- Uniform management, improvement patient care

Salivary FNA Variances (aka errors)

- **False Positive**
  - Interpretive
  - Monomorphic Adenoma
  - Warthin's with squamous and mucinous metaplasia with atypia
  - Intraparotid lymph node
  - Oncocytoma
  - Granulomatous sialadenitis
- **False negative**
  - Sampling
  - Interpretive
  - Acinic cell carcinoma
  - Low grade MECarcinoma
  - Lymphoma
  - Adenoid cystic carcinoma
  - Low grade angiosarcoma(cutaneous)

Figures and tables



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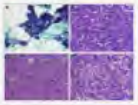

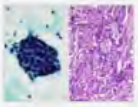

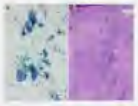

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Original article

Diagnostic accuracy of fine-needle aspiration cytology of salivary gland lesions: A 6-year retrospective review

Erin N. Consamus, MD, Deborah Smith, CT (ASCP), Sergio Pina Oviedo, MD, Dina R. Mody, MD, Hidehiro Takei, MD

Show more

http://doi.org/10.1016/j.jasc.2014.11.003

Introduction

The aim of this study was to evaluate the diagnostic accuracy of salivary gland fine-needle aspiration (FNA) in comparison to histologic examination and to recognize possible pitfalls in diagnosis.

Materials and methods

The diagnoses and demographics of all cases of salivary gland FNAs with concurrent or subsequent histologic correlation at our institution over a 6-year period (2006-2011) were retrospectively reviewed and compared for discrepancies. Discrepancies were categorized as either major or minor and due to sampling or interpretive variance.

Results

Overall, the following values were calculated: sensitivity 80.6%, specificity 97.5%, positive predictive value 92.6%, negative predictive value 92.8%, accuracy 92.7%, and concordance rate 90.9%. In addition, concordance rates were calculated for the 2 most common diagnoses: pleomorphic adenoma (97.1%, n = 35) and Warthin tumor (88.9%, n

Salivary Glands Statistics

	Our results (%)	Literature results (%)
Sensitivity	80.6	86-100
Specificity	97.5	81-100
Positive Predictive value	92.6	
Negative Predictive value	92.8	
Accuracy	92.7	48-94 (specific neoplasm),(B9vs Malig) 81-100
Pleomorphic Adenoma	97.1 (concordance)	
Warthin's	88.9 (concordance)	

Salivary Gland Lesions/Neoplasms

Usually Diagnostic	Sometimes Diagnostic	Descriptive ..I call them DIDGOs
Acute/chronic sialadenitis	Mucocoele	Basal adenoma (other than membranous)
Reactive lymph node	Adenoid cystic carcinoma	Basal cell adenocarcinoma
Lympho epithelial cyst	Acinic cell carcinoma	Mucoepidermoid ca High grade
Pleomorphic adenoma	Mucoepidermoid ca (low grade)	Salivary duct carcinoma
Warthin's	Oncocytoma	Polymorphous low grade adenoca
Basal cell adenoma, membranous type	Carcinoma ex PA	Epithelial-myoepithelial carcinoma
	Small cell carcinoma	(Mammary analogue) Secretory carcinoma
	Metastasis	

Management of Salivary Gland Lesions/conditions

- If inflammatory → Medical management
- Lymphoma → Heme Onc referral
- Metastasis → Resection or radical neck dissect
- Benign or low grade primary neoplasm → Limited resection
- High grade carcinoma → Radical resection

The Milan System for Salivary Gland Cytopathology

- ASC and IAC co sponsors
- Over 40 participants, 14 countries
- Evidence based
- Print atlas in early 2018…already out!
- Web based atlas also available through ASC
- Co chairs Drs Bill Faquin and Diana Rossi
- Others include Drs Baloch, Barkan, Foschini, Kurtyz, Pusztaszeri, Vielh
- Online survey data..49 questions, 515 participants, 54% academic
- >95% agreed with new reporting structure
- Both Romanowsky and pap staining essential

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SPECIAL ARTICLE

The Milan System for Reporting Salivary Gland Cytopathology (MSRSGC): an ASC-IAC–sponsored system for reporting salivary gland fine-needle aspiration

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KEYWORDS
Fine-needle aspiration;
Salivary gland;
Benign lesions;
Standardized reporting;
Malignant lesions

The diagnostic role of salivary gland fine-needle aspiration (SG-FNA) is well established in the preoperative evaluation of patients with salivary gland lesions. At present, most salivary SG-FNA specimens are diagnosed based on conventional diagnostic criteria. Nevertheless, there exists a lack of uniform reporting for these specimens to guide the clinical management of patients. This void motivated a group of experienced cytopathologists to spearhead the development of a uniform reporting system. This international panel, under the sponsorship of the American Society of Cytopathology (ASC) and the International Academy of Cytology (IAC), gathered in September 2015 at the European Congress of Cytology, held in Milan, Italy, to propose "The Milan System for Reporting Salivary Gland Cytopathology. This effort sparked the interest of many and brought forth an agreement to develop an evidence-based tiered classification consisting of 6 diagnostic categories. We hope that this standard reporting system will enhance the overall effectiveness of SG-FNA reporting across institutions, with the ultimate result being better communication and improved patient care.

This article is being published jointly by Acta Cytologica and Journal of the American Society of Cytopathology.
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The Milan System for Reporting Salivary Gland Cytopathology

William C. Faquin
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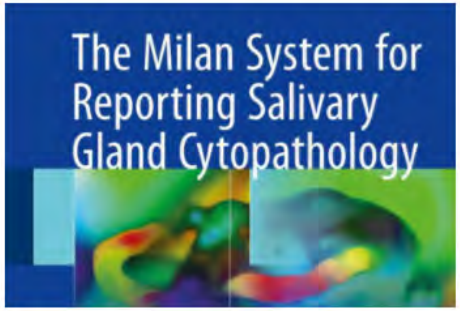
Springer

HOME / MILAN SYSTEM / ATLAS / VIDEOS / FNA CASES

The Milan System for Reporting Salivary Gland Cytopathology



Milan System Interobserver Reproducibility Study

Posted on January 12, 2018 By Milan System

We invite you to evaluate a series of images from the new Milan System for Reporting Salivary Gland Cytopathology Atlas. The responses will be recorded...

Classification System

Posted on December 8, 2017 By Milan System

Be the first of your friends to like this

Milan System for Reporting Salivary Gland Cytopathology
about a month ago

Appropriately toasting the release of the @MilanSystem with prosecco! #USCAP2018

The Milan System for Reporting Salivary Gland Cytopathology (MSRSGC)

Diagnostic Category	Risk of Malignancy (ROM)	Management
I. Non-Diagnostic	~25%	Clinical/radiologic correlation, repeat FNA
II. Non - Neoplastic	~10%	Clinical follow up, radiologic correlation
III. Atypia of Undetermined Significance(AUS)	~20%	Repeat FNA or surgery
IVa. Neoplasm: Benign	<5%	Follow or conservative surgery
IVb. Salivary gland Neoplasm of Uncertain malignant potential (SUMP)	~35%	Conservative surgery
V. Suspicious for malignancy	~60%	Surgery, decide if low grade or High grade and manage accordingly
VI. Malignant (low vs High grade)	~90%	Same as above

ROM depends on salivary gland site and nature of specimen

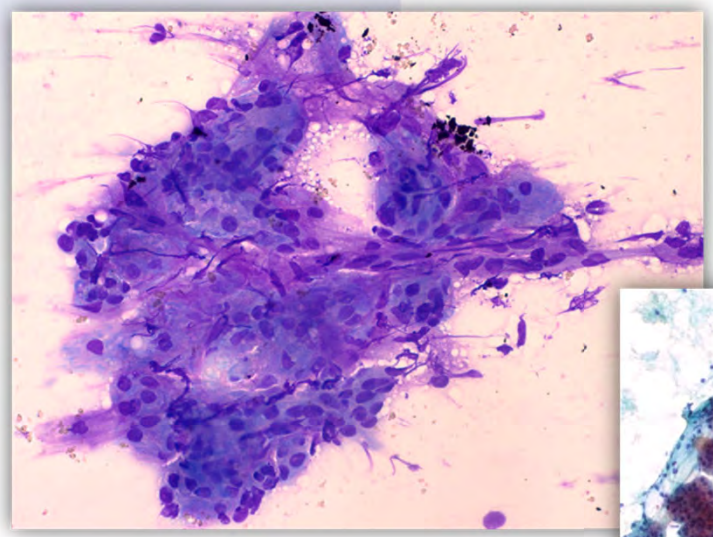
Salivary Gland Mass sampling

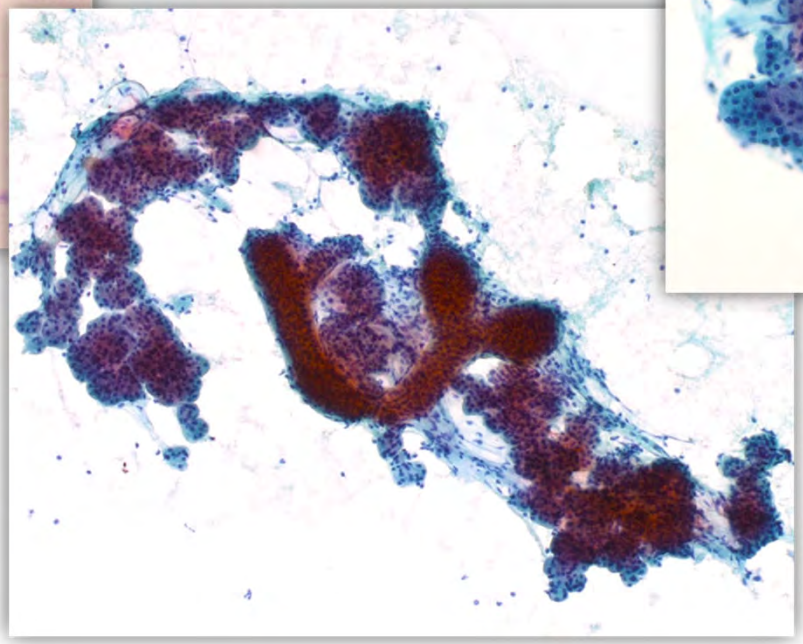
- Palpation or Ultrasound guidance
- FNA preferred
- Both Romanowsky and Pap/H&E stains preferred
- Cell block preparation encouraged
- Core needle biopsies an option but….
  - Tracking
  - Facial nerve injury, especially with larger cores

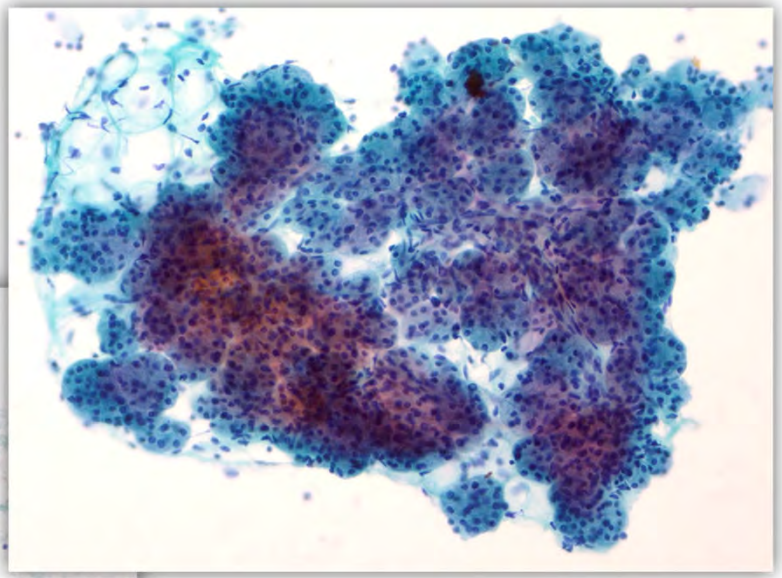
Non Diagnostic

- Currently no validated criteria in literature
- Call non diagnostic after everything is processed and examined and correlated clinically and radiologically
- Insufficient material qualitative or quantitative for a diagnosis
- 10% or less targeted reporting rate (hopefully!)
- Exceptions: matrix material, mucinous cyst contents, acute inflammation, any atypia
- ? Minimum of 60 lesional cells for adequacy…like thyroid?
- Repeat Sampling using US or CT guidance

Normal Salivary Gland Cytology







Non Diagnostic..continued

- E.g. Salivary duct stone with cyst…aspiration yields clear fluid, no more mass…then adequate as it explains the scenario
- Bilateral enlarged salivary glands with no definite mass, then adequate
- However, if mass, and all you get is normal salivary gland tissue…
  - Then non diagnostic as it does not explain the mass/"it"

The Milan System for Reporting Salivary Gland Cytopathology (MSRSGC)

Diagnostic Category	Risk of Malignancy (ROM)	Management
I. Non-Diagnostic	~25% (range 0-67%)	Clinical/radiologic correlation, repeat FNA
II. Non - Neoplastic	~10% (range 0-20%)	Clinical follow up, radiologic correlation
III. Atypia of Undetermined Significance(AUS)	~20%	Repeat FNA or surgery
IVa. Neoplasm: Benign	<5%	Follow or conservative surgery
IVb. Salivary gland Neoplasm of Uncertain malignant potential (SUMP)	~35%	Conservative surgery
V. Suspicious for malignancy	~60%	Surgery, decide if low grade or High grade and manage accordingly
VI. Malignant (low vs High grade)	~90%	Same as above

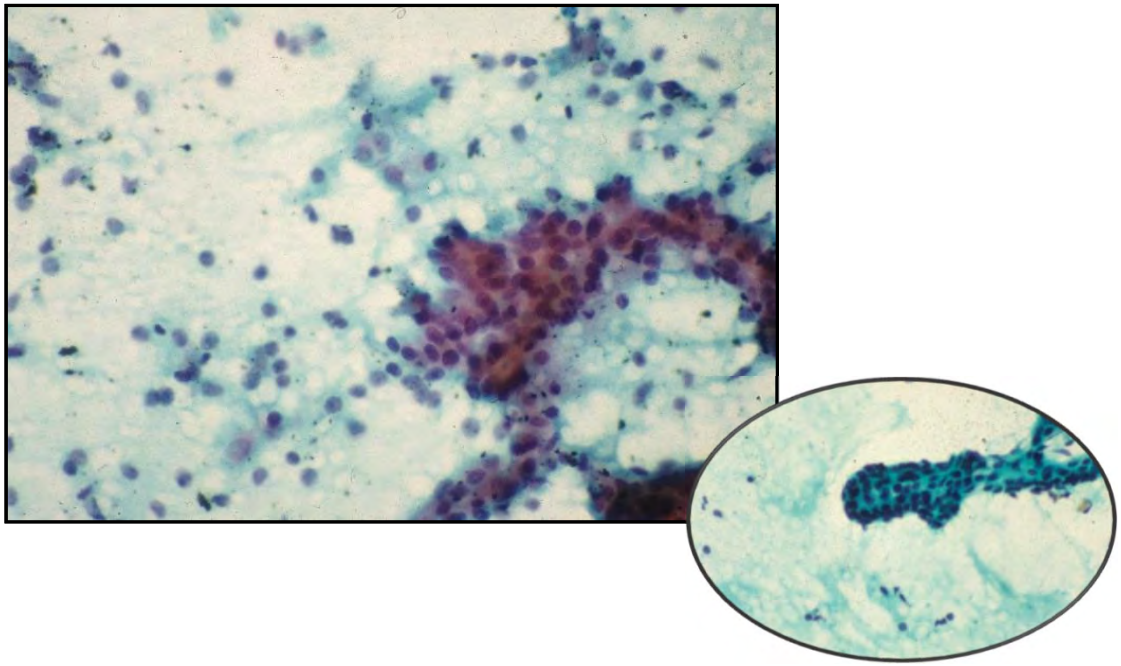
ROM depends on salivary gland site and nature of specimen Personal communication Drs Faquin and Rossi and presentation at ASC meeting in Phoenix, Nov 2017

Non Neoplastic

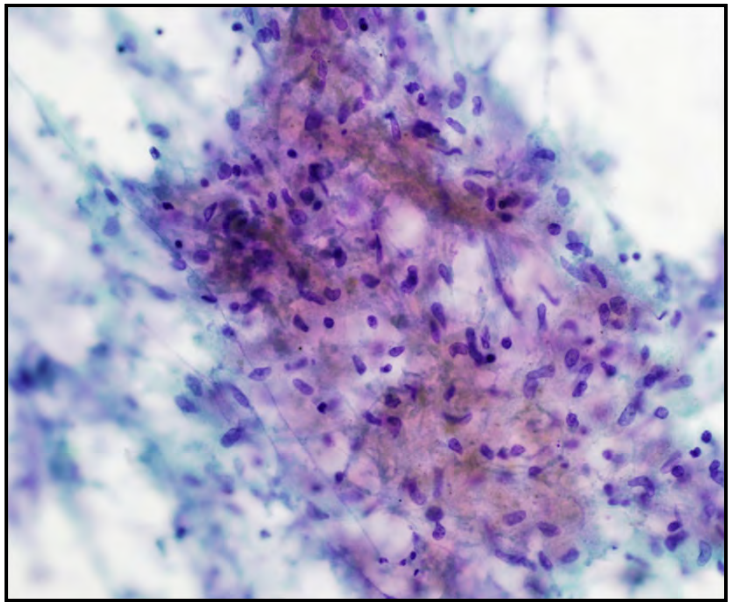
- Chronic and granulomatous Sialadenitis
- Sialolithiasis
- Lymph nodes (reactive) within or adjacent to salivary gland
  - Recommend flow if clinically and cytologically worrisome, older age
- Other benign conditions like cysts etc..
- Risks of malignancy should be low if adequately sampled
- A subset will need surgical excision to exclude a poorly sampled neoplasm

Non Neoplastic

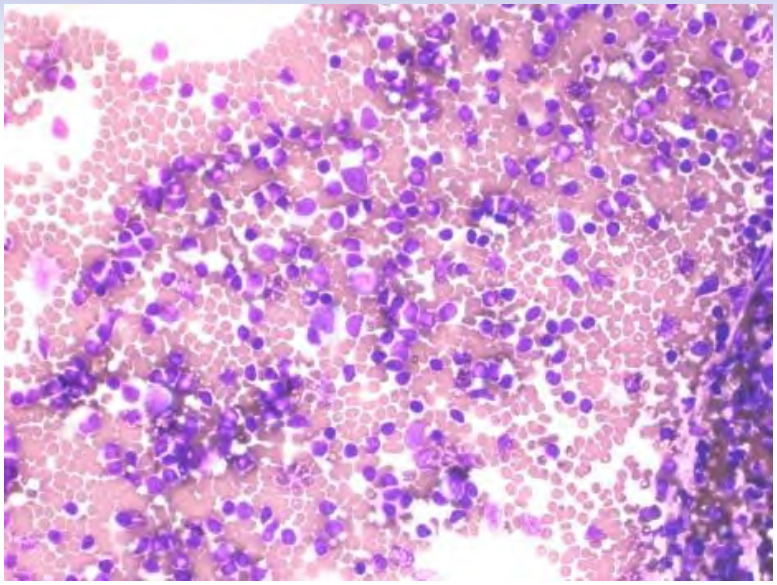
- Chronic Sialadenitis



- Granulomatous Sialadenitis



Lymph nodes on Salivary FNA



- Reactive lymph nodes
  - Polymorphous population
  - Age, usually <50
  - Tingible body macrophages
  - But all of above can be seen in lymphomas
  - Flow cytometry if worrisome or older patient
    - Even that may be problematic as some large cell lymphomas, Hodgkin's, T cell rich B cell Lymphomas negative by flow
    - Recommend excision if uncertain
    - Make sure representative of lesion
    - Note of caution, consider follow up/excision if does not go away

Milan 3.Atypia of Undetermined Significance

- Heterogeneous category with majority being due to poor sampling or preparation/compromised specimen(air drying, blood clot, artefact)
- Cannot entirely exclude a neoplasm
- <10% reporting rate (hopefully!)
- Example is mucinous cyst contents only (cannot exclude a low grade Mucoepidermoid carcinoma)

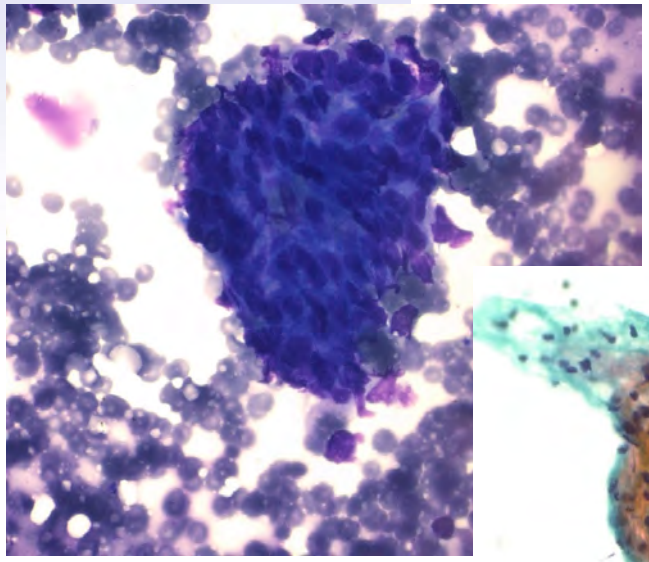
Atypia of Undetermined Significance..Scenarios

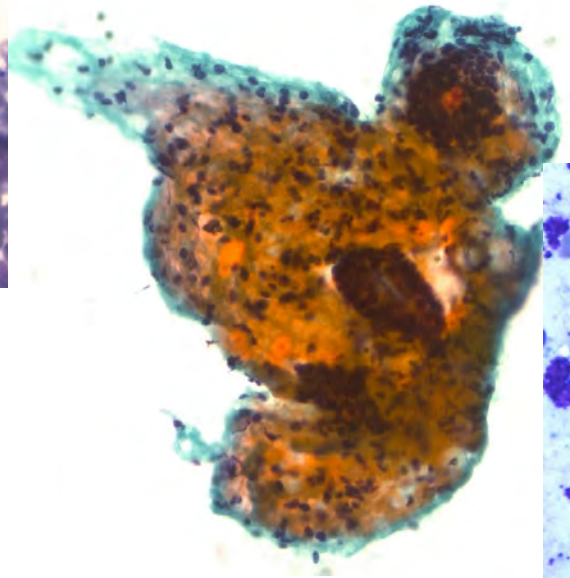
- Oncocytic metaplasia (vs neoplasm)
- Reactive/reparative atypia, cannot rule out a neoplasm
- Low cellularity specimen, worrisome for but not diagnostic of a neoplasm
- Salivary gland lymph nodes, indefinite for a lymphoma on morphology alone(do flow or excise)
- Sclerosing polycystic adenosis
- Lymphoepithelial cyst with squamous atypia in cyst lining

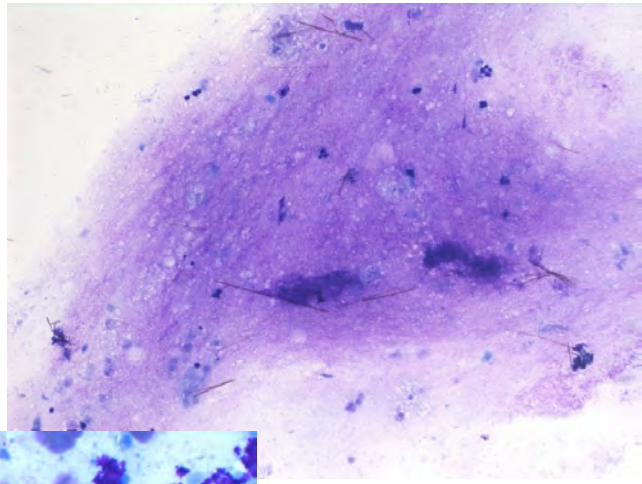
Cystic salivary Gland Aspirates ..Intrinsic

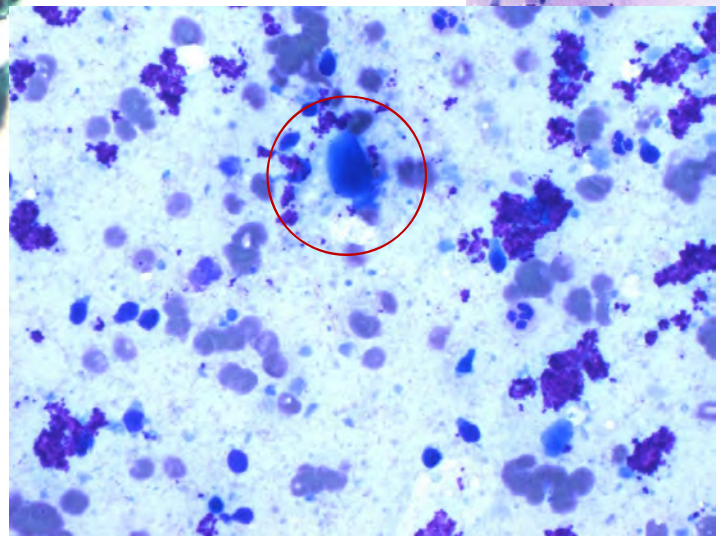
- Non neoplastic
  - Salivary duct cyst
  - Lymphoepithelial cyst
  - Polycystic disease
- Neoplastic
    - Warthin's, Pleomorphic adenoma
    - Muco epidermoid ca, Acinic cell ca
    - Cystadenoma/ca
    - Secretory carcinoma

Atypia of Undetermined Significance…Examples









Cystic salivary Gland Aspirates ..Extrinsic

- Non neoplastic
  - Branchial cleft cyst
- Neoplastic
  - Metastatic carcinoma (with cystic degeneration/necrosis to an intra or peri salivary gland lymph node (especially parotid and sometimes sub mandibular)

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III. Atypia of Undetermined Significance(AUS)	~20% (range is 10-35%)	Repeat FNA or surgery
IVa. Neoplasm: Benign	<5%	Follow or conservative surgery
IVb. Salivary gland Neoplasm of Uncertain malignant potential (SUMP)	~35%	Conservative surgery
V. Suspicious for malignancy	~60%	Surgery, decide if low grade or High grade and manage accordingly
VI. Malignant (low vs High grade)	~85-95%	Same as above

ROM depends on salivary gland site and nature of specimen Personal communication Drs Faquin and Rossi and presentation at ASC meeting in Phoenix AZ NOV 2017

Atypia of Undetermined Significance..sample reports

Evaluation limited by scant cellularity

Atypia of Undetermined Significance

Histiocytes with scant epithelial cells in an abundant mucinous background. Differential includes a mucocele, mucus retention cyst and low grade mucoepidermoid carcinoma

Satisfactory for evaluation

Atypia of Undetermined Significance

Aspirate is suggestive of a reactive lymph node. However, in absence of flow cytometry, a low grade lymphoma cannot be ruled out. Clinical and radiological considerations recommended.

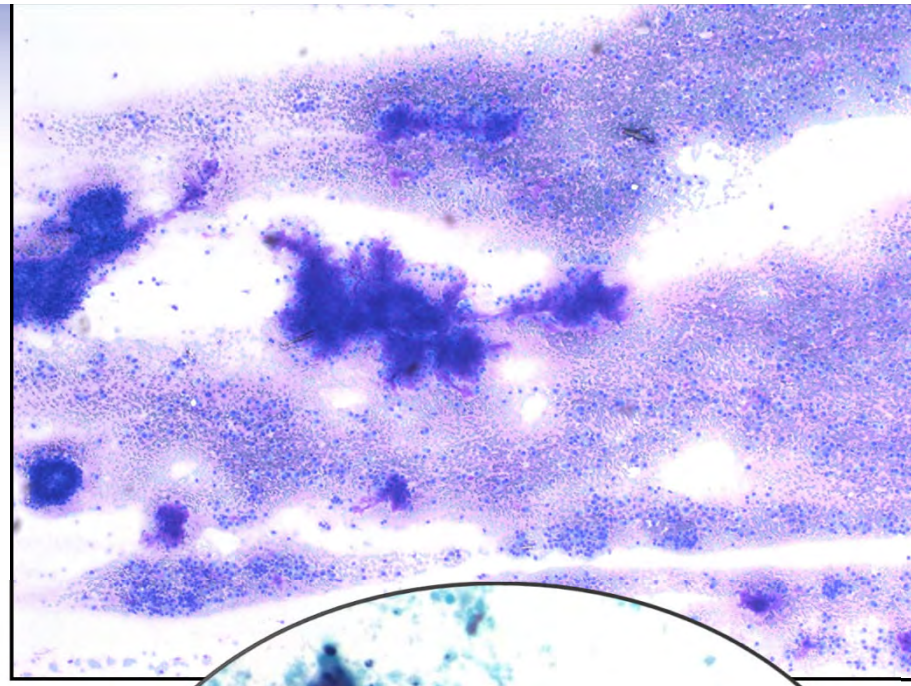
From The Milan System for reporting salivary gland cytopathology by Faquin and Rossi, Springer 2018

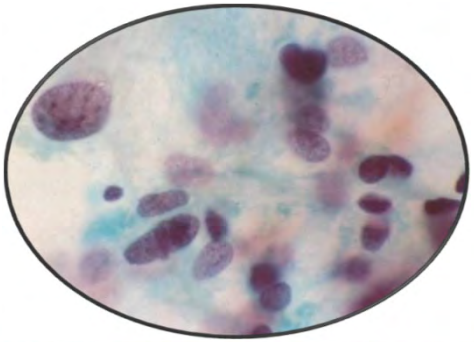
Milan 4. Neoplasm

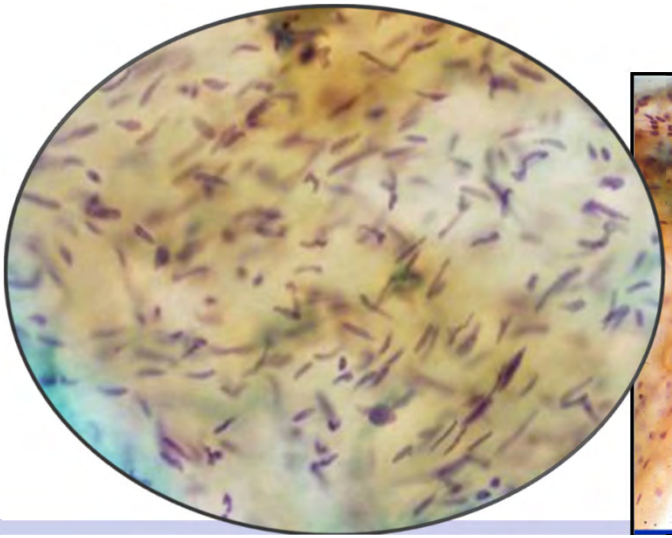
- Benign Neoplasm
- Salivary gland neoplasm of uncertain malignant potential

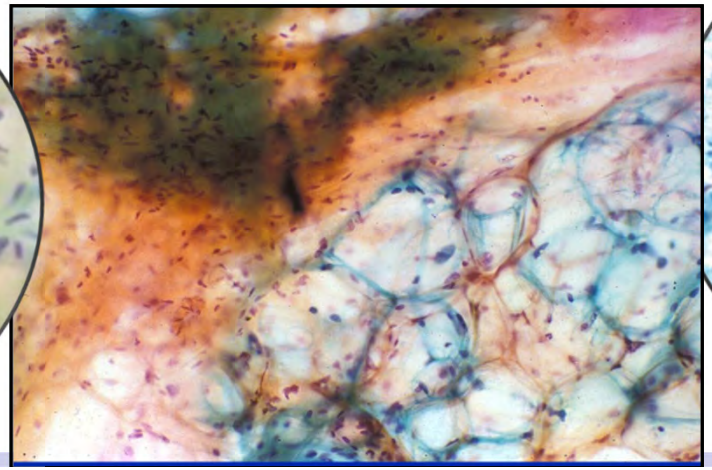
Neoplasm: Benign

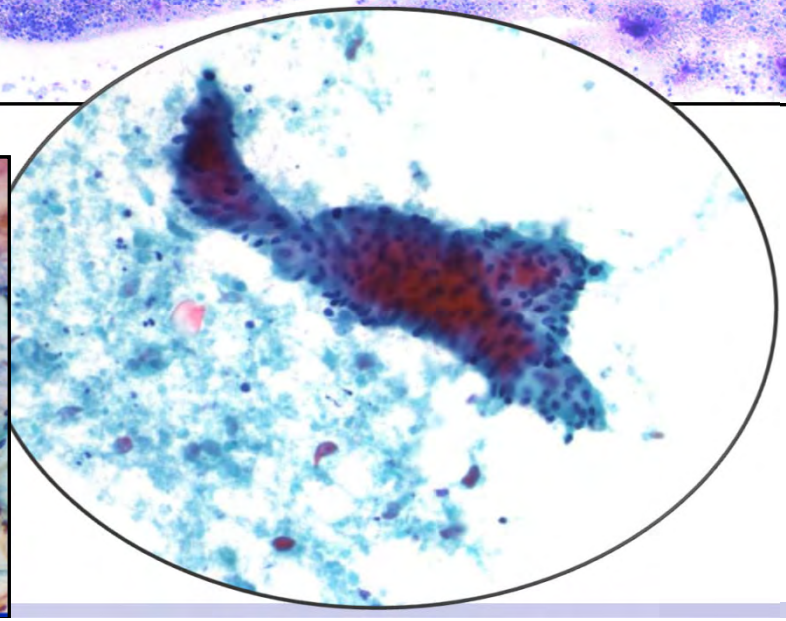
- Pleomorphic Adenomas
- Warthin's
- Lipomas
- Schwannomas





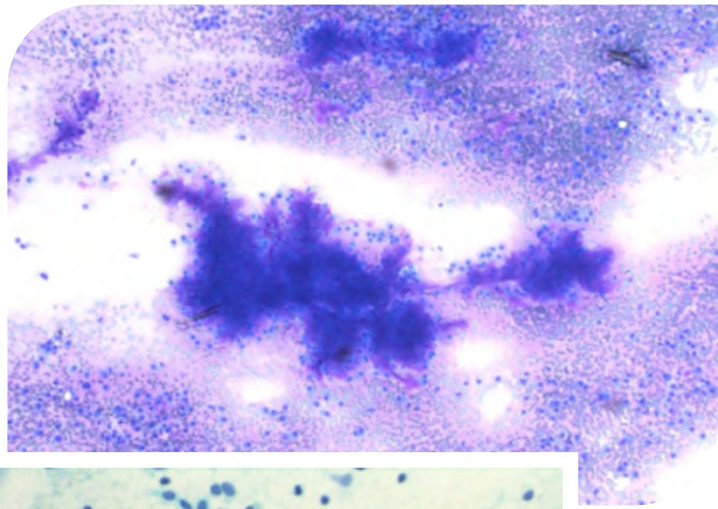


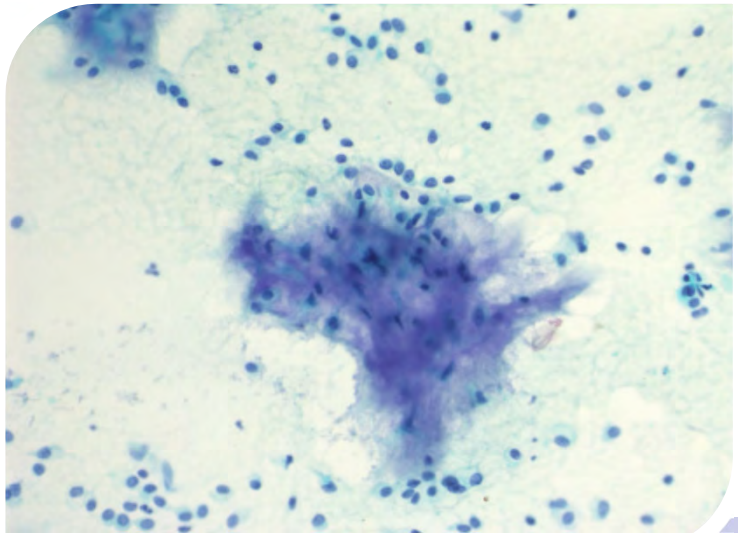


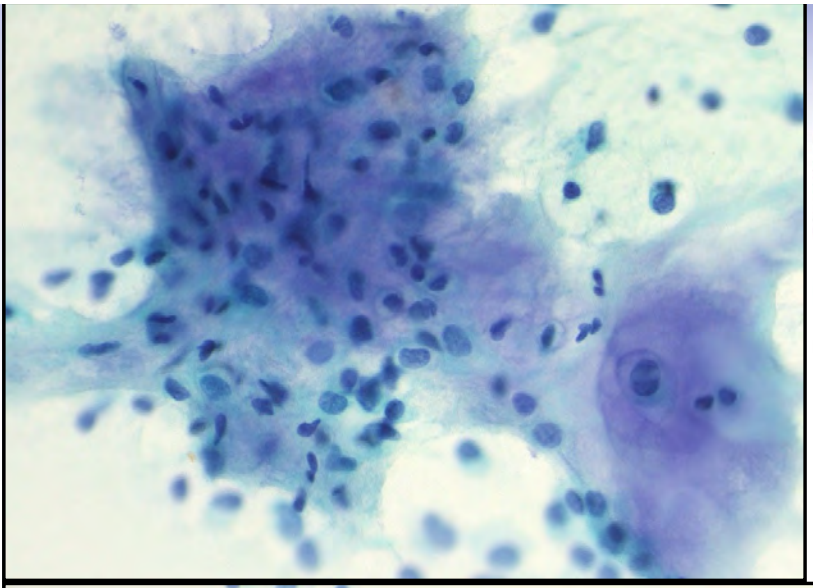


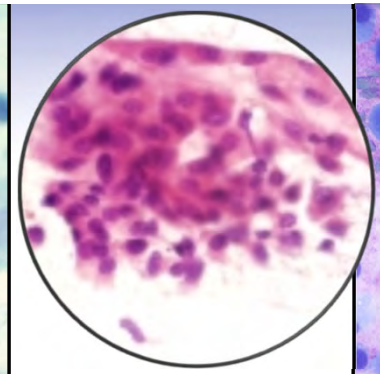
Pleomorphic Adenoma(Benign Mixed Tumor)

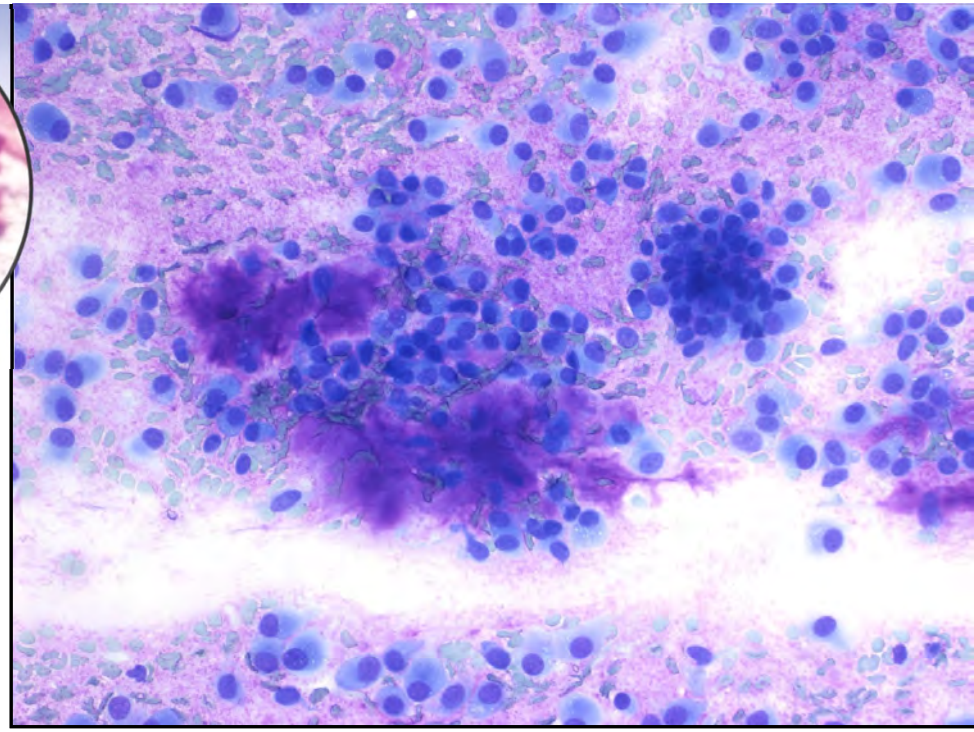
- Most common salivary neoplasm
- Parotid most common site
- Fibrillary chondromyxoid stroma
  - Metachromatic on DQ
  - Greyish blue on Pap
- Ductal cells
  - Small cuboidal to polygonal cells
- Myoepithelial cells
  - Plasmacytoid, dyshesive, bland

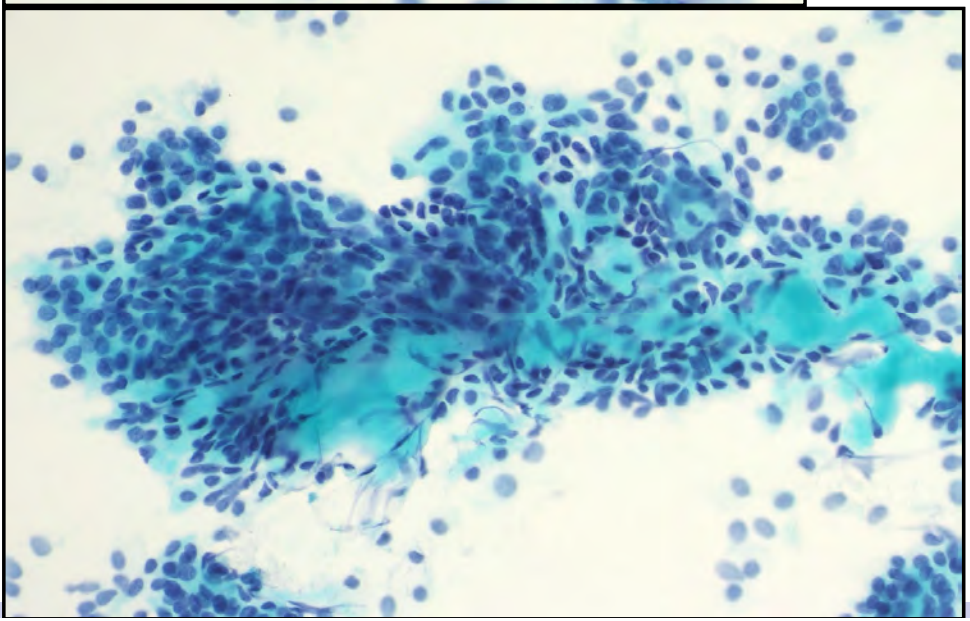


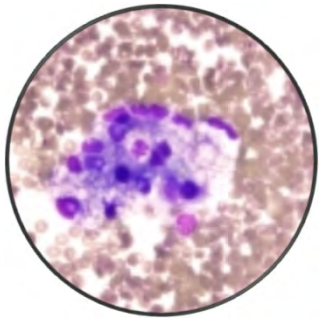


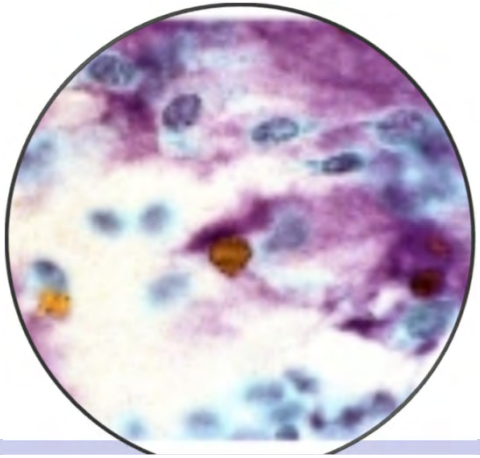


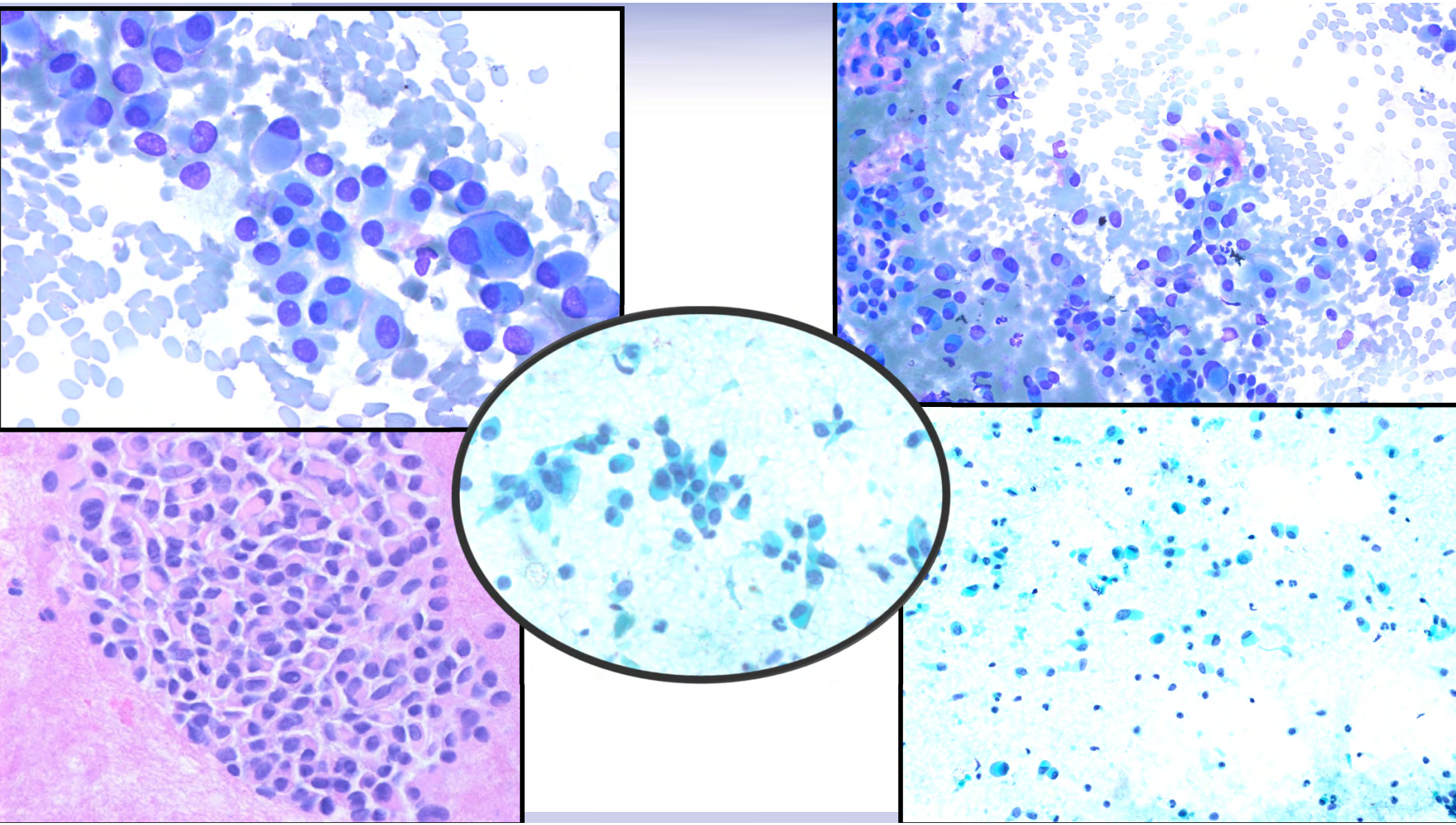













KEEP
CALM
AND
GO
ROGUE

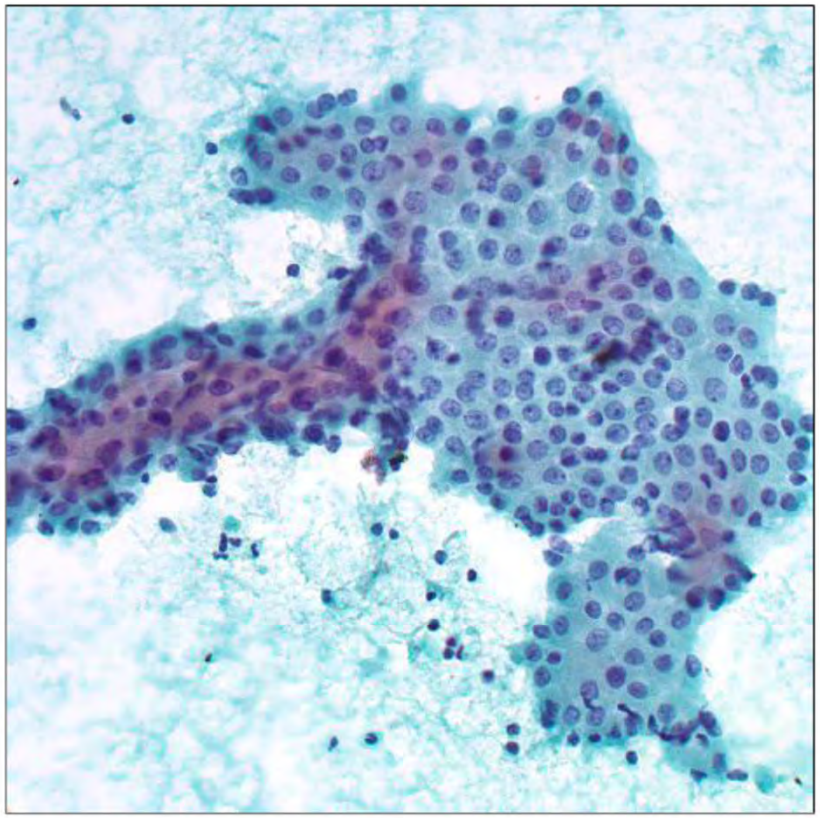
Carcinoma ex Pleomorphic Adenoma

- Carcinoma arising from Pleomorphic adenoma
- Requires concurrent PA or history of PA at same site
- 80% occur in major salivary glands especially Parotid
  - 7-10% of PAs (especially long standing), 6th to 8th decade (20 yrs later than PA)
  - 6th most common salivary gland malignancy in adults
- Cellular specimen with predominantly epithelial cells
- 2 distinct patterns, benign PA with malignant or equivocally malignant cells with or without necrosis, mitosis
  - Malignant component could be adenocarcinoma, salivary duct carcinoma, ACC, MEC, PLGA, epi-myoepithelial carcinoma

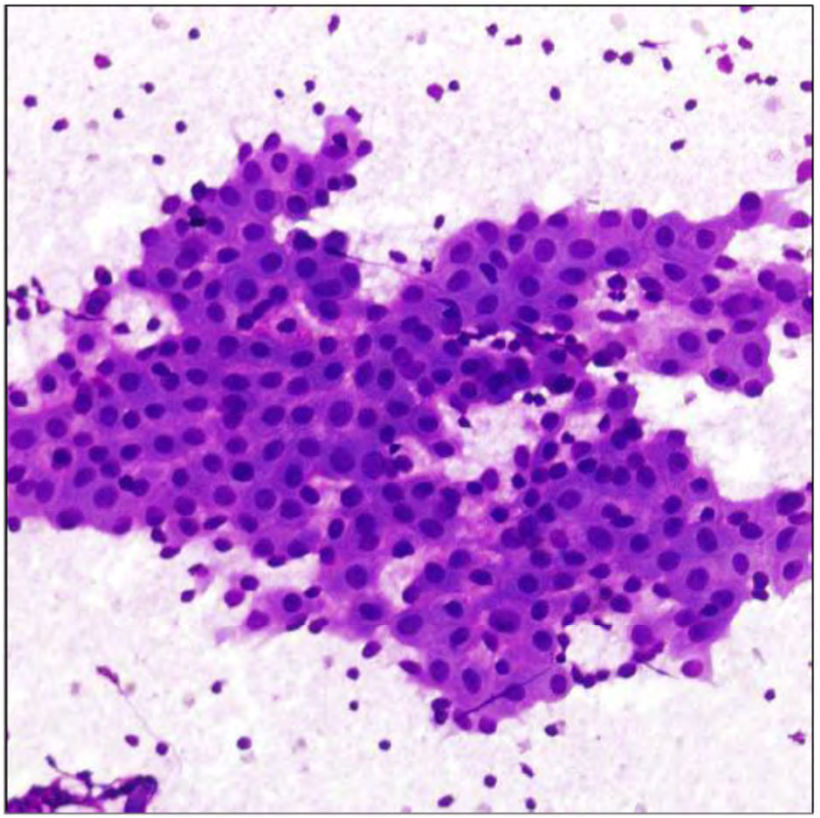
Warthin's Tumor

- 2nd most common benign salivary gland tumor
- Smokers, typically 5th -7th decade, M>F
- Almost exclusively Parotid, superficial lobe in the tail
- Painless mass with a doughy feel
- Aspiration usually yields a drop or two of thick, tan brown fluid (looks like motor oil)
- Bimorphic population of lymphocytes and oncocytes, some papillary configuration
- DD MECarcinoma, Oncocytoma, lymphnode, Sq ca

WARTHIN TUMOR (PAPILLARY CYSTADENOMA LYMPHOMATOSUM)

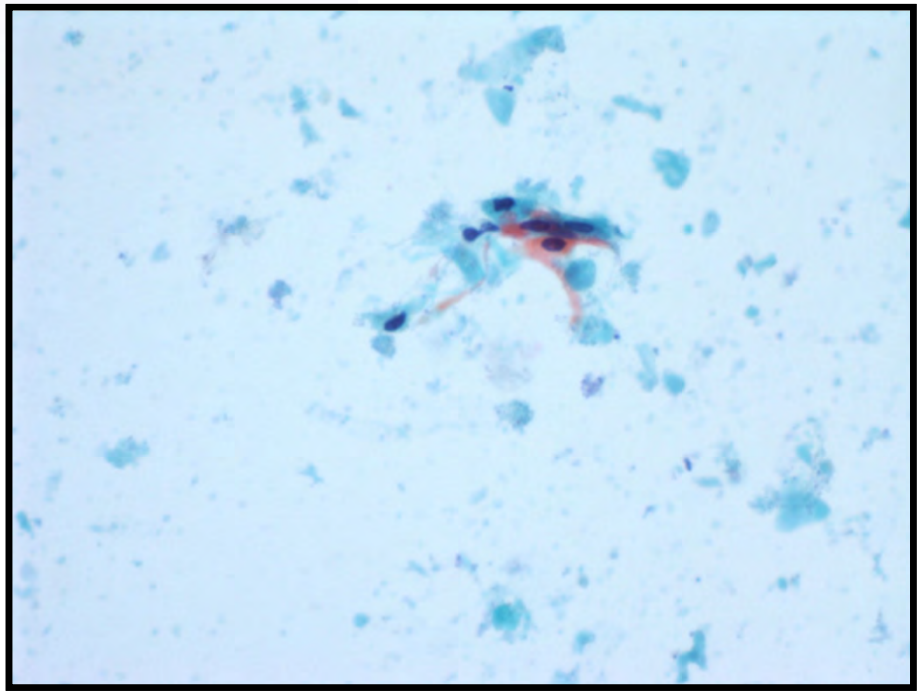


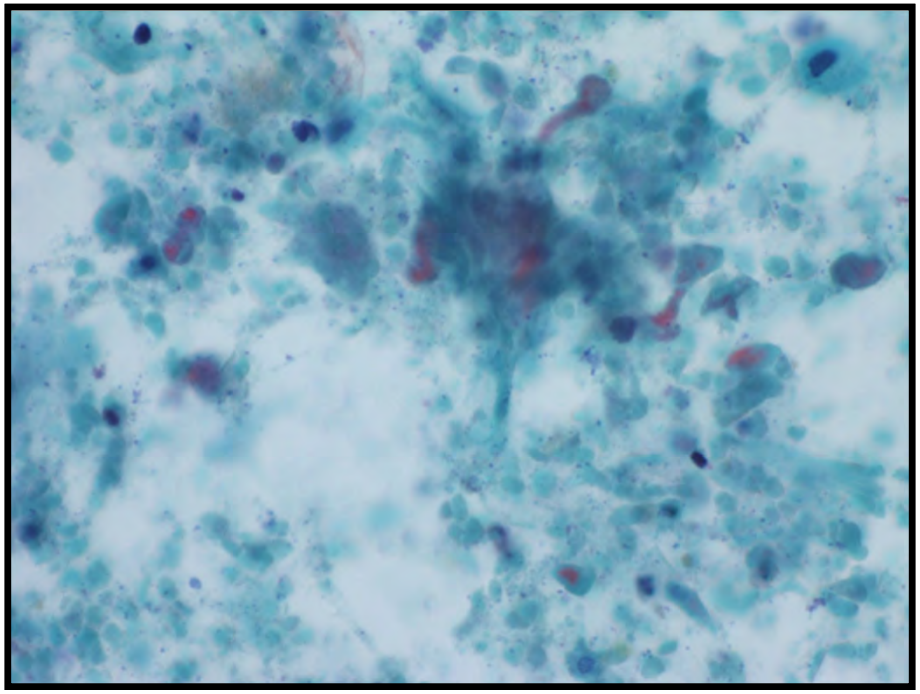
A sheet or honeycomb of oncocytic cells. Note the well defined borders and a suggestion of papillary architecture.



This air dried material shows the remarkable oncocytic nature of the proliferation. There is a monotony to the cells. Note the lymphoid cells in the background.

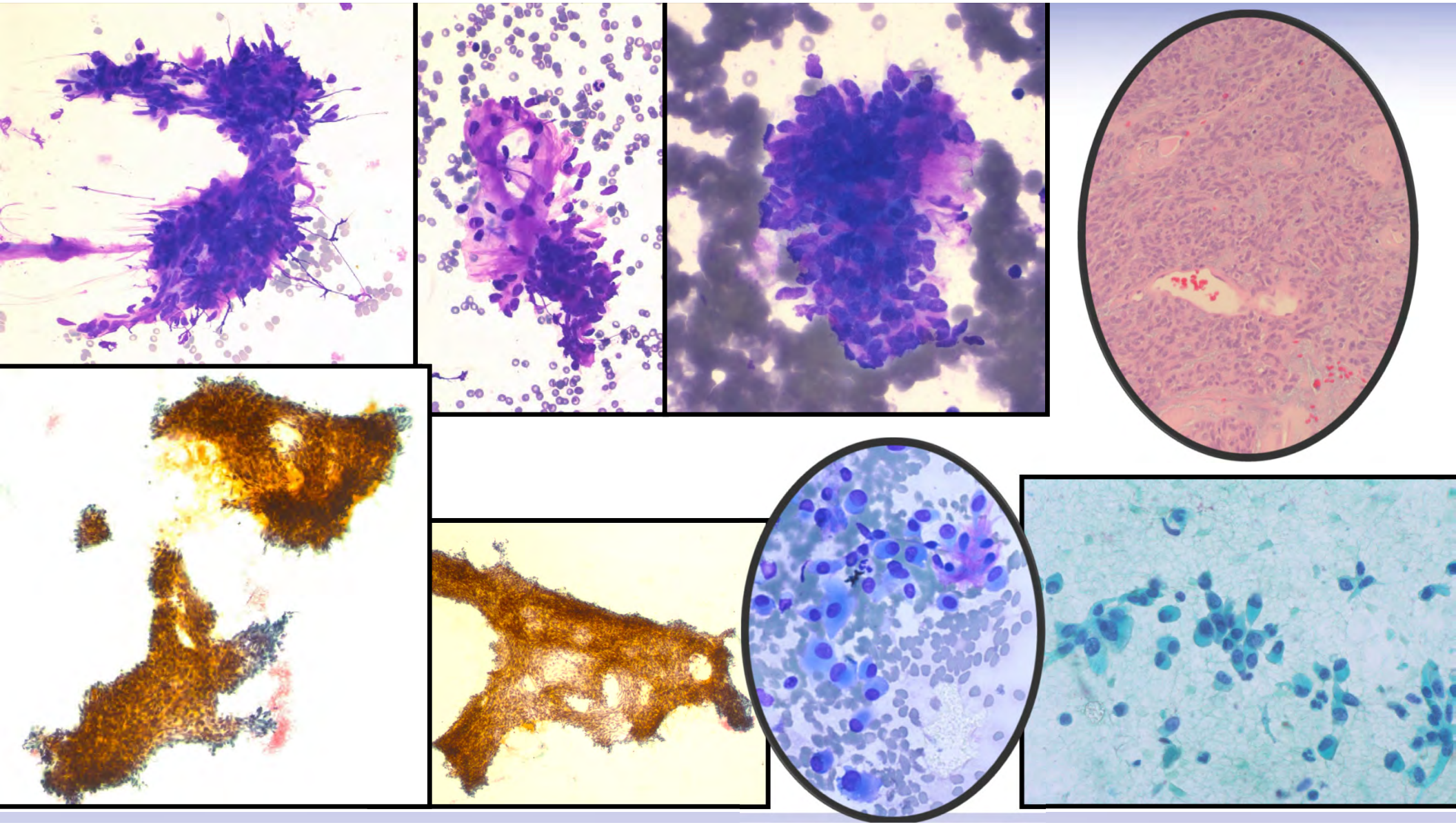
Warthin's with atypical Squamous metaplasia





Myoepithelioma

- Benign myoepithelial tumor, 2% of salivary gland neoplasms, 6% of minor salivary gland tumors
- 3rd-5th decade, M:F (1:1), slowly growing, painless mass
- Two cell types, spindle or plasmacytoid or may be mixed.
- Collagenized stroma, chondroid or chondromyxoid areas
- Looks like PA but without ductal cells
- DD PA, Plasmacytoma,myoepithelial carcinoma (has necrosis, atypical mitosis, invasion into surrounding)



Neoplasm: Uncertain Malignant Potential (SUMP)

- Can diagnose as a neoplasm but cannot tell what type/specific diagnosis
- Malignancy cannot be excluded
- Majority will consist of cellular benign neoplasms with atypical/confusing features or low grade carcinomas
  - Myoepithelioma
  - Stroma poor Pleomorphic adenoma
  - Warthin's with atypical metaplasia
  - Basiloid tumors(adenoma vs carcinoma)

Neoplasm: Uncertain Malignant Potential (SUMP)

- Subgroups include;
  - Cellular Basaloid neoplasm
    - (fibrillary stroma) Pleomorphic adenoma (PA), Myoepithelioma/ca, Basal cell adenoma/ca
    - (Hyaline stroma) Basal cell adenoma/ca, Adenoid cystic ca (Adcc), Polymorphous ACA, epi-myo epithelial carcinoma
    - (Mixed/other stroma) Adenoid cystic ca, Polymorphous ca
    - Scant Stroma: Cellular PA, Adcc, canalicular adenoma, myoepith ca
  - Cellular oncocytic/Oncocytoid neoplasm
    - Warthin's, Oncocytoma, acinic cell ca, MASC,meta RCC, MEC, myoepithelioma
  - Cellular neoplasm with clear cell features

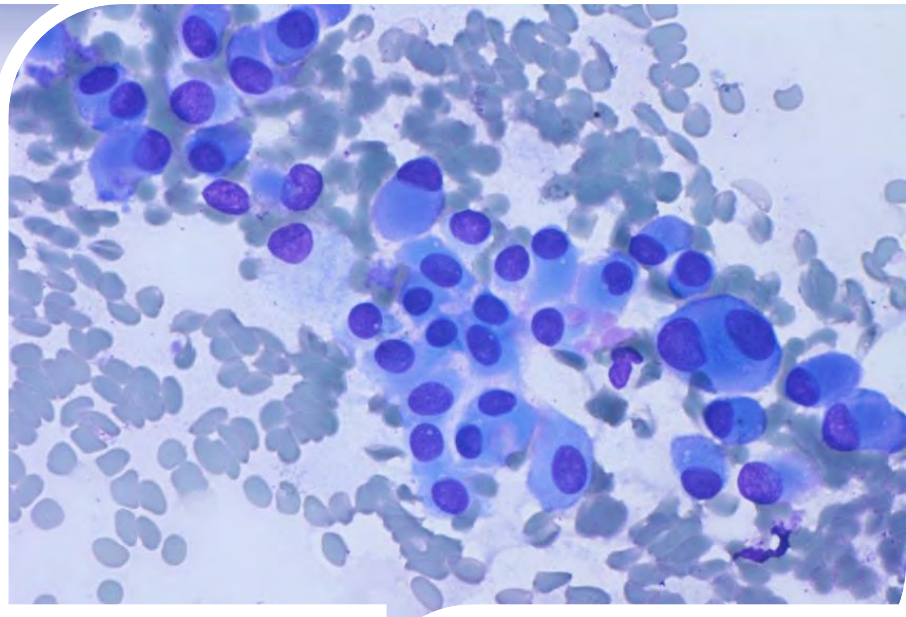
The Milan System for Reporting Salivary Gland Cytopathology (MSRSGC)

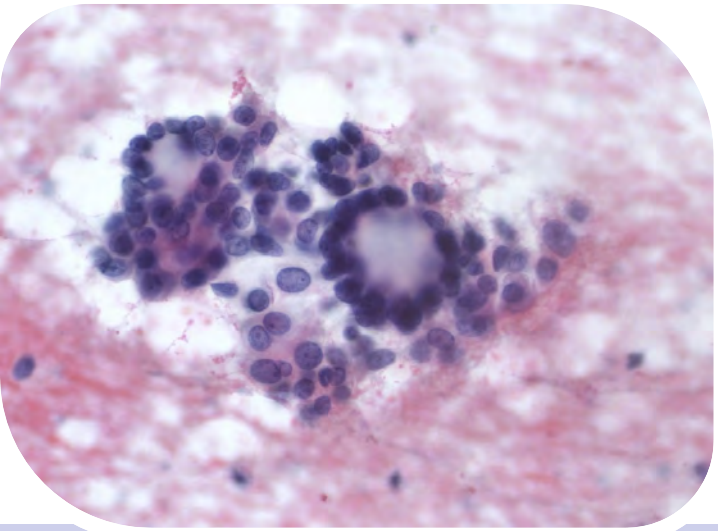
Diagnostic Category	Risk of Malignancy (ROM)	Management
I. Non-Diagnostic	~25%	Clinical/radiologic correlation, repeat FNA
II. Non - Neoplastic	~10%	Clinical follow up, radiologic correlation
III. Atypia of Undetermined Significance(AUS)	~20%	Repeat FNA or surgery
IVa. Neoplasm: Benign	<5% (range 0-13%)	Follow or conservative surgery
IVb. Salivary gland Neoplasm of Uncertain malignant potential (SUMP)	~35% (range 0-100%)	Conservative surgery
V. Suspicious for malignancy	~60%	Surgery, decide if low grade or High grade and manage accordingly
VI. Malignant (low vs High grade)	~90%	Same as above

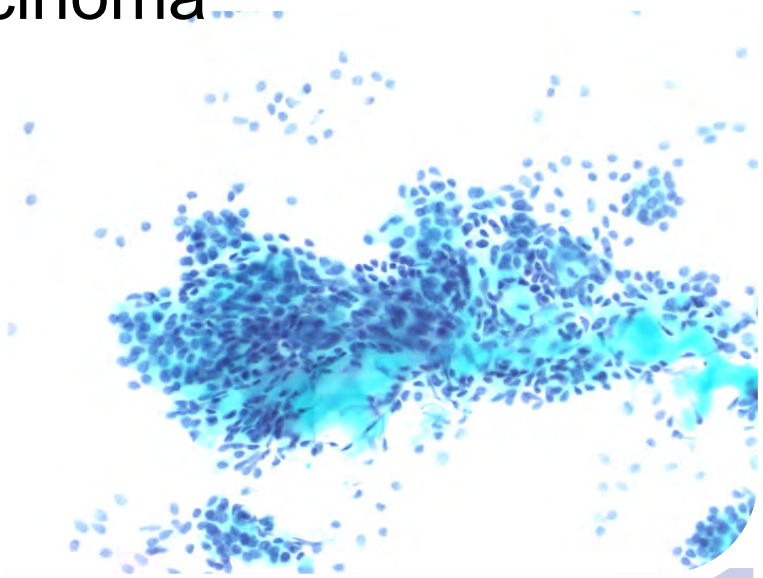
ROM depends on salivary gland site and nature of specimen Personal communication Drs Faquin and Rossi and presentation at ASC meeting in Phoenix AZ Nov 2017

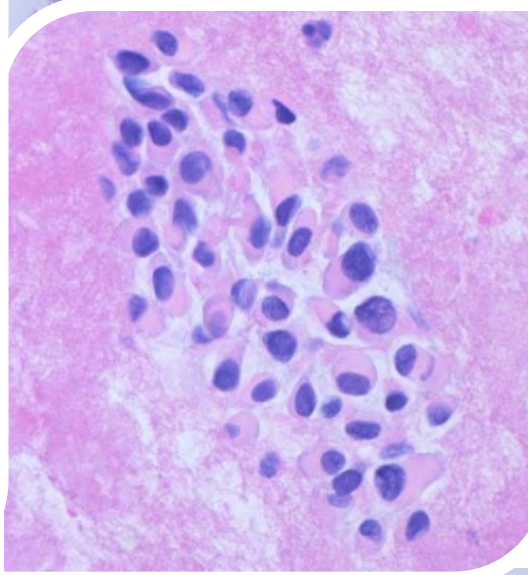
Neoplasm: SUMP

- Pleomorphic Adenoma with myoepithelial cell prominence
- PA with focal areas questionable for Adenoid cystic carcinoma









Sample Reports

Neoplasm, Benign

Satisfactory for evaluation

Neoplasm: Benign

Pleomorphic Adenoma

SUMP

Satisfactory for evaluation

Neoplasm: Salivary Gland neoplasm of Uncertain Malignant Potential

Cellular basaloid neoplasm. See note: Specimen consists of mostly basaloid cells with minimal nuclear atypia, lack of necrosis or mitosis. Although a diagnosis of pleomorphic adenoma is favored, a basal cell adenoma/carcinoma cannot be ruled out.

From: The Milan System for reporting salivary gland cytopathology by Faquin and Rossi, Springer 2018

Suspicious for Malignancy

- Aspirates with features highly suggestive of carcinoma but qualitatively or quantitatively fall short of a definitive diagnosis
- An attempt should be made to subcategorize if worried about low or high grade malignancy
- Majority (but not all) will be cases of high grade carcinomas with compromised sampling/preparation

Suspicious for malignancy…sample reports

Example 1

Satisfactory for evaluation

Suspicious for malignancy

Rare highly malignant cells, suspicious for high grade carcinoma

Example 2

Evaluation limited by scant cellularity

Suspicious for malignancy

Atypical cells in a mucinous background, suspicious for low grade muco epidermoid carcinoma

The Milan System for Reporting Salivary Gland Cytopathology (MSRSGC)

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VI. Malignant (low vs High grade)	~90% (57-100%)	Same as above

ROM depends on salivary gland site and nature of specimen Personal communication Drs Faquin and Rossi and presentation at ASC meeting in Phoenix AZ Nov 2017

Malignant

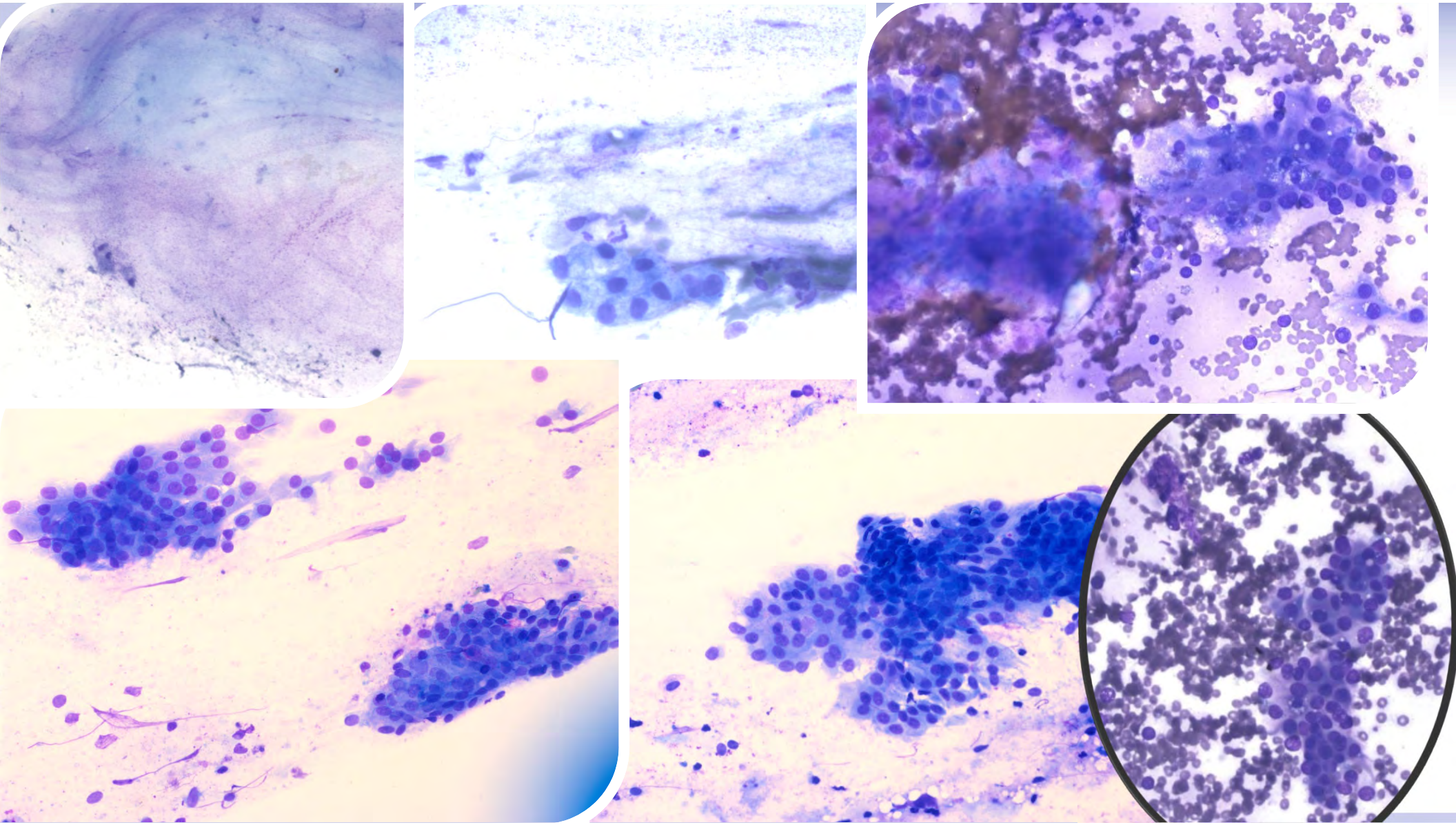
- Aspirates diagnostic of malignancy
- Every attempt should be made to classify into specific type/ grade when possible as grading is critical for management
  - Low grade(low grade mucoepidermoid carcinoma)
  - High Grade (Salivary duct carcinoma)
- Other malignancies like Metastasis, Lymphomas and Sarcomas also belong here but should be specified as to type etc..

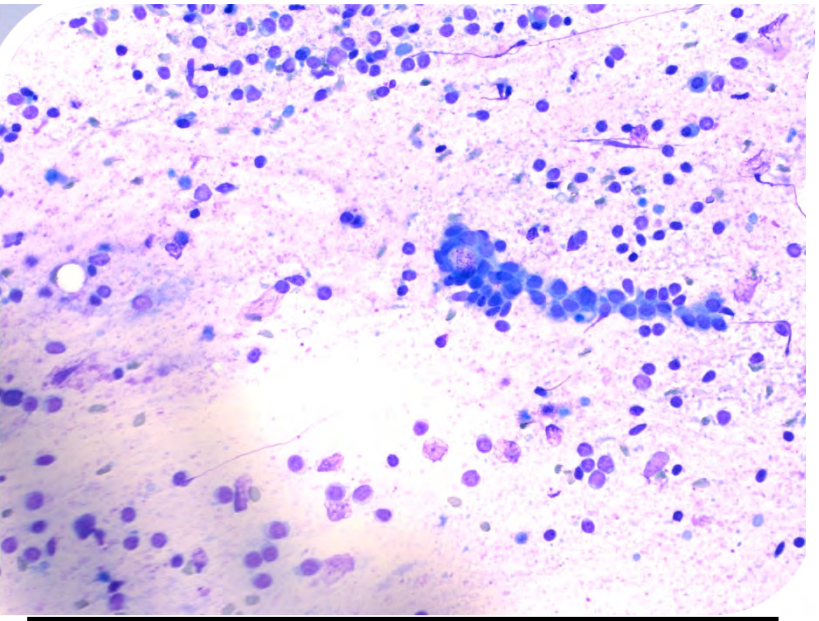
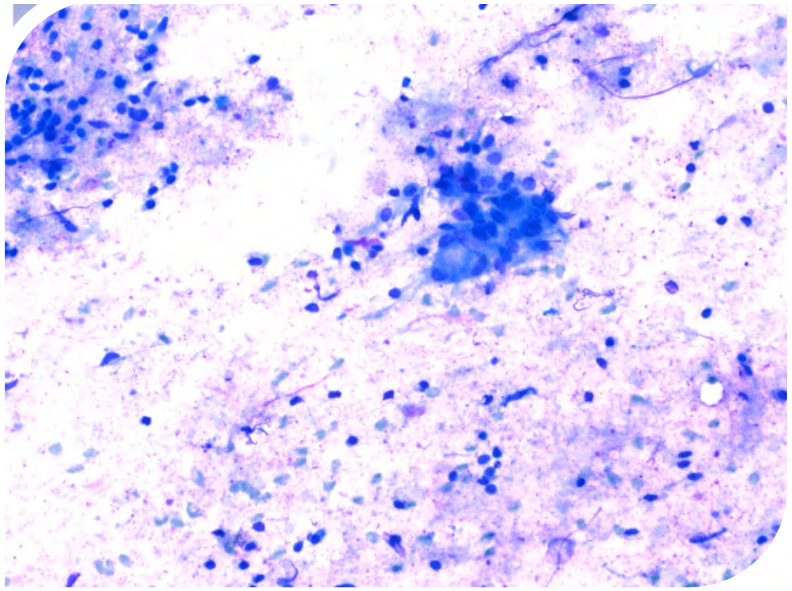
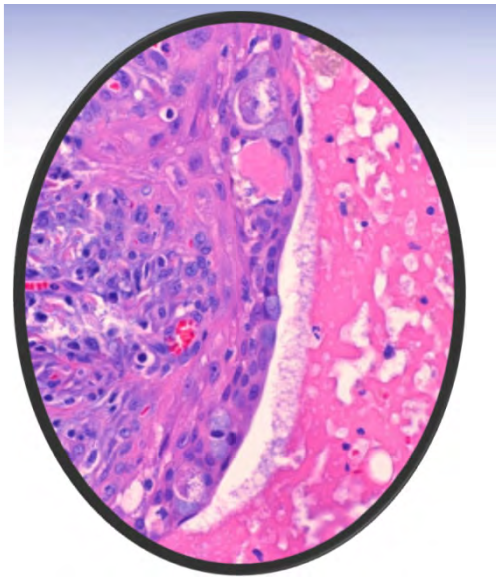
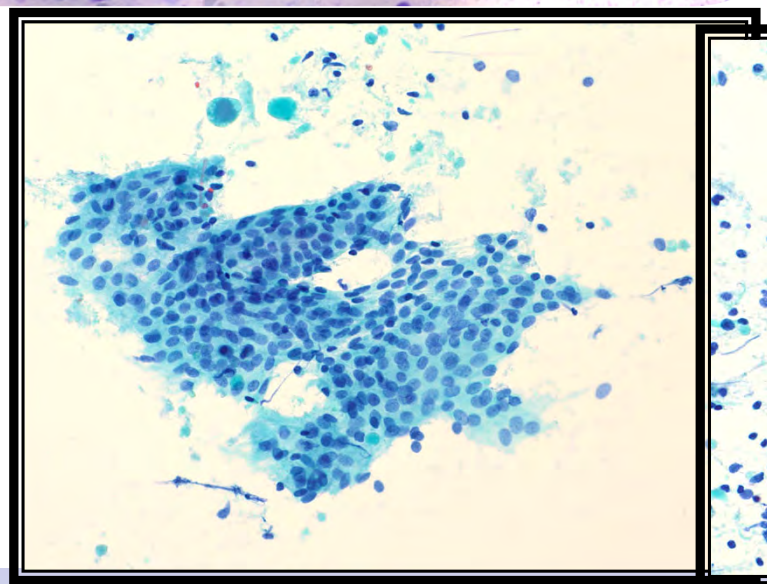
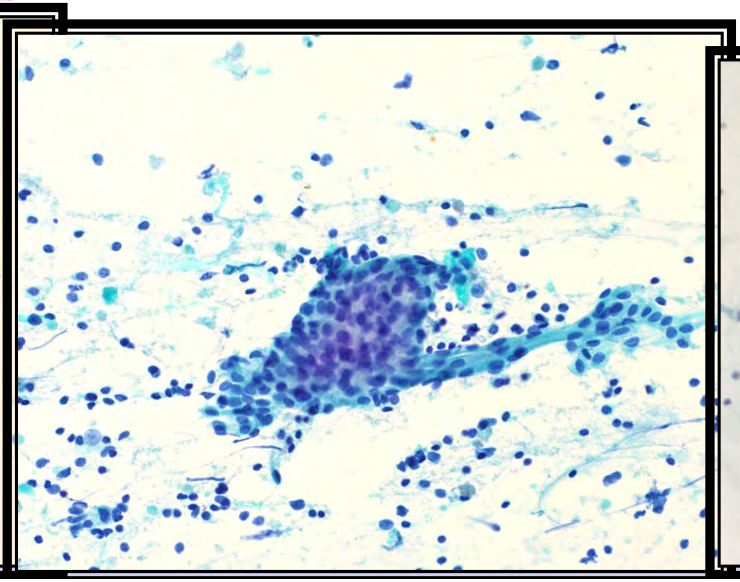
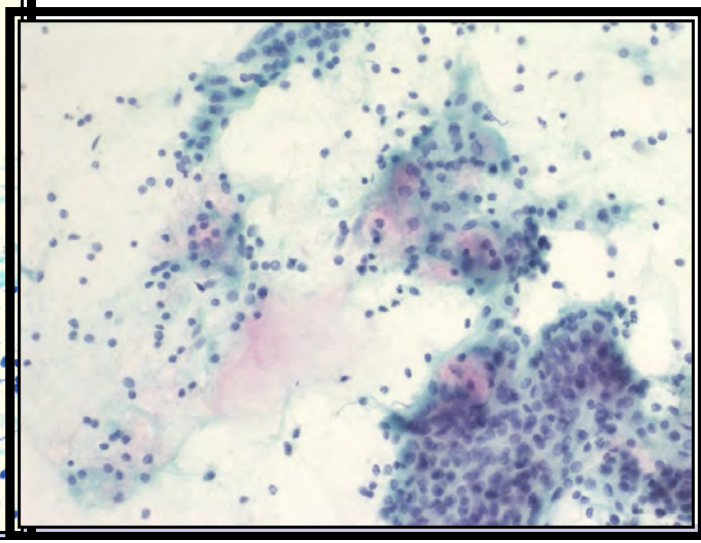
Mucoepidermoid Carcinoma

- Most common malignant salivary gland tumor in children and adults, wide age range
- Major and minor glands affected, size varies
- Low and High grade types
- Low grade, 98% Disease Specific Survival
- High grade metastatise, 65% DSS
- 3 cell types, mucus, intermediate and epidermoid cell
- High grade difficult to diagnose on cytology, often call high grade carcinoma/squamous ca

Mucoepidermoid Carcinoma…continued

- Low grade may have abundant Mucin and few cells
- MEC has 3 cell types: Clusters of bland intermediate, epithelial cells and mucocytes
- Mucin producing cells may be columnar, cuboidal or histiocyte like
- Intermediate cells often found in nests or sheets, can be polygonal/epidermoid in appearance
- Epidermoid cells are polygonal and appear in nests or scattered



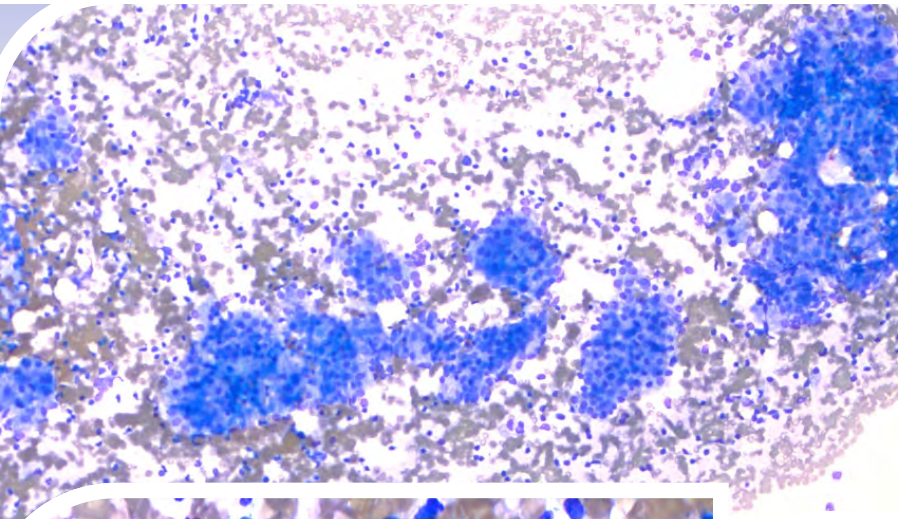







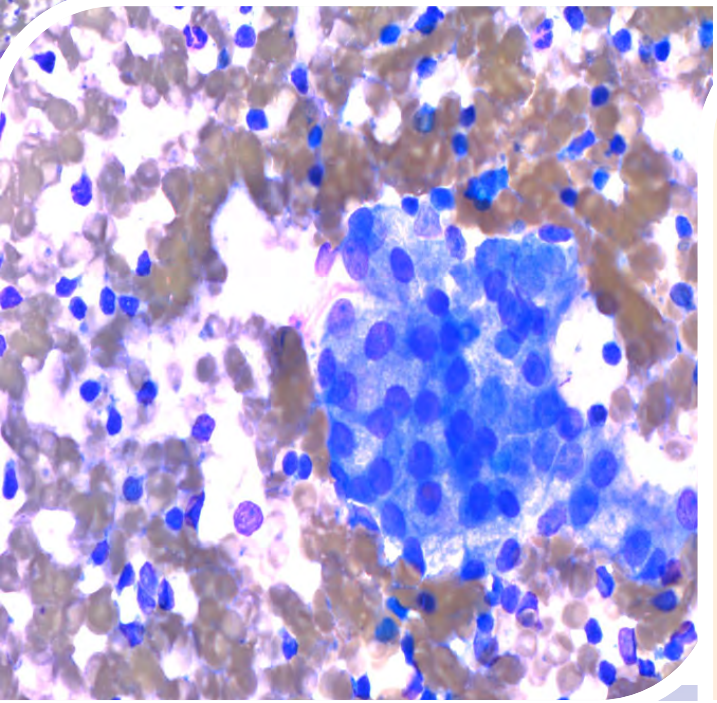
Mucoepidermoid Carcinoma

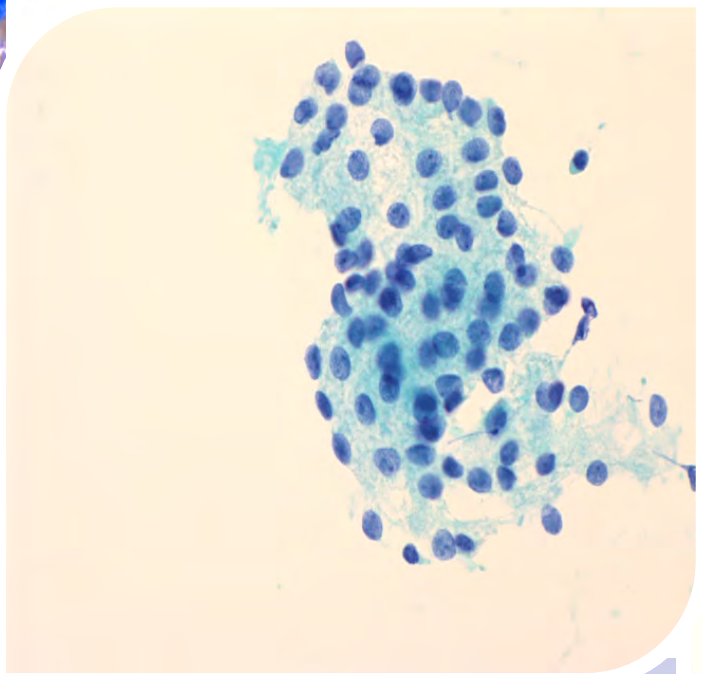
- IHC: Her 2+ in 60% of high grade MECs
- EGFR high copy numbers in high grade
- P16 + in 60%..NOT HPV related
- Molecular: t(11;19)(q21;p13) seen in 55-65% of MEC
  - This translocation fuses CREB-regulated transcription coactivator 1 (*CRTC1*, formerly *MECT1*) (exon 1 of gene at 19p13) with Mastermind-like gene family (*MAML2*) (exons 2–5 of gene at 11q21)
  - Identified in low- to intermediate-grade tumors usually
  - Tumors with few copy number alterations (usually *CRTC1-MAML2*) seem to have better prognosis

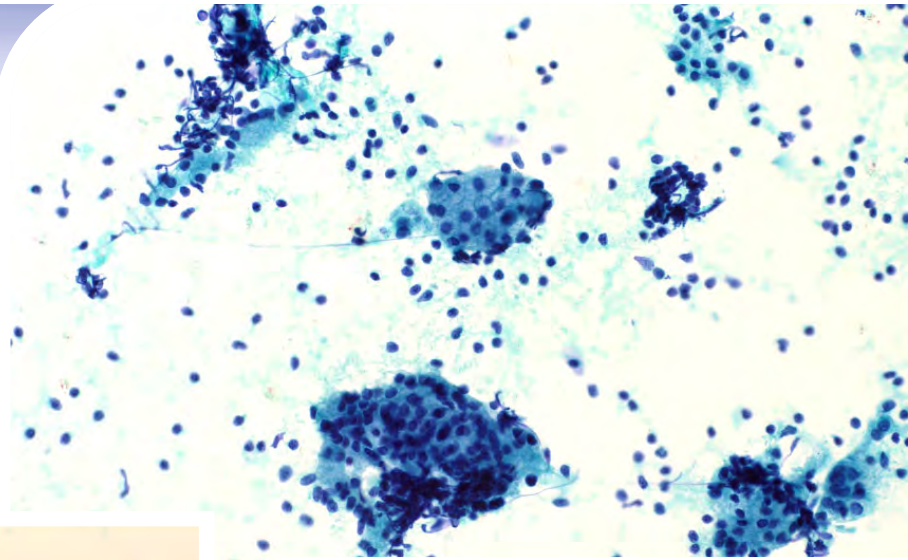
Acinic Cell carcinoma

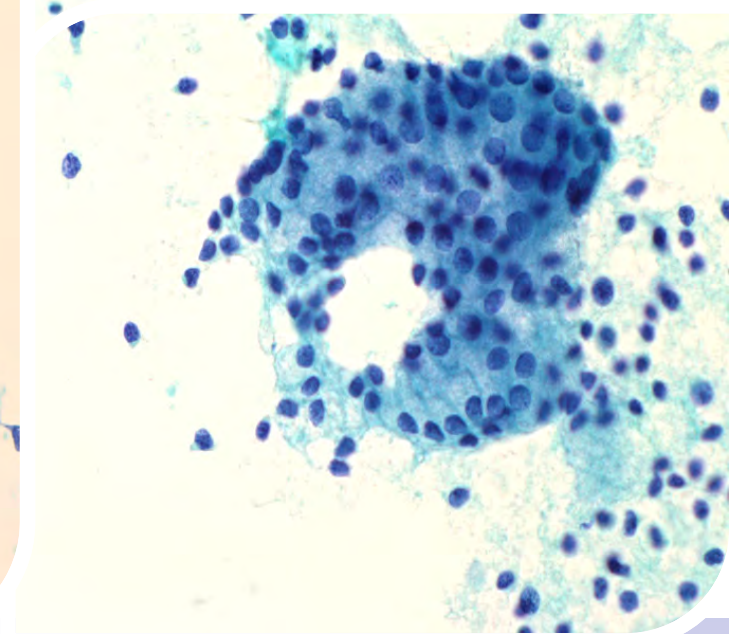
- 80% occur in Parotid gland, 2nd most common malignant salivary gland tumor(10-12%), 6% of all salivary tumors
- F:M=3:2, wide age range, mean mid 40s
- 2nd most common malignant salivary tumor in kids
- Slowly growing, may have pain or facial nerve paralysis
- High cellularity, loose or tight acinar structures
- Many stripped bare tumor nuclei in background
- Ample granular vacuolated fragile cytoplasm











Acinic Cell carcinoma

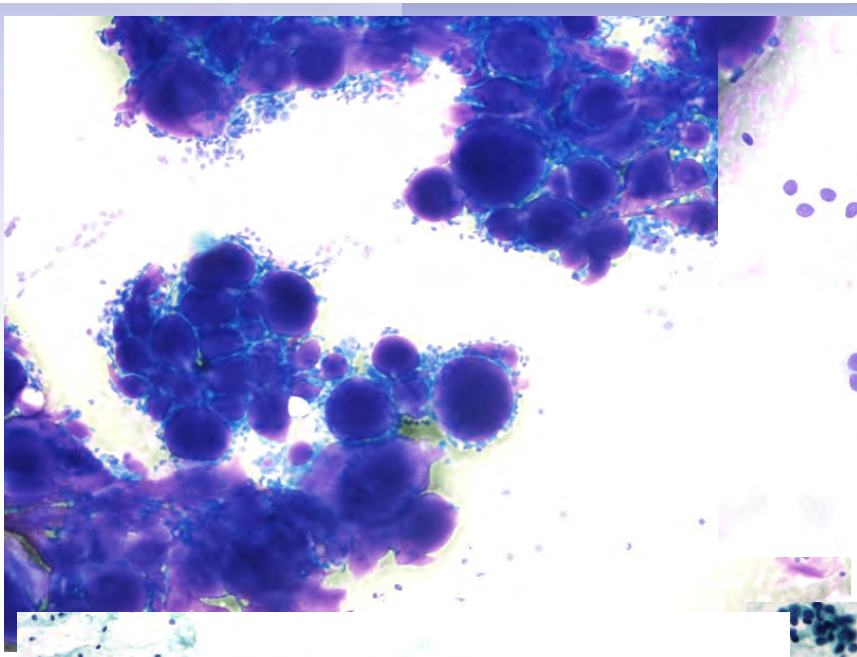
- High false negative rate
- Mistaken for normal salivary gland(note ducts and adipocytes missing, acini tight in normal)
- Other DD Warthin's, MEC, other clear cell tumors
- PAS+ diastase resistant granules (not useful in cytology)
- No specific IHC profile
- No specific genetic/molecular test
- 5 yr survival around 90%, local recurrenin in 35%

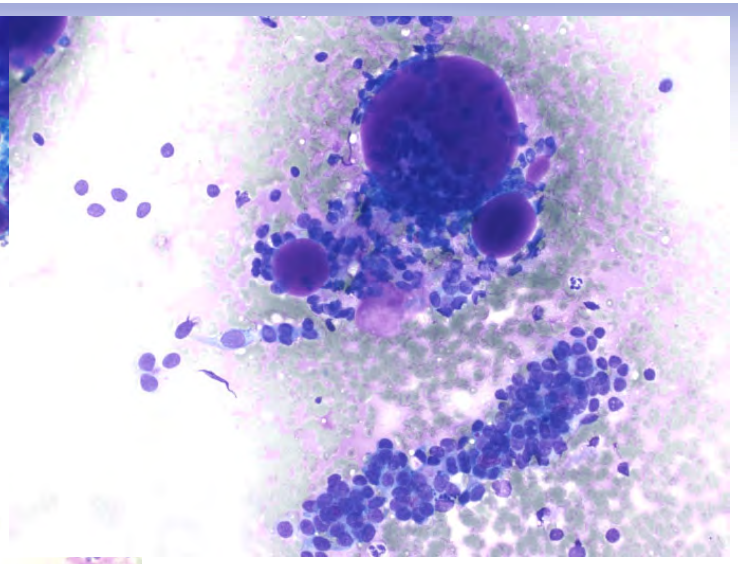
Adenoid Cystic Carcinoma

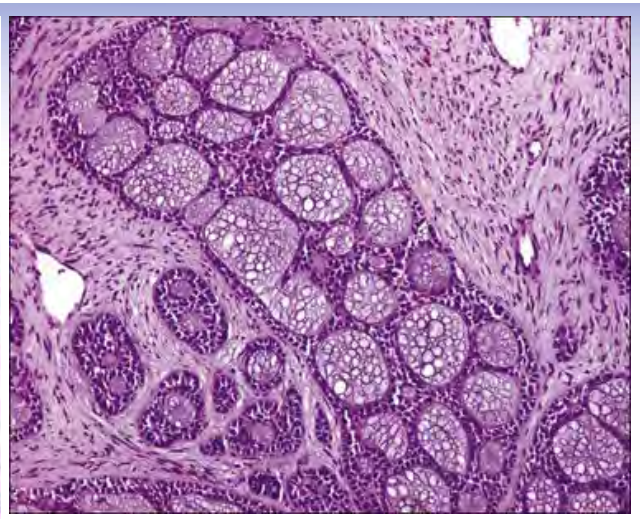
- 4th most common malignant salivary gland tumor, F:M=3:2, peak age 6th decade
- Major and minor salivary glands, Parotid most frequent
- Mass, pain, tenderness, facial nerve paralysis
- Treated with radical excision
- Poorly circumscribed infiltrative tumor with multiple patterns
- Survival based on stage, stage I 75%, II 43%, 3&415%

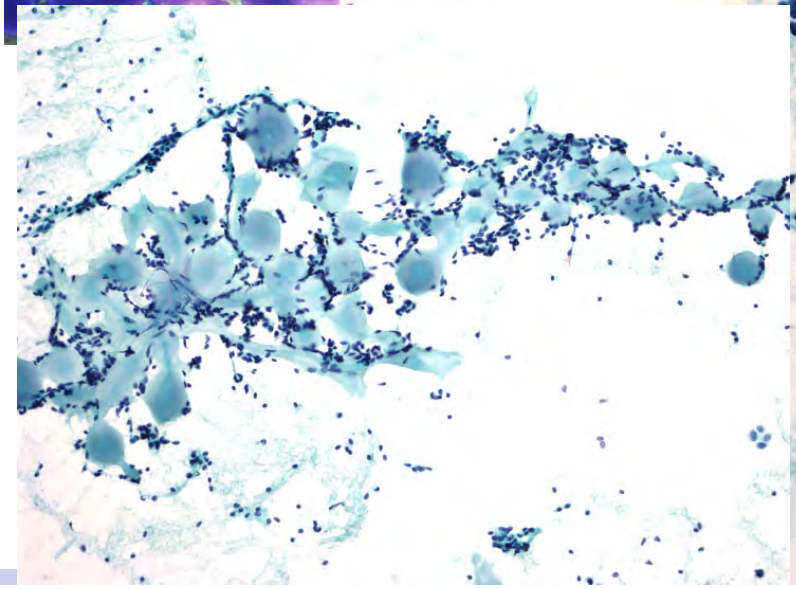
Adenoid Cystic Carcinoma

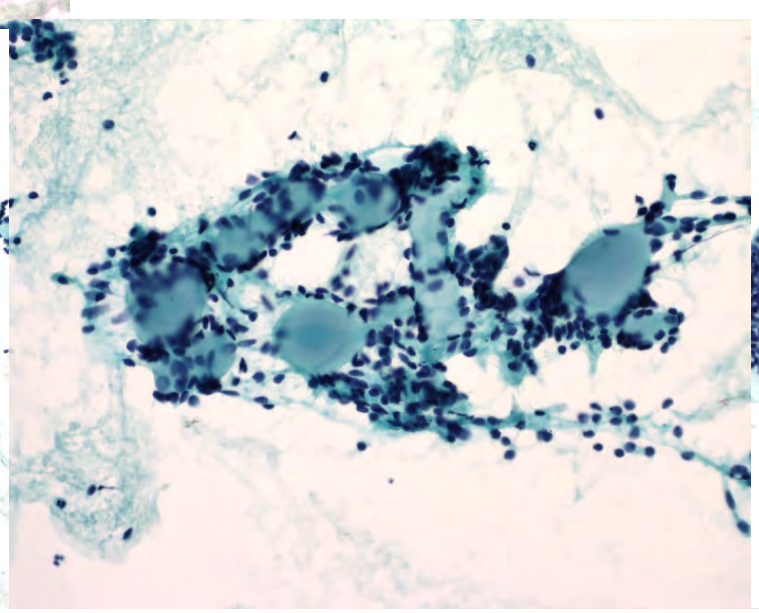
- Variety of patterns (cribiform, tubular, solid, combination)
- Small to medium cells with clear to eosinophilic cytoplasm
- Cohesive cellular clusters surrounding balls of metachromatic material (distinct cells and stroma)
- High N:C ratio, dark nuclei with scant cytoplasm
- Difficult to distinguish from other salivary neoplasms in absence of metachromatic stroma
- DD PA, other basaloid salivary tumors, B9 or malignant

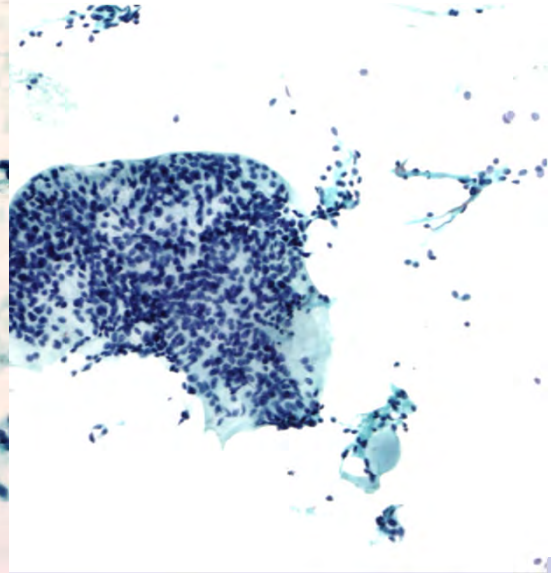


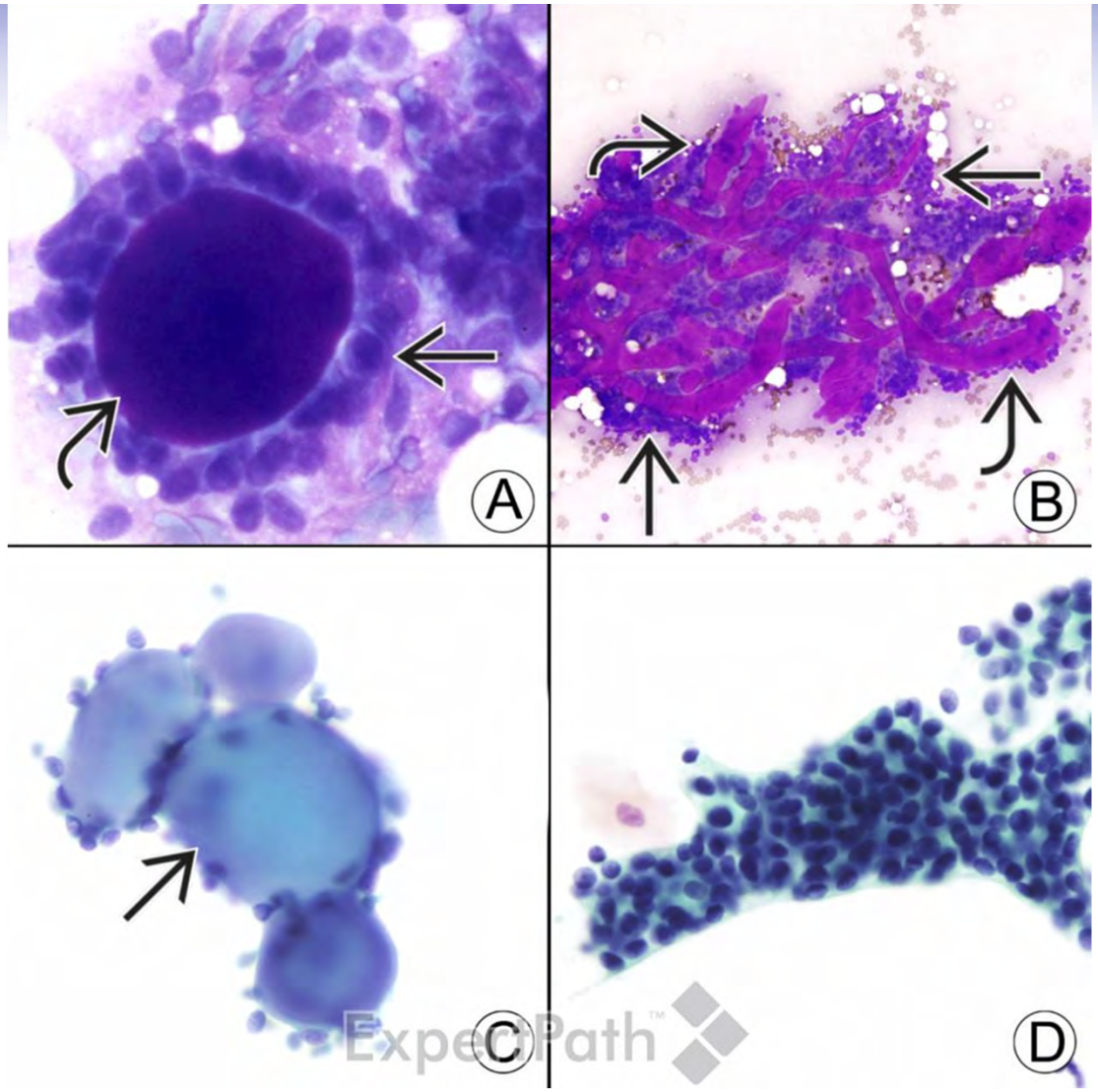











A
B
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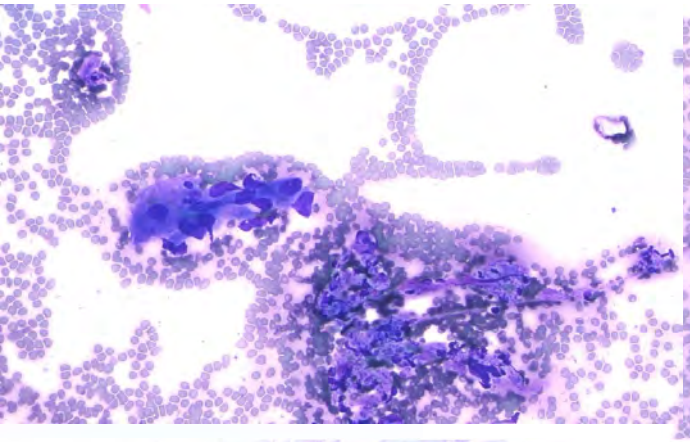
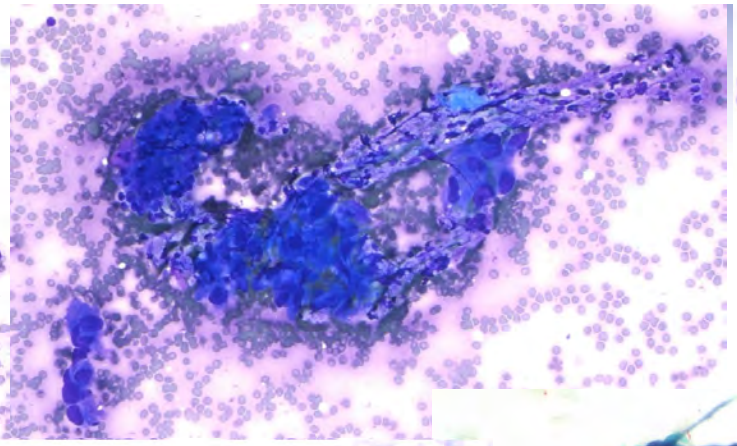
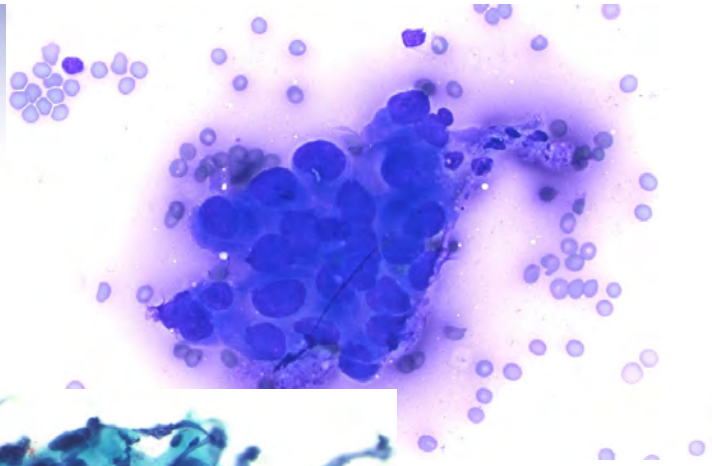
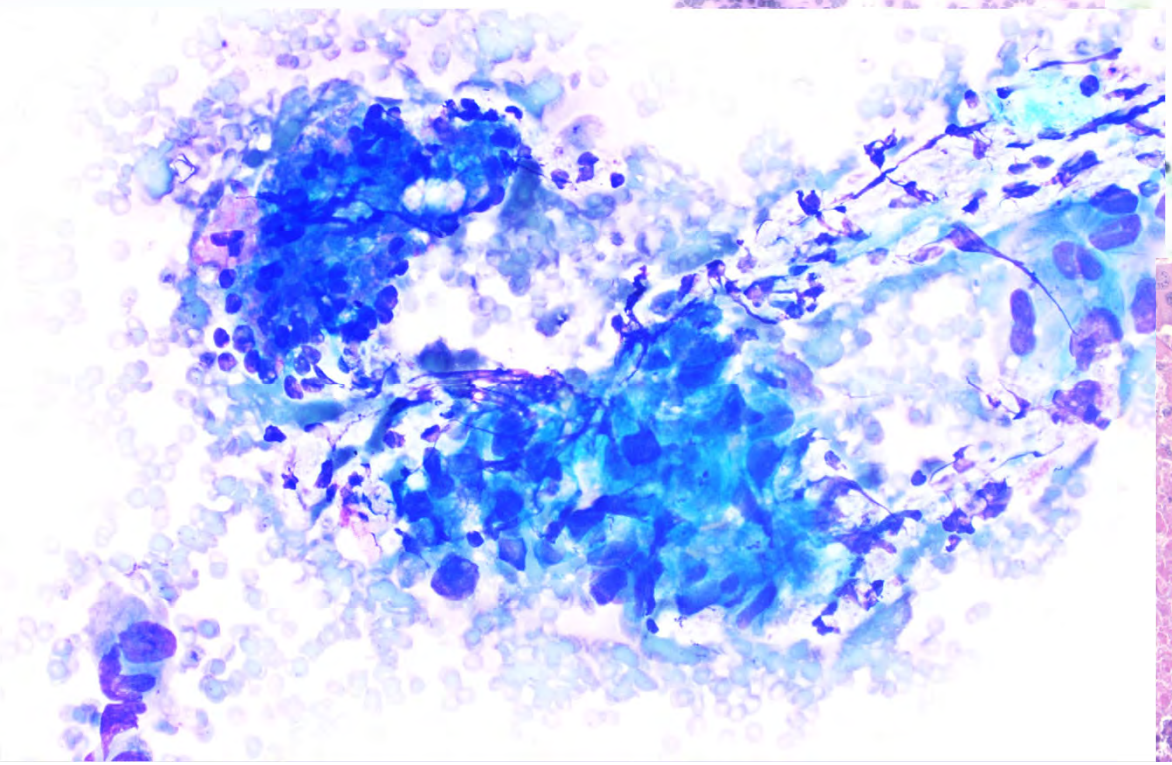
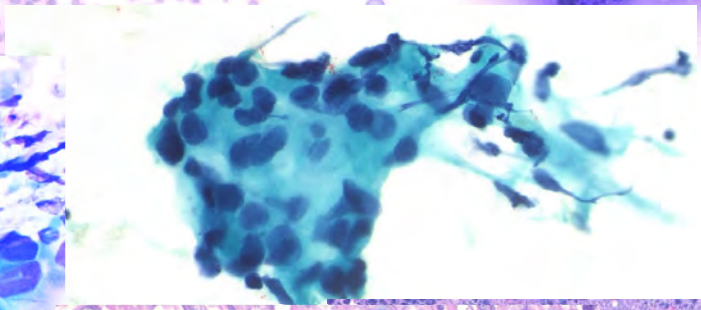
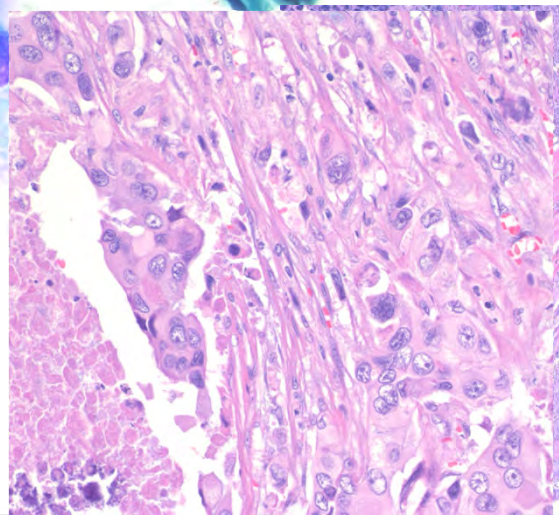
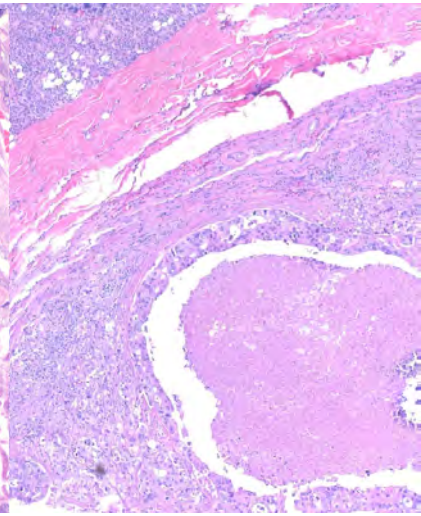
D
ExpertPath

Adenoid Cystic Carcinoma…Ancillary tests

- Immunohistochemistry of limited practical use as tumors in DD react similarly
- Ckit
- Molecular testing:
  - *MYB-NFIB* fusion protein up regulates MYB protein expression
  - Rare cases do not rely on MYB overexpression for tumorigenesis

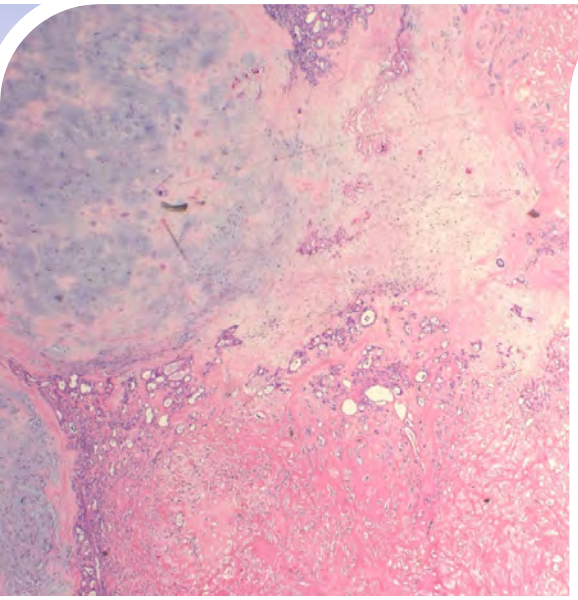
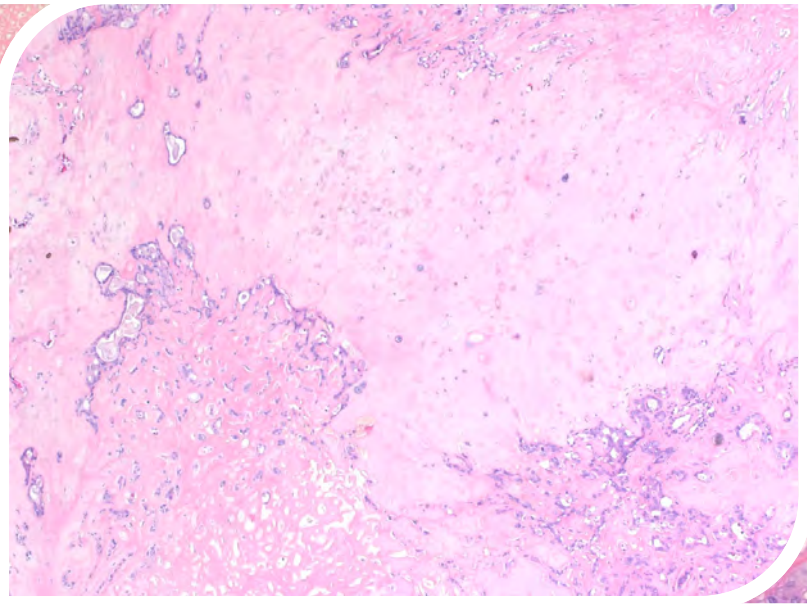
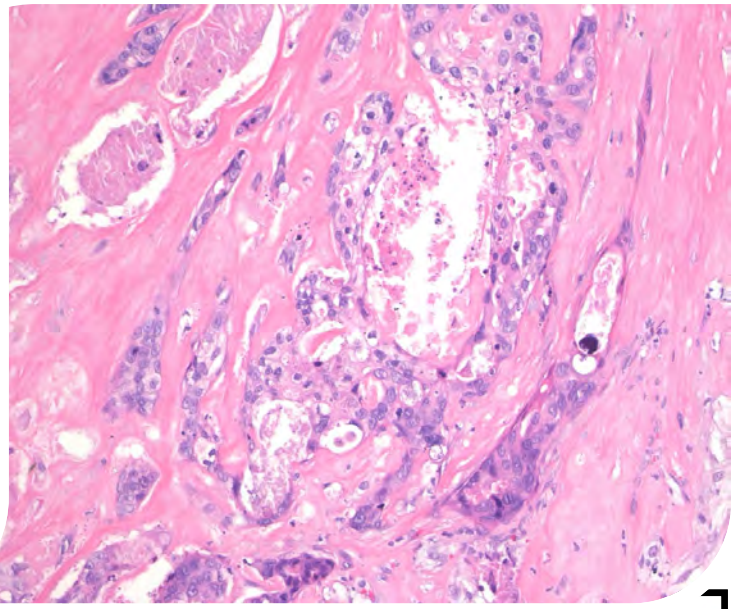
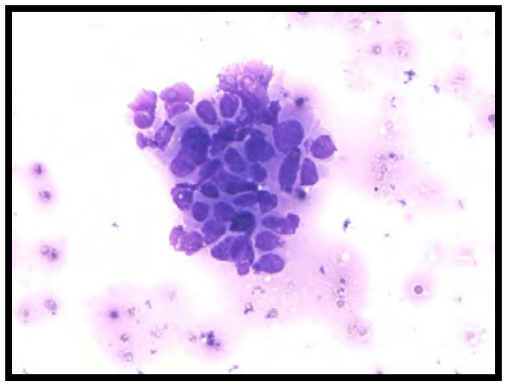
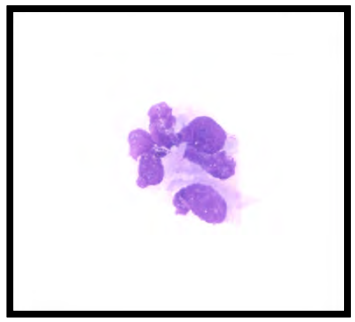
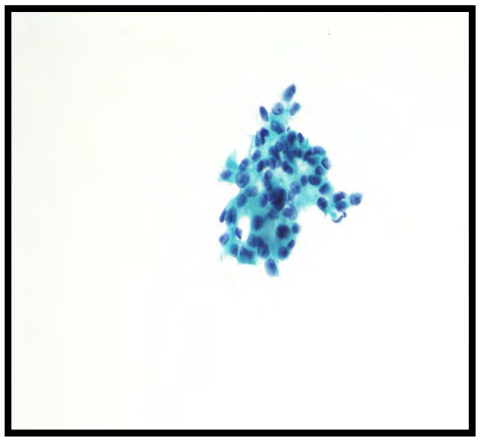
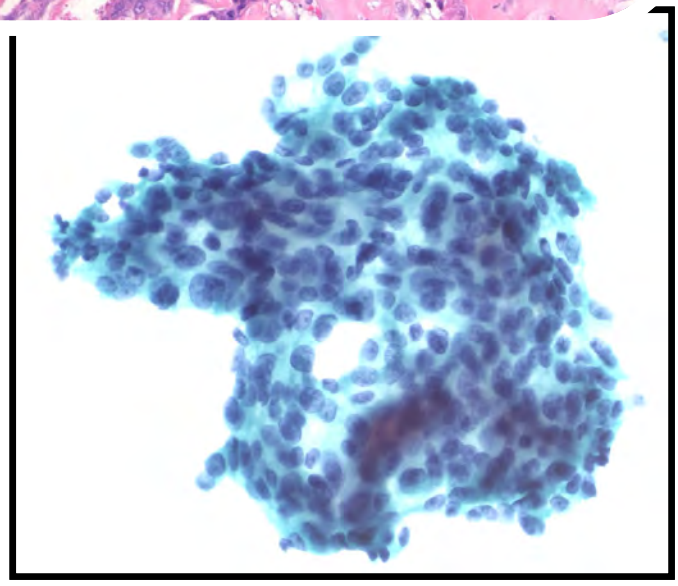
Salivary Duct Carcinoma

- High grade carcinoma resembling breast ca
- 7^{th} decade, parotid, M:F-2-4:1
- Rapid growth with facial nerve involvement
- Cytology shows features of high grade adenocarcinoma with necrosis and mitosis
- Cribiform, papillary, sheets and single cells
- Immunoreactive for epithelial markers, Androgen receptor and Her 2

Carcinoma ex Pleomorphic Adenoma

- Carcinoma arising from Pleomorphic adenoma
- Requires concurrent PA or history of PA at same site
- 80% occur in major salivary glands especially Parotid
  - 7-10% of PAs (especially long standing), 6th to 8th decade (20 yrs later than PA)
  - 6th most common salivary gland malignancy in adults
- Cellular specimen with predominantly epithelial cells
- 2 distinct patterns, benign PA with malignant or equivocally malignant cells with or without necrosis, mitosis
  - Malignant component could be adenocarcinoma, salivary duct carcinoma, ACC, MEC, PLGA, epi-myoepithelial carcinoma

Fine-Needle Aspiration, Superficial: Salivary Gland

Approach to Interpretation of Salivary Gland Aspiration Biopsies and Reporting Terminology (Milan System)

PATTERNS OF SALIVARY GLAND ASPIRATES

Cystic Lesions

- Acellular clear fluid
  - Normal gland
  - Sialocele
  - Lymphoepithelial cyst (LEC)
- Cloudy/mucoid fluid ± cells
  - Duct obstruction
  - Abscess
  - Mucocele
  - LEC
  - Warthin tumor
  - Low-grade mucoepidermoid carcinoma (MEC)
  - Acinic cell carcinoma (ACC) (rarely)
  - Cystic degeneration in any neoplasm, benign or malignant

Inflammatory Cells

- Abscess

Lymphocytic Cell Pattern

- Chronic sialadenitis
- Lymphoepithelial sialadenitis
- LEC
- Lymph node
- Lymphoma (monotonous cells)
- Warthin tumor
- ACC

Basaloid Cell Pattern

- Basal cell (monomorphic) adenoma or carcinoma
- Cellular pleomorphic adenoma (PA)
- Adenoid cystic carcinoma (AdCC)
- Myoepithelial carcinoma
- Polymorphous (low-grade) adenocarcinoma
- Small cell carcinoma, primary or metastatic
- Secondary involvement by cutaneous basal cell carcinoma
- Sialoblastoma

Stroma Patterns in Neoplasms

globules
cinoma: Dense, ropy, membranous
myxoid stroma
lioma: Fibrillary
ade) adenocarcinoma: Fibrillary

Cribriform Adenocarcinoma

KEY FACTS

TERMINOLOGY
- Known as cribriform adenocarcinoma of minor salivary gland (CAMSG) or tongue (CAT)
- May be subtype of polymorphous adenocarcinoma but has different clinicopathologic features

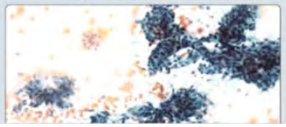
CLINICAL ISSUES
- Very rare with no gender predilection
- Arises in minor salivary gland sites, primarily base of tongue
- Indolent despite nodal metastasis at presentation in 3/4

CYTOPATHOLOGY
- Sheets and clusters of cells with irregular outline; focal papillary patterns may be seen
  - Cribriform pattern in sheets is characteristic
- Very few dissociated cells imparting clean background
- Nuclei resemble papillary carcinoma of thyroid
  - Overlapping, ground-glass appearance with grooves and pseudoinclusions
- Cytoplasm is pale eosinophilic with focal vacuolization
- Metachromatic stroma is variable, reminiscent of colloid, seen in background or within spaces

ANCILLARY TESTS
- Positive immunohistochemistry: S100, vimentin, CK7
- Variable expression of myoepithelial markers: p63(±) and calponin (±)
- Negative: C-kit, thyroglobulin, TTF-1
- Rearrangement of PRKD genes

TOP DIFFERENTIAL DIAGNOSES
- Papillary thyroid carcinoma metastatic to lymph nodes
  - Primary tumor in thyroid seen by ultrasound
  - Positive thyroglobulin and TTF-1
- Polymorphous adenocarcinoma
  - Nuclei not as reminiscent of papillary thyroid
  - Nodal involvement at presentation is rare
  - Palate is most common site with female predilection

Irregular Branching Sheets



Monomorphic Tumor Cells

(Left) *Low-power view of this Pap-stained FNA shows several large clusters of tumor cells forming sheets of cells with irregular branching projections.* (Right) *On higher power of the same Pap-stained sample, the uniformity*

Fine-Needle Aspiration, Superficial: Salivary Gland

Secretory Carcinoma

KEY FACTS

TERMINOLOGY
- a.k.a. mammary analogue secretory carcinoma
- Previously considered "zymogen-poor acinic cell carcinoma"

CLINICAL ISSUES
- Usually slow-growing, painless mass
  - Uncommon high-grade variants may present with faster growth and nerve injury
- Most (70%) are in parotid
  - Can also arise in other major and minor salivary glands and in thyroid

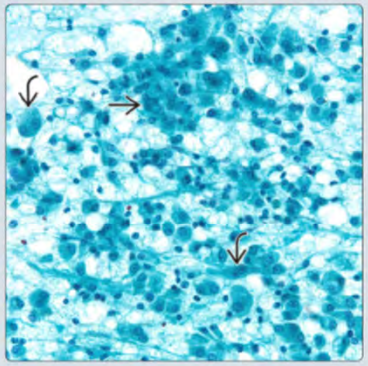
CYTOPATHOLOGY
- Diverse architecture
  - Papillary configurations with transgressing vessels
  - Acinar-like cell clusters
  - Sheets of cells
- Cystic tumors may have abundant secretory material
- "Histiocytoid" cells are characteristic
  - Abundant cytoplasm with vacuoles, mostly small but may be signet ring-like
  - Nuclei are typically uniform and bland

MOLECULAR
- *ETV6* translocations are characteristic, usually detected by FISH break-apart probes
- t(12,15)(p13;q25) *ETV6-NTRK3* translocation is typical
  - Specific to secretory carcinoma (in salivary gland)
- *ETV6* can also rarely have other translocation partners

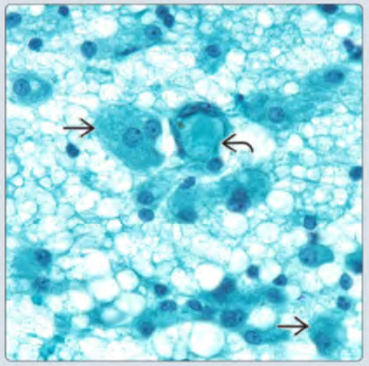
ANCILLARY TESTS
- Mammaglobin and S100 positive; not specific to secretory carcinoma among salivary gland tumors
- Mucin vacuoles stain with mucicarmine, alcian blue, and PAS without diastase

TOP DIFFERENTIAL DIAGNOSES
- Acinic cell carcinoma
- Low-grade salivary duct carcinoma

Secretory Carcinoma With High Cellularity

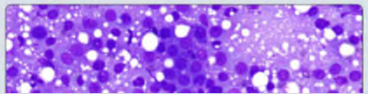


Small and Large Cytoplasmic Vacuoles



(Left) *Pap-stained smear contains numerous tumor cells with focal cohesive sheets but predominantly dispersed individual cells. Note that occasional binucleated cells are present in this example. (Courtesy S. Ali, MD.)* (Right) *Higher power shows that many of the cells have obvious cytoplasmic vacuoles visible by Pap stain. Most cells have [illegible] vacuoles, but occasional cells have a single large vacuole creating a signet ring-like cell configuration with nuclear displacement. (Courtesy S. Ali, MD.)*

Uniform Cell Population

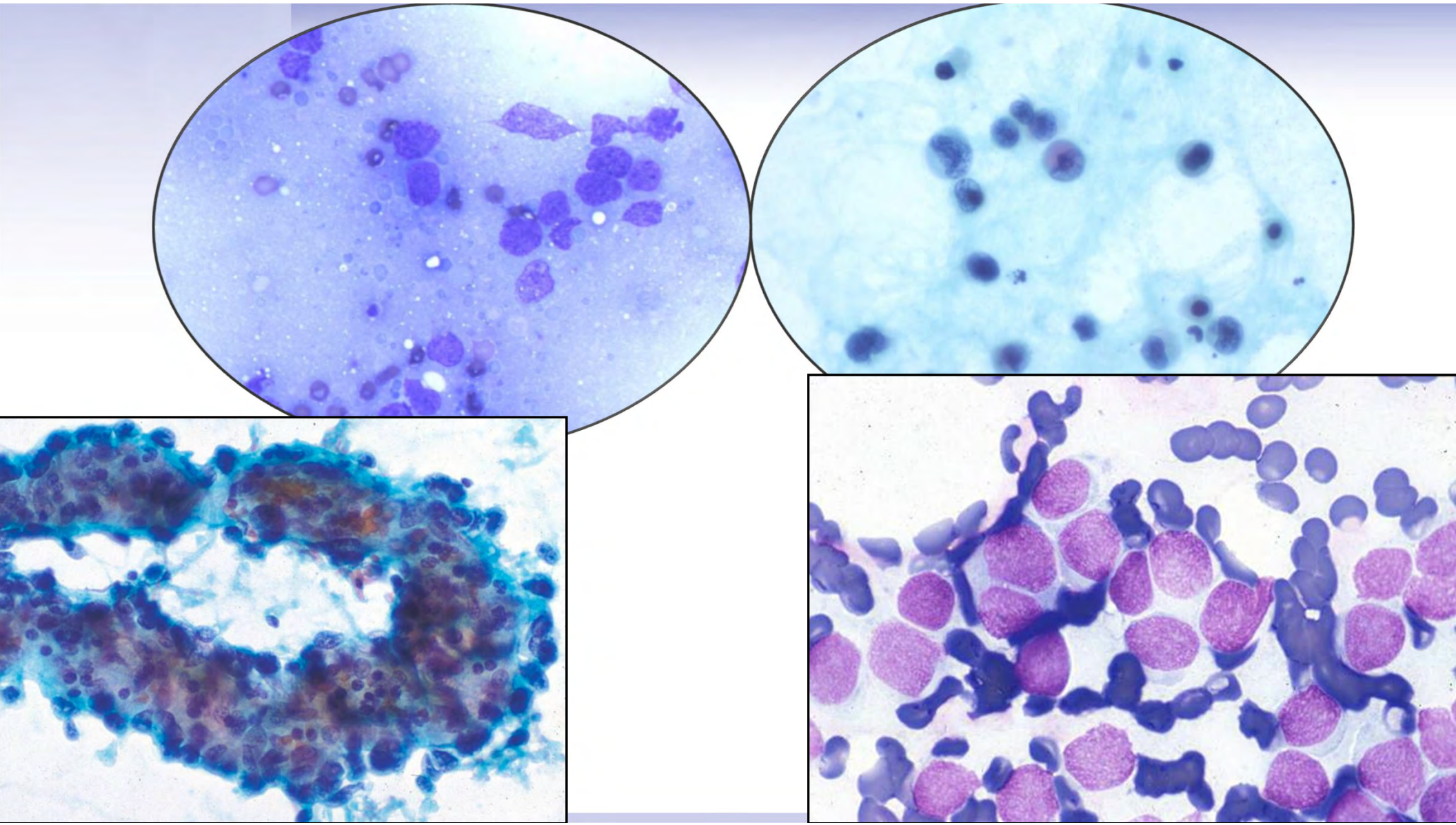


Histiocyte-Like Appearance of Tumor Cells

(Left) *Diff-Quik-stained smear demonstrates a fairly uniform population of cells with round nuclei having smooth contours. Abundant secretory*

Other Primary and Metastatic Malignancies in Salivary Gland

- Squamous cell carcinoma, primary or mets/direct extension
- Lymphomas primary or secondary
- Melanomas usually mets or direct extension
- Small cell carcinoma/Merkel cell ca
- Angiosarcomas, usually direct extension from cutaneous
- Other metastasis
- Parotid most frequent reciepent of mets



Milan System Reporting

- Statement on adequacy
- Brief description of cytological features
- Specific diagnosis as to nature of process(neoplastic or non neoplastic)
- If above not possible, then reason for categorization
- Do not use category numbers without the category name
- Optional to report ROM, depends on laboratory

Molecular Testing specific to Salivary Gland Tumors

- **Pleomorphic Adenoma & ca ex PA**
  - Most show overexpression of PLAG1 protein
  - Some have *HMGA2* gene amplification or rearrangement
  - Some show neither PLAG1 protein overexpression nor *HMGA2* gene
- **Mucoepidermoid Carcinoma**
  - *CRTC1-MAML2* or *CRTC3-MAML2* fusion proteins disrupt Notch signaling pathway
  - By FISH or NGS
- **Adenoid Cystic Carcinoma**
  - *MYB-NFIB* fusion protein up regulates MYB protein expression
  - Rare cases do not rely on MYB overexpression for tumorigenesis
- **(Mammary Analog) Secretory Carcinoma**
  - *ETV6-NTRK3* gene fusion
    - *ETV6*: Transcriptional regulator
    - *NTRK3*: Membrane receptor kinase
- **Hyalinizing Clear Cell Carcinoma**
  - *EWSR1-ATF1* gene fusion

Additional Molecular Testing for Salivary Gland Tumors

- Basal cell adenoma
  - CTNNB1 mutations
- Cribriform adenocarcinoma
  - PRKD rearrangement

Immunocytochemistry for Salivary Gland Neoplasms

Tumor	Positive Markers	Negative Markers
Pleomorphic Adenoma	(Epith) CK7, CEA, EMA, SOX10 (Myoep)SMA, S-100, Calponin, CK5/6, P63, GFAP, PLAG1, HMGA2	MYB
Adenoid Cystic carcinoma	(EPITH) CK7, CEA, EMA (Myoep) SMA, calponin, S-100, CK5/6, P63, SOX10 CD117(>90%+) MYB+, MYB translocation by FISH is specific for ACC	
Basal cell adenoma/ca	CK7, CEA, EMA + for myoep markers Beta catenin overexpression, LEF-1+	
Acinic cell carcinoma	DOG1 strong diffuse staining SOX10, strong diffuse nuclear staining in most ACC, PAS-D	
Oncocytoma		DOG1, SOX10, PAS-D

IHC and Molecular profiles of Salivary Gland Neoplasms

(that we know of now…)

Tumor	Genetic Alteration	Genes	FISH probe	IHC markers +
Pleomorphic adenoma(& ca ex)	Translocation 8q12 Translocation 12q13-15	*PLAG1* *HMGA2*	*PLAG1* *HMGA2*	PLAG1 HMGA2
Basal cell adenoma	3p22.1 mutation	*CTNNB1, CYLD*		Beta catenin, LEF-1
Adenoid Cystic carcinoma	T(6;9)(q21-23;p23-24)	*MYB-NFIB*	*MYB*	MYB (82% test +)*
Mucoepidermoid carcinoma	T((11;19)(q21;p13) T(11;15)(q21;q26)	*CRTC1-MAML2* *CRTC3-MAML2*	*MAML2*	P63/p40
Secretory carcinoma (MASC)	T(12;15)(p13;q25)	*ETV6-NTRK3*	*ETV6*	S-100, Mammoglobin
Clear cell carcinoma	T(12;22)(q13;q12)	*EWSR1-ATF1*	*EWSR1*	

From presentation by Dr Krane at American society of cytopathology meeting, Phoenix AZ, Nov 2017

** Basiloid squamous cells may test positive*

Table 3. Ancillary Testing for Major Salivary Gland Tumors

Tumor	Immunohistochemistry (useful positive markers)	Molecular, Genes Involved (Prevalence in %)
Acinic cell carcinoma (ACC)	DOG1, SOX10	
Adenoid cystic carcinoma (AdCC)	MYB, DOG-1, CD117, Sox10, S100, calponin, CK5/6, p63, p40, CK7	*MYB–NFIB* translocation (25-64)
Basal cell adenoma/carcinoma	β Catenin overexpression, CK7, myoep markers, GATA-3*, PLAG-1*	*CTNNB1* mutations (60-70), *CYLD* loss (75-80)
Hyalinizing Clear cell carcinoma	Pan CK, Low and HMWkeratins,p63*	*EWSR1-ATF* gene fusion (85)
Mucoepidermoid carcinoma	P63, p40, GATA-3*, CD117*	*CRTC1-MAML2 (40-60)* or *CTRC3-MAML2* fusion (~5)
Pleomorphic Adenoma	PLAG1, SMA, calponin, p63, p40, SOX10, GFAP,CK7,S100, GATA-3*	*PLAG1, CTNNB1, LIFR (50-60), HMGA2* amplification or fusion
Salivary Duct carcinoma	GATA-3, Androgen receptor, Her-2*	*ERBB2* ampl (~40), *PIK3CA* mutation (~20)
(Mammary Analogue) Secretory carcinoma	GATA-3, S100, keratins, Mammoglobin	*ETV6-NTRK3* gene fusion (90-100)

**variable positivity, ampl=amplification*

From: Diagnostic Pathology Cytopathology 2edition by Mody, Thrall, Krishnamurthy Elsiever 2018

SOX10 in Salivary Gland neoplasms

Positive	Negative
Acinic cell carcinoma	Salivary duct carcinoma
Adenoid cystic carcinoma	Mucoepidermoid carcinoma
Epithelial-Myoepithelial carcinoma	Warthin's
Myoepithelial carcinoma	Oncocytoma
Pleomorphic Adenoma	

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