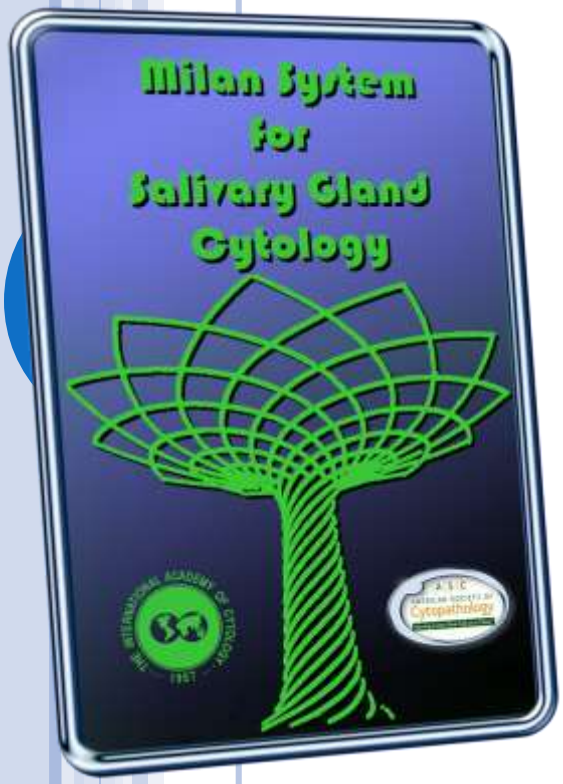
New proposal for terminology in salivary gland cytology



Esther Rossi MD PhD MIAC

Division of Anatomic Pathology and Cytology

Catholic University of Sacred Heart

Rome, Italy

Salivary gland Cytology- Basic facts

Rapid, safe, few complications

Preoperative distinction of benign and malignant lesions

Often specific diagnoses

Helps anticipate need for frozen sections

Aids in conservative management of benign/low grade malignancies

Allows palliative treatment for high grade and metastases

IS FNA ACCURATE AND FEASIBLE?

Wide range of sensitivity (from 62 to 97.6%)

Specificity (from 94.3 to 100%)

High diagnostic accuracy for benign lesions but lower for malignant tumors

Accuracy of type-specific diagnoses of malignant lesions is quite poor

IS FNA ACCURATE AND FEASIBLE?

Benign masses and inflammatory diseases account for over 80% of all lesions

Carcinomas and lymphomas are 10% of all salivary FNA

5-10% inadequate rate reported by literature

Fine-Needle Aspiration Cytology of Salivary Gland Lesions: A Systematic Review

Giuseppe Colella, MD, MDS, Rosangela Cannavale, DDS,†*

Table 4. ACCURACY OF FNA TECHNIQUE IN DISTINGUISHING MALIGNANT FROM BENIGN AND NON-NEOPLASTIC LESIONS

	Cytology			
Histology	Malignant	Benign	Non-neoplastic	Total
Malignant	387 (93.25%)	55 (4.31%)	42 (19%)	484
Benign	22 (5.3%)	1,219 (95.46%)	34 (15.38%)	1,275
Non-neoplastic or normal tissue	6 (1.45%)	3 (0.23%)	145 (65.61%)	154
Total	415	1277	221	1,913

Colella et al. FNA Cytology of Salivary Gland Lesions. J Oral Maxillofac Surg 2010.

Table II. Diagnostic Problems in Salivary Gland Lesions

- Sampling error
  - Fibrosis
  - Hyalinization
  - Necrosis
  - Hemorrhage
  - FNAC needle positioned outside lesion
- Smear cellularity
  - Paucicellular—nondiagnostic/nonrepresentative
  - Cellular smears—PA mimicking BCA
- Heterogeneous nature of salivary gland neoplasms
- Low grade tumor mimicking normal salivary gland cells
- Cystic lesions/change
- Benign versus malignant nature of the same type of tumor
  - Myoepithelioma versus moepithelial carcinoma
  - Basal cell adenoma versus basal cell adenocarcinoma
- Lymphoid rich lesions
- Overlapping cytological features
  - Hyaline globules
  - Clear cell pattern
  - Squamous metaplasia
  - Oncocytic changes
  - Spindle cells

Diagnostic Problems of Salivary Gland Tumors

Ruchita Tyagi, M.B.B.S., M.D., D.N.B., P.D.C.C. AND
Pranab Dey, M.B.B.S., M.D., M.I.A.C., F.R.C.PATh*

Cancer Cytopathology

The Impact of FNAC in the Management of Salivary Gland Lesions: Institutional Experiences Leading to a Risk-Based Classification Scheme

Esther Diana Rossi, MD, PhD, MIAC[1]; Lawrence Q. Wong, MS, CT (ASCP), IAC[2]; Tommaso Bizzarro, BD[1]; Gianluigi Petrone, MD[1]; Antonio Mule, MD[1]; Guido Fadda, MD, MIAC[1]; and Zubair M. Baloch, MD, PhD[2]

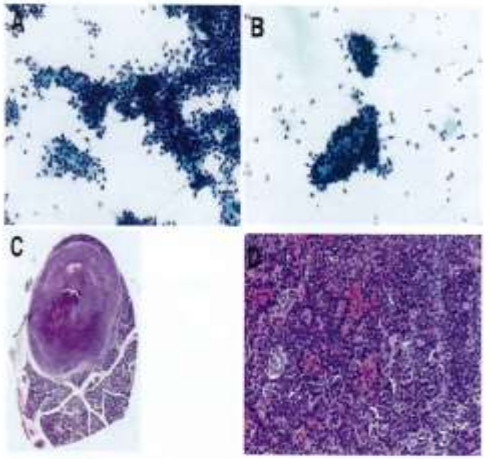


TABLE 3. Cytohistologic Correlation of the 46 False-Negative and 13 False-Positive Fine-Needle Aspiration Cases[a]

Findings	Histologic Follow-Up (No. of Cases)
False-negative cases	
Chronic sialadenitis, n = 7	Malt lymphoma (1), non-Hodgkin lymphoma (6)
Cystic lesions, n = 11	Non-Hodgkin lymphoma (5), mucoepidermoid Ca (2), sarcoma (1), salivary duct Ca (1), epimyoepithelial Ca (1), metastasis (1)
Pleomorphic adenoma, n = 8	Epimyoepithelial Ca (4), adenoid cystic Ca (2), mucoepidermoid Ca (1), metastasis (1)
Neoplasm NOS, n = 15	Mucoepidermoid Ca (7), acinic cell Ca (3), adenoid cystic Ca (1), ex-PA Ca (1), salivary duct Ca (1), adenocarcinoma NOS (1), metastasis (1)
Oncocytoma, n = 1	Adenocarcinoma NOS (1)
Myoepithelioma, n = 1	Poorly differentiated Ca (1)
Basal cell/monomorphic adenoma, n = 2	Adenocarcinoma NOS (2)
Spindle cell neoplasm, n = 1	Sarcoma (1)
False-positive cases	
Atypical epithelial/Lymphoid/NOS, n = 7	Cysts (3), sialoadenosis (2), Warthin tumor (1), spindle cell neoplasm NOS (1)
Epithelial neoplasm suspicious for malignancy, n = 6	Warthin tumor (2), basal cell adenoma (2), sialoadenosis (1), pleomorphic adenoma (1), papillary lesion (1)

Abbreviations: Ca, carcinoma; ex-PA, expleomorphic adenoma; NOS, not otherwise specified.
[a] Twenty-nine inadequate cases were excluded from this correlation.

Table I. Diagnostic Accuracy of Salivary Gland Tumors

Study	*Year*	*Total cases*	*False positive (no)*	*False negative (no)*	*Sensitivity (%)*	*Specificity (%)*
Ali et al.[14]	2011	129	2	5	86	98
Brennan et al.[16]	2010	103	5	7	70	94
Deneuve et al.[17]	2010	78	4	0	100	94
Ashraf et al.[19]	2010	100	1	3	98	87
Jafari et al.[20]	2009	101	3	1	67	96
Carrillo et al.[21]	2009	135	1	5	92	99
Daneshbod et al.[18]	2009	376	10	13	87	96
Burgess and Serpell et al.[22]	2008	72	4	2	75	94
Herrera Hernandez et al.[23]	2008	46	3	6	54	91
Zbaren[24]	2008	110	5	18	74	88
Orell[8]	1995	325	1	8	85.5	99.5
MacLeod et al.[25]	1993	582	3	16	92	99
Jayaram et al.[26]	1989	195	2	2	81	94
Layfield et al.[27]	1987	171	6	8	96	77

ALL IN THIS "ERA" OF PRE-CLASSIFICATION SYSTEM

The development of an international system

SCIENTIFIC TERMINOLOGY

< AKA NOMENCLATURE >

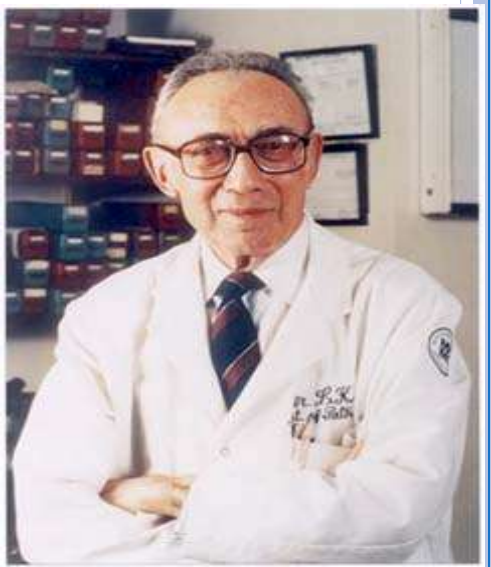
"As ideas are preserved and communicated by means of words, it necessarily follows that we cannot improve the language of any science, without at the same time improving the science itself; neither can we, on the other hand, improve a science without improving the language or nomenclature which belongs to it"

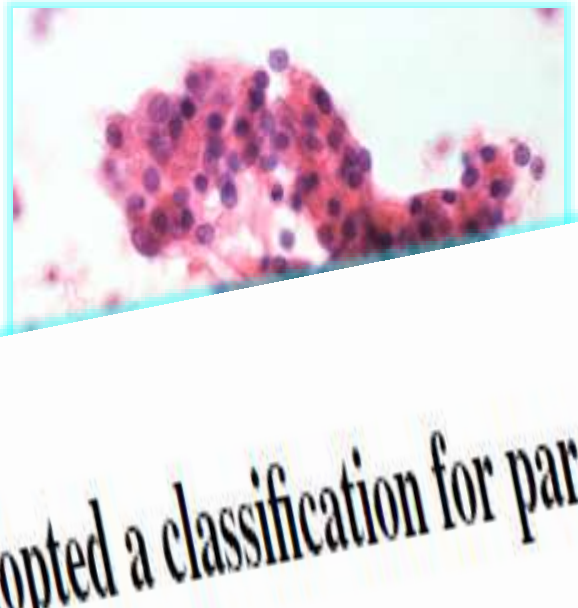
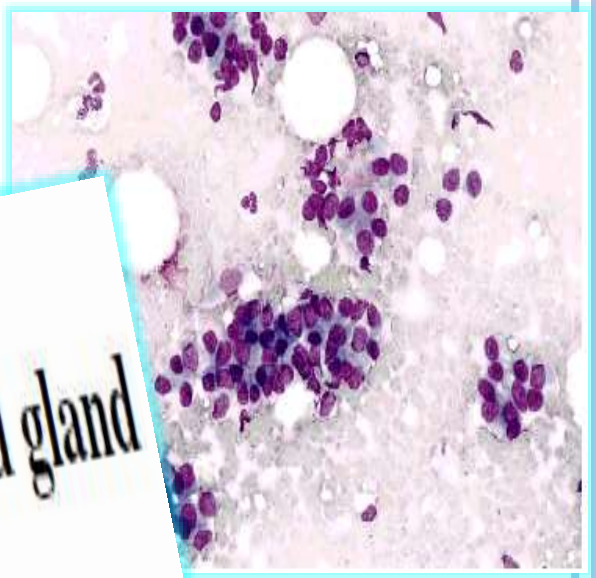
Antoine-Laurent Lavoisier (1743-1794), French chemis

ON REPORTING TERMINOLOGY -

"an accurate cytologic diagnosis of disease is both possible and desirable: therefore, the reports should be expressed in simple language that can be readily understood by the clinician."

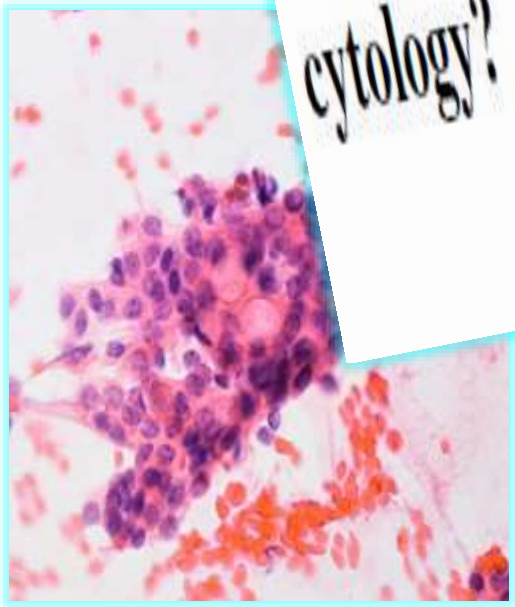
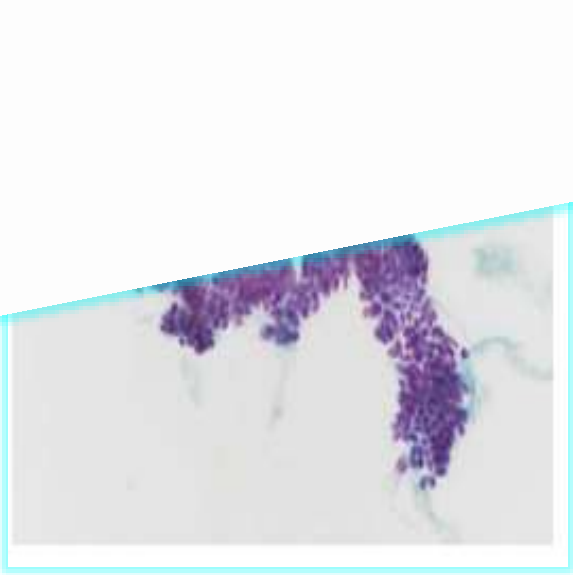
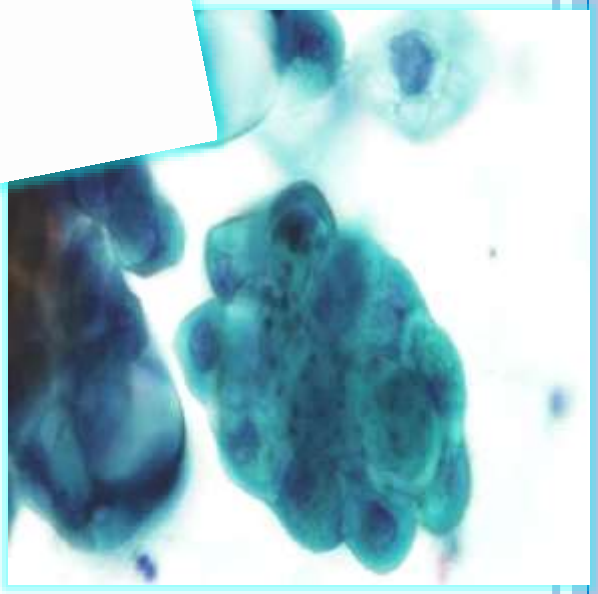
Leo Koss – Diagnostic Cytology and its Histopathologic B



Editorial

Is it time we adopted a classification for parotid gland cytology?

WHY DO WE NEED A REPORTING SYSTEM FOR SALIVARY GLAND CYTOLOGY?

- **Current reporting confusion:**
  - **Diversity of diagnostic categories, *vs.***
  - **Descriptive reports (no categories), *vs.***
  - **Surgical pathology terminology**

- **General agreement on the need for a defined set of diagnostic categories for salivary gland FNA**
  - **Clarity of communication (implicit cancer risk)**
  - **Exchange of data across institutions**

The Milan System for Reporting Salivary Gland Cytopathology

Why Milan?


MILANO


39TH ECC
EUROPEAN CONGRESS OF CYTOLOGY
SEPTEMBER 20TH-23TH, 2015
MILAN
www.cytology2015.com


Milan

The Milan System for Reporting Salivary Gland Cytopathology

- Sponsored by the ASC and the IAC
- practical classification system that will be user-friendly and internationally accepted
- evidence-based system with a useful format for clinicians
- The classification system and ROM for the diagnostic categories was further refined according to literature

The Benefits of a Uniform Reporting System for Salivary Gland Cytopathology

- Improve communication between pathologists and clinicians
- Improve patient care
- Facilitate cytologic-histologic correlation
- Promote research into the epidemiology, molecular biology, pathology, and diagnosis
- Foster sharing of data from different laboratories for collaborative studies

The Milan System for Reporting Salivary Gland Cytopathology

Core Group

Co-Chairs: Bill Faquin & Esther D. Rossi

Zubair Baloch

Guliz Barkan

Maria Pia Foschini

Daniel Kurtycz

Marc Pusztaszeri

Philippe Vielh

The Milan System for Reporting Salivary Gland Cytopathology

- 1) Non-Diagnostic
- 2) Non-Neoplastic
- 3) Atypia of undetermined significance (AUS)
- 4) Neoplastic:
  - a) Benign
  - b) Uncertain malignant potential (SUMP)
- 5) Suspicious for Malignancy
- 6) Malignant

PARTICIPANTS:
47 MEMBERS FROM 15 COUNTRIES
CYTOPATHOLOGISTS, SURGICAL PATHOLOGISTS, MOLECULAR PATHOLOGISTS, ENT SURGEONS

- **1. Overview of Diagnostic Terminology and Reporting:**
  - **Zubair Baloch and Andrew Fields (leads), Bruce Wenig, Raja Seethala, Andrew Field , Nora Katabi**

- **2.Nondiagnostic/Unsatisfactory:**
  - **Mariapia Foschini and Esther Diana Rossi (lead), Kayoko Higuchi, Ivana Kholova, Jhala Nirag,, Makato Urano, Laszlo Vass, Philippe Vielh,**

- **3. Non-neoplastic:**
  - **Bill Faquin (lead), Massimo Bongiovanni, Fabiano Callegari, Tarik Elsheik, Dan Kurtycz, Oscar Lin, Marc Pusztaszeri**

4. AUS:
- **Marc Pusztaszeri (lead), Zubair Baloch, Bill Faquin, Diana Rossi, Laura Tabatabai**

- **5. Neoplastic (benign & SUMP):**
  - **Zubair Baloch (lead), Jeff Krane, Lester Layfield, Marc Pusztaszeri, Jerzey Klijanienko, Ritu Nayar, Celeste Powers, Pinar Firat, Guido Fadda**

- **6.Suspicious for Malignancy:**
  - **Esther Diana Rossi and Andrew Fields (leads), Syed Ali, Ashish Chandra, Yun Gong, Zarha Maleki, Bo Ping, He Wang**

- **7.Malignant:**
  - **Güliz Barkan (lead), He Wang, Philippe Vielh, Stefan E. Pambuccian, Swati Mehrotra, Mousa Al-Abbadi, Eva Wojcik**

- **8. Ancillary Studies:**
  - **Mark Pusztaszeri (lead), Jorge Reis-Filho, Fernando Schmitt, Raja Seethala**

- **9. Clinical Management:**
  - **Mark Varvares (lead), Piero Nicolai , Mandeep Bajwa**

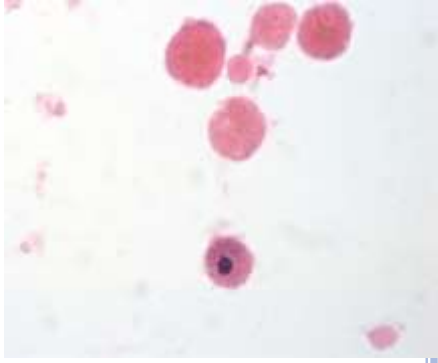

USCAP –SEATTLE 2016


USCAP, San ANTONIO 2017

CLASSIFICATION SYSTEM

Diagnostic Category	***% ROM[a] (ROM range)***	***Management[b]***
I. Non-Diagnostic [c]	25% (0-67%)	Clinical and radiologic correlation/ repeat FNA
I. Non-Neoplastic	10% (0-20%)	Clinical follow-up and radiologic correlation
I. III. Atypia of Undetermined Significance (AUS)	10-35%*	Repeat FNA or surgery
IV A. Neoplasm *i. Benign*	<5% (0-13%)	Surgery or clinical follow-up[d]
IV B. *ii. Salivary Gland Neoplasm of Uncertain Malignant Potential (SUMP)*[e]	35% (0-100%)	
V. Suspicious for Malignancy	60% (0-100%)	Surgery[f]
VI. Malignant	90% (57-100%)	Surgery[g]

Non-Diagnostic



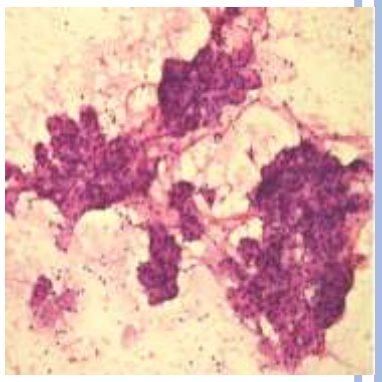
- **Insufficient quantitative and/or qualitative cellular material to make a cytologic diagnosis**

- **10% would be a target maximum rate**

- **Includes aspirates with benign elements only**

Includes non-mucinous cyst contents

Non-Neoplastic



- <u>Specimens lacking evidence of a neoplastic process:</u>

  - **Inflammatory, metaplastic, and reactive (I.e acute, chronic, and granulomatous sialadenitis,sialadenosis, etc…)**

  - **Reactive lymph nodes (flow cytometry is needed)**

  - **Clinico-radiological correlation is essential to ensure that the specimen is representative of the lesion**

Atypia of Undetermined Significance (AUS)

- Cannot entirely exclude a neoplasm.
- Heterogeneous category
- A majority will be reactive atypia or poorly sampled neoplasms
- Specimens are often compromised (eg, air-drying, blood clot)
- Should be used rarely (<10 % of all salivary gland FNAs)

The diagnosis of AUS can be used in the following scenarios:

•Reactive and reparative atypia indefinite for a neoplasm

•Squamous, oncocytic, or other metaplastic changes indefinite for a neoplasm

•Low cellularity specimens that are suggestive of, but not diagnostic of a neoplasm

•Specimens with preparation artifacts hampering distinction between a non-neoplastic and neoplastic process

•Mucinous cystic lesions with an absent or very scant epithelial component

•Salivary gland lymph nodes or lymphoid lesions which are indefinite for a lymphoproliferative disorder

Atypia of Undetermined Significance (AUS)

Common cytologic patterns classified as AUS :

Low cellularity specimens and/or technically compromised specimens that may be suggestive but not diagnostic of a neoplasm (eg, scant monomorphic basaloid, spindle or oncocytic cells)

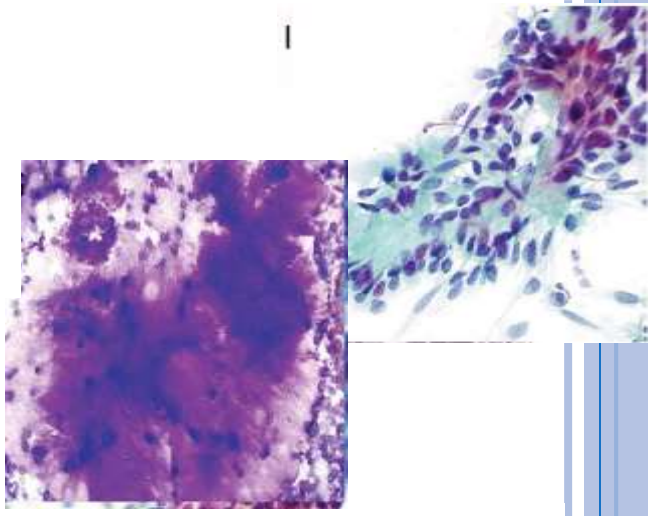
Salivary gland lesions rich in lymphocytes (including intra or perisalivary gland lymph nodes

Cystic lesions:

- **without mucin – watery proteinaceous cyst fluid**
- **with mucin**

Other patterns (Not otherwise categorized)

NEOPLASM



- ***i) Benign Neoplasm*:**
- Reserved for clear-cut benign neoplasms

- ***ii) Salivary Gland Neoplasm of Uncertain Malignant Potential***:

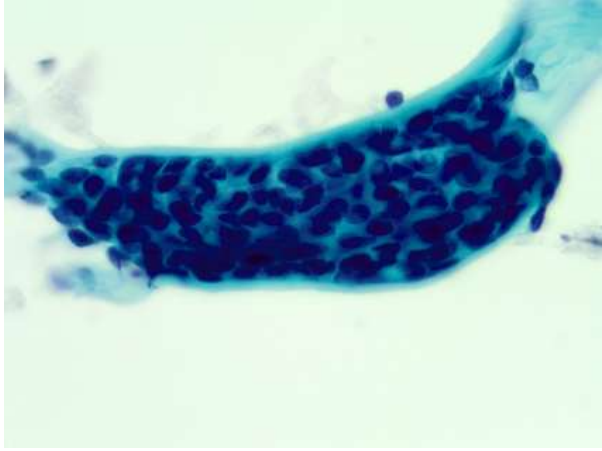
BENIGN NEOPLASM

Diagnostic category reserved for benign neoplasms diagnosed based on established cytomorphologic criteria

Benign Neoplasm Entities

- **Pleomorphic Adenoma**
- **Warthin Tumor**
- **Oncocytoma**
- **Soft Tissue Tumors**
  - Lipoma
  - Schwannoma
  - Lymphangioma
  - Hemangioma

SUMP



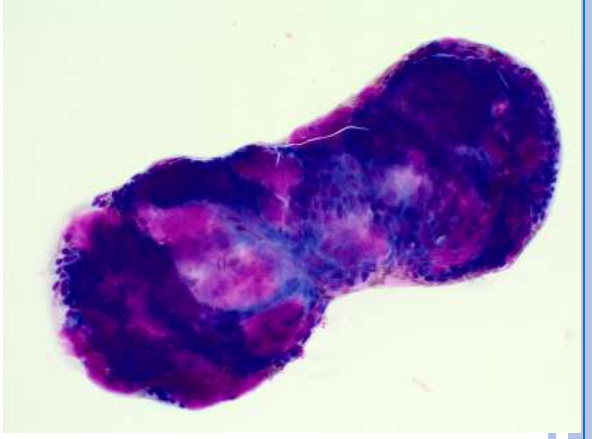
reserved for:

Diagnostic of a neoplasm; however, a diagnosis of a specific entity cannot be made.

A malignant neoplasm cannot be excluded.

Majority of these cases will include: cellular benign neoplasms, neoplasms with monomorphic lesional cells, basaloid neoplasms, oncocytic neoplasms, neoplasms with atypical features, and low grade carcinomas

SUMP ENTITIES



Cellular Basaloid Neoplasm

Oncocytoid Neoplasm

Neoplasm with Granular and/or Vacuolated or clear cells

Suspicious for Malignancy

- Aspirates which are highly suggestive of malignancy but not definitive
- Often high grade carcinomas with limited sampling or other limitation

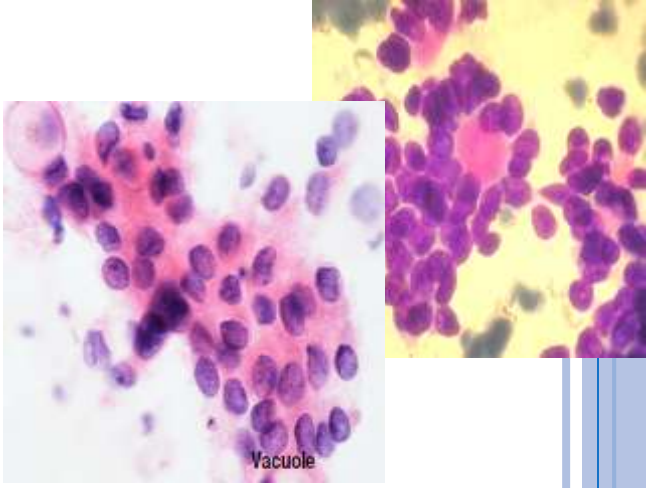
•Markedly atypical cells with poor smear preparation, poor cell preservation, fixation artifact, or obscuring inflammation and blood

•Presence of limited cytologic features of a specific malignant lesion (e.g. adenoid cystic carcinoma, mucoepidermoid carcinoma, acinic cell carcinoma) in an otherwise sparsely cellular aspirate

•Presence of markedly atypical and/or suspicious cytologic features in a subset of cells but admixed with features of a benign salivary gland lesion. Atypical features can include prominent nucleoli or macronucleoli, anisonucleosis, increased nuclear to cytoplasmic ratio, nuclear molding, prominent nuclear pleomorphism, atypical mitosis, and clumped, coarse chromatin

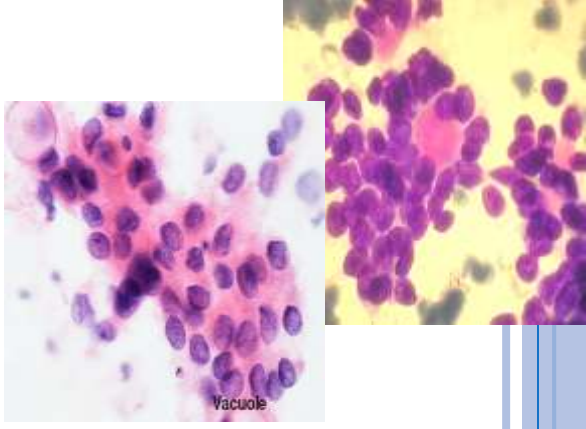
•Scant sample with atypical features suggestive of a neuroendocrine neoplasm

Malignant



- Aspirates which are diagnostic of malignancy
- Sub-classify into specific types and grades of carcinoma: e.g. low grade vs high grade
- "Other" malignancies such as lymphomas, sarcomas and metastases are also included in this category and should be specifically designated.

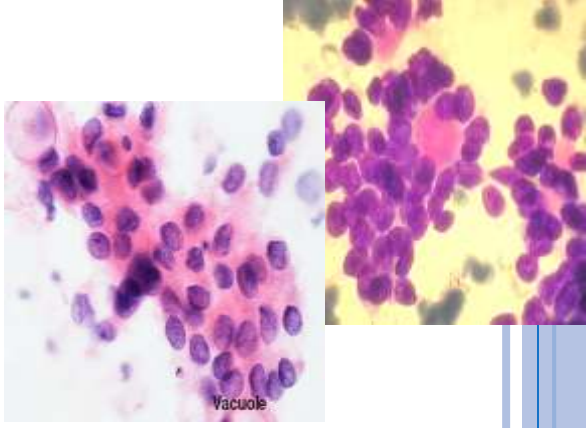
Malignant



- Introduction
- Detailed discussion of the following entities:

Acinic cell carcinoma
Adenoid cystic carcinoma
Mammary analogue secretory carcinoma
Salivary duct carcinoma
Mucoepidermoid carcinoma
Carcinoma ex pleomorphic adenoma
Epithelial myoepithelial carcinoma
Myoepithelial carcinoma
Lymphoepithelial carcinoma
High grade transformation in cancers
Small cell carcinoma
Hematolymphoid tumors
Secondary malignant tumors

Malignant



The following entities are not detailed as the first 3 predominantly afflict minor salivary glands and are unlikely to undergo FNA and the latter 2 are rare.

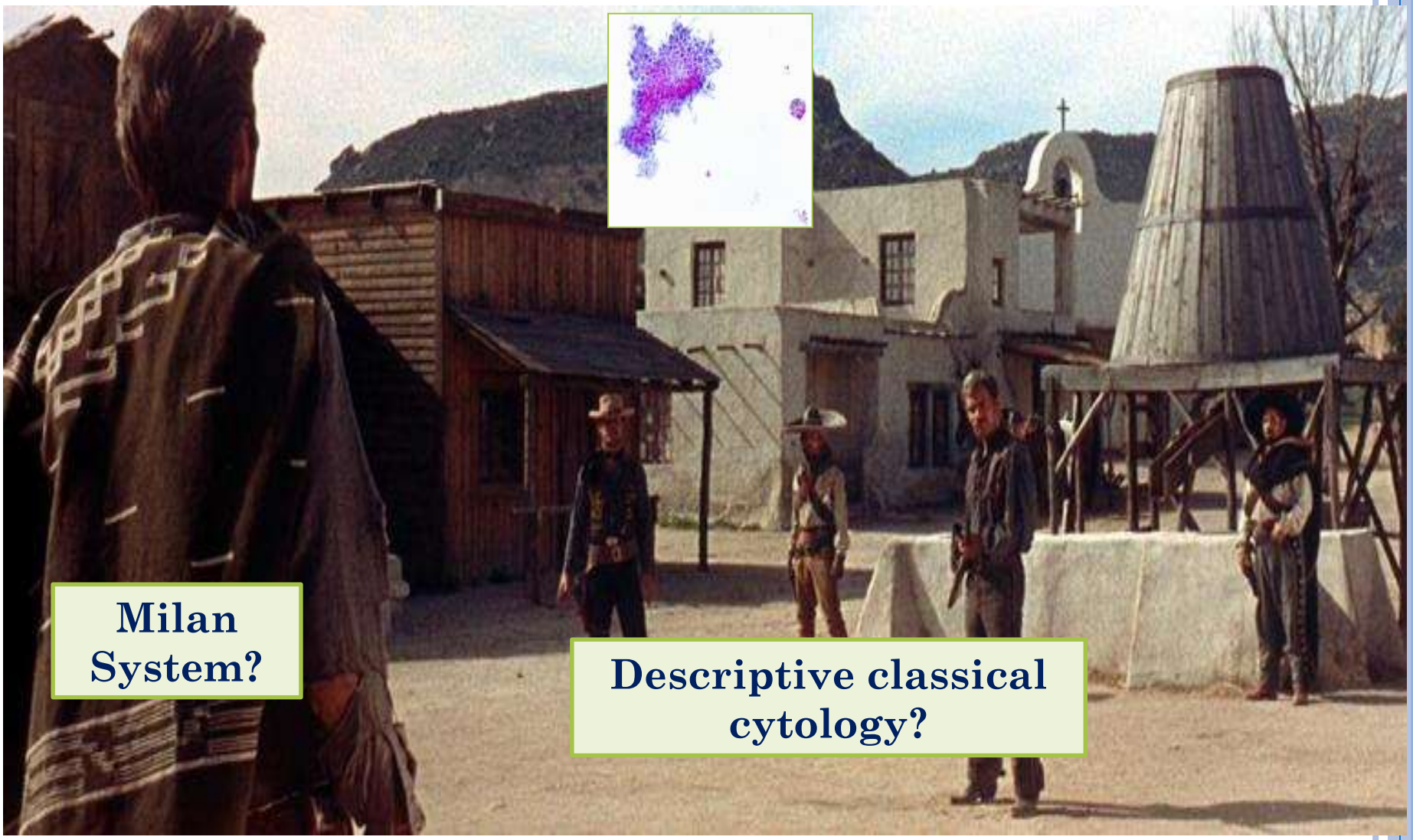
1. **Polymorphous low grade adenocarcinoma**
2. **Hyalinizing clear cell carcinoma**
3. **Cribriform adenocarcinoma of the tongue and minor salivary glands**
4. **Sebaceous carcinoma**
5. **Sialoblastoma**

- **In the explanatory notes we have briefly touched upon special stains and immunocytochemistry, specific translocations present in some tumors**

Ancillary Studies

1. Introduction
2. Translocations and fusion oncogenes in salivary gland tumors
   - 2.1 Pleomorphic adenoma and carcinoma ex pleomorphic adenoma
   - 2.2 Mucoepidermoid carcinoma
   - 2.3 Adenoid cystic carcinoma
   - 2.4 Mammary analogue secretory carcinoma
   - 2.5 Hyalinizing clear cell carcinoma
   - 2.6 Polymorphous low grade adenocarcinoma
3. Material and Methods
   - 3.1 Special stains
   - 3.2 Immunocytochemistry (ICC)
     - 3.2.1 ICC markers in basaloid neoplasms
     - 3.2.2 ICC markers in oncocytic lesions
     - 3.2.3 ICC markers in clear cell neoplasms
   - 3.3. Fluorescent in situ hybridization (FISH)
   - 3.4. Polymerase chain reaction (PCR)
   - 3.5. Next generation sequencing
   - 3.6. Flow cytometry (FC)

THE HIGH NOON OF SALIVARY CYTOLOGY??



Diagnostic Category & Definition	Explanatory Notes
I. Non-Diagnostic Insufficient cellular material for a cytologic diagnosis.	- This diagnostic category should only be used after all the material has been processed and examined. - Exceptions include matrix material and mucinous cyst contents
I. Non-Neoplastic Benign entities such as chronic sialadenitis, reactive lymph node, granulomas, infection etc.	- The ROM for this category would be expected to be low if strict inclusion criteria are applied. - Specimens will include those lacking cytomorphologic evidence of a neoplastic process - Inflammatory, metaplastic and reactive changes. - Specimens showing evidence of reactive lymphoid tissue (flow cytometry is recommended based on clinical and morphologic suspicion).
I. Atypia of Undetermined Significance (AUS) (≤10% of all salivary gland FNA samples); containing limited atypia; indefinite for a neoplasm	- Samples are indeterminate for a neoplasm; a neoplastic process cannot be excluded after examination of all the cellular material. - A majority of these FNA's will represent reactive atypia or poorly sampled neoplasms.
I. Neoplasm ***1) Benign Neoplasm*** Reserved for benign neoplasms diagnosed based on established cytologic criteria ***1) Salivary Gland Neoplasm of Uncertain Malignant Potential (SUMP)*** Reserved for FNA samples which are diagnostic of a neoplasm; however, a diagnosis of a specific entity cannot be made.	- This category will include classic cases of pleomorphic adenoma, Warthin tumor, lipoma, etc. - This diagnosis should be used for cases where a malignant neoplasm cannot be excluded. - A majority of these cases will include cellular benign neoplasms, neoplasms with atypical features, and low grade carcinomas
I. Suspicious for Malignancy This category is for FNA samples showing features that are highly suggestive of, but not unequivocal for malignancy.	- The FNA report should state which type of malignant tumor is suspected or provide a differential diagnosis. - A majority of specimens in this category will be high-grade carcinoma.
I. Malignant This category is for FNA specimens which are diagnostic of malignancy	- An attempt should be made to sub-classify the neoplasm into specific types and grades of carcinoma: e.g. low grade (low grade mucoepidermoid carcinoma) vs. high grade (salivary duct carcinoma). - "Other" malignancies such as lymphomas, metastases, and sarcomas are also included in this category and should be specifically designated.

The Milan System for Reporting Salivary Gland Cytopathology

Diagnostic Category	% ROM[a] (ROM range)	Management[b]
I. ***Non-Diagnostic*** [c]	25% (0-67%)	Clinical and radiologic correlation/ repeat FNA
I. ***Non-Neoplastic***	10% (0-20%)	Clinical follow-up and radiologic correlation
I. ***III. Atypia of Undetermined Significance (AUS)***	10-35%*	Repeat FNA or surgery
IV A. ***Neoplasm*** *i. Benign*	<5% (0-13%)	Surgery or clinical follow-up[d]
IV B. *ii. Salivary Gland Neoplasm of Uncertain Malignant Potential (SUMP)*[e]	35% (0-100%)	
V. ***Suspicious for Malignancy***	60% (0-100%)	Surgery[f]
VI. ***Malignant***	90% (57-100%)	Surgery[g]

The ROM will depend upon the nature of the Specimen and the salivary gland site.

**Based on literature review, criteria have not been validated; SUMP-Salivary gland neoplasm of uncertain malignant potential; TBD: Needs further literature review and data.*

TAKE HOME MESSAGE

FNA shows a high diagnostic accuracy in salivary gland lesions

Liquid based cytology may be a complementary feasible/reliable method

FNAC with a classification system may offer valid information for the approach to the management of salivary lumps

A classification system requires robust testing in terms of validity and reproducibility

Deadline for the Atlas: WINTER 2018


THANK YOU
FOR YOUR ATTENTION