In the name of God
The Milan System for Reporting Salivary Gland Cytopathology

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Salivary gland tumors are one of the most heterogenous groups of neoplasms. So what role is there for FNA?
Salivary Gland FNA

Effectiveness of Cytomorphology alone:

- Sensitivity: 86-100%
- Accuracy:
  - High for neoplastic vs. non-neoplastic lesions
  - High for Benign/low grade vs HGmalignant: 90-100%

Part of the reason for the high accuracy:

- Majority of benign SG neoplasms are PA & WT
Role of Salivary gland FNA

- Is it neoplastic?
- Is it malignant?
- Is it hematopoietic?
- Is it metastatic?
- Is it high grade?
Salivary Gland FNA

- Rationale for FNA:

  Guide the clinical management/pre-op strategy:

  - Non-neoplastic
  - Benign tumor/low-grade carcinoma
  - Metastatic disease to parotid LNs
  - Lymphoma
  - High-grade primary carcinoma

  Clinical follow-up
  Limited resection
  LN resection
  Heme-Onc referral
  Radical resection+LN
Why do we need a new reporting system for salivary gland cytology?

- Current reporting confusion:
  - Diversity of diagnostic categories
  - Descriptive reports (no categories)
  - Surgical pathology terminology
The Benefits Of An 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
WHY MILAN?
The Milan System for Reporting Salivary Gland Cytopathology (SGC)

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 SGC

- 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
Reporting System for SGC

Even if you do not adopt the Milan System in your practice, reviewing the structure of a reporting system will provide insight into salivary gland FNA!
The Milan System for Reporting SGC

Diagnostic Categories

1) Non-Diagnostic
2) Non-Neoplastic
3) Atypia of undetermined significance
4) Neoplastic:
   a) Benign
   b) Uncertain malignant potential
5) Suspicious for Malignancy
6) Malignant
**Table 1.2** The Milan System for Reporting Salivary Gland Cytopathology: implied risk of malignancy and recommended clinical management

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Risk of malignancy (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Management&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Non-Diagnostic&lt;sup&gt;c&lt;/sup&gt;</td>
<td>25</td>
<td>Clinical and radiologic correlation/repeat FNA</td>
</tr>
<tr>
<td>II. Non-Neoplastic</td>
<td>10</td>
<td>Clinical follow-up and radiologic correlation</td>
</tr>
<tr>
<td>III. Atypia of undetermined significance (AUS)</td>
<td>20&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Repeat FNA or surgery</td>
</tr>
<tr>
<td>IV. Neoplasm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Neoplasm: Benign</td>
<td>&lt;5</td>
<td>Surgery or clinical follow-up&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>B. Neoplasm: Salivary Gland Neoplasm of Uncertain Malignant Potential (SUMP)</td>
<td>35</td>
<td>Surgery&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>V. Suspicious for malignancy (SM)</td>
<td>60</td>
<td>Surgery&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>VI. Malignant</td>
<td>90</td>
<td>Surgery&lt;sup&gt;f, g&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Non-Diagnostic

- Insufficient **quantitative and/or qualitative** cellular material to make a cytologic diagnosis
Non-Diagnostic Cytologic Criteria

- Rare or absent cells; **less than 60 lesional cells**

- Non-neoplastic (normal) salivary gland elements in the setting of a clinically or **radiologically defined mass**

- **Non-mucinous cyst fluid** without an epithelial component should be subcategorized as “Non-Diagnostic, cystic fluid only”

- Poorly prepared slides with artifacts that preclude the evaluation of the cellular component
Non-Diagnostic:

Blood, debris, & rare inflammatory cells are present
Non-Diagnostic:

Benign salivary gland elements only
Non-Diagnostic:

Non-mucinous cyst contents

DDX: Ductal cyst, pseudocyst, cystic neoplasm

Absence of an epithelial component
Non-Diagnostic:

Exceptions:

- **Mucinous cyst fluid contents** without an epithelial component should be interpreted as “Atypia of Undetermined Significance (AUS)” instead of “Non-Diagnostic”.
Non-Diagnostic:

Exceptions:

➢ In the absence of neoplastic cells, the presence of a matrix component suggestive of a neoplasm should not be classified as “Non-Diagnostic”.

[Image of tissue sample]
Non-Diagnostic:

Exceptions ... cont

- The presence of abundant inflammatory cells without an epithelial component can be interpreted as adequate.

- Any salivary gland aspirate with significant cytologic atypia cannot be classified as “Non-Diagnostic”
Non-Diagnostic:

Sample Report

Example 2:
Evaluation limited by non-neoplastic salivary gland elements only.

**NON-DIAGNOSTIC**

Non-neoplastic benign salivary gland elements only. See note.

Note: The finding of “non-neoplastic” salivary gland elements only, *does not explain the presence of a clinically or radiologically defined mass*. Therefore, the FNA sample *is not considered representative of the lesion* detected on clinical and/or radiologic examination. **Repeat fine-needle aspiration** under radiologic guidance is recommended if clinically indicated.
Non-Diagnostic: Sample Report

Example 3:
Evaluation limited by preservation artifact
NON-DIAGNOSTIC
Minimal poorly preserved cells, insufficient for diagnosis. See note.
Note: This specimen is Non-Diagnostic due to both scant cellularity and poor sample preservation.
The Milan System for Reporting SGC

Diagnostic Categories

1) Non-Diagnostic

2) **Non-Neoplastic**

3) Atypia of undetermined significance

4) Neoplastic:
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Non-Neoplastic

Specimens lacking evidence of a neoplastic process & show benign non-neoplastic changes:

• Inflammatory, metaplastic, and reactive
• Reactive lymph nodes (flow cytometry is needed)

Clinico-radiological correlation is essential to ensure that the specimen is representative of the lesion.
Non-Neoplastic:
Reactive Lymph Node

Mixed population of lymphocytes, Tingible body macrophages
Non-Neoplastic:

Reactive Lymph Node

- Caution is recommended, particularly when evaluating aspirates of lymph nodes in the elderly, lymph nodes larger than 3 cm, and multiple enlarged or matted lymph nodes.

- Patients with autoimmune disease such as Sjögren’s syndrome are at increased risk of developing primary parotid gland lymphomas.
Non-Neoplastic:
Reactive Lymph Node

A subset of lymphomas can yield an aspirate with a heterogeneous appearance mimicking reactive lymphoid hyperplasia, namely extranodal marginal zone lymphoma as well as others such as Hodgkin lymphoma, some T-cell lymphomas, and T-cell rich B-cell lymphoma.
Non-Neoplastic:
Reactive Lymph Node

- For any case of a salivary gland lymph node aspirate where lymphoma is in the differential diagnosis, flow cytometry using an aliquot of unfixed material is highly recommended.
For negative lymph nodes, caution is warranted:

- A note suggesting repeat FNA or tissue biopsy if lymphadenopathy persists
Non-Neoplastic: Benign Lymphoepithelial Lesion (LESA)

**Cytologic Criteria**

- Cellular aspirate
- Lymphoepithelial lesions
- Mixed population of lymphocytes, with predominance of small mature lymphocytes
Non-Neoplastic: Sialolithiasis

Cytologic Criteria:

- Hypocellular aspirate; Scant or absent acinar cells
- Groups of benign ductal cells; Inflammatory background ± mucin
- Calcifications (stone fragments)
Non-Neoplastic:

Acute Sialadenitis

Aspiration of any residual mass should be performed after resolution of the inflammatory process since tumor diathesis in high-grade cancers can mimic acute sialadenitis.
Non-Neoplastic: Chronic Sialadenitis

Hypocellular, cohesive basaloid groups, inflammation
Non-Neoplastic: Granulomatous Sialadenitis

DDX includes infection and sarcoidosis

Commonly a response to extravasated ductal contents, particularly mucin,
Non-Neoplastic:
Sample Report

Example 4:
Satisfactory for evaluation
NON-NEOPLASTIC
Consistent with reactive lymphoid hyperplasia. See note.
Note: Corresponding flow cytometry is benign, supporting the diagnosis. Clinical follow-up is recommended, and if lymphadenopathy persists, additional evaluation may be indicated.
Non-Neoplastic:

Sample Report

Example 2:
Evaluation limited by scant cellularity
NON-NEOPLASTIC
Consistent with chronic sialadenitis. See note.
Note: Clinical and radiological correlations are recommended to ensure that the aspirate is representative of the lesion.
Example 3:
Satisfactory for evaluation
NON-NEOPLASTIC
Granulomatous inflammation. See note.
Note: Non-necrotizing granulomas are present admixed with acute and chronic inflammation. Diagnostic considerations include a non-specific reaction secondary to obstructive sialadenopathy, infection, and sarcoidosis. Correlation with microbiologic studies is suggested.
Diagnostic Categories

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Atypia of Undetermined Significance (AUS)

SG FNA that lacks either qualitative or quantitative cytomorphologic features to be diagnosed with confidence as non-neoplastic or neoplastic (can not entirely exclude a neoplasm).
Atypia of Undetermined Significance (AUS)

- 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 ROM is 20%.
Atypia of Undetermined Significance

**Cytologic Criteria**

- Low cellularity specimens suggestive of, but not diagnostic of a neoplasm

- Squamous, oncocytic, or other metaplastic changes indefinite for a neoplasm
Atypia of Undetermined Significance

Cytologic Criteria ... cont

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

- Salivary gland lymph nodes or lymphoid lesions that are indefinite for a lymphoproliferative disorder
Atypia of Undetermined Significance:

Oncocytic changes indefinite for a neoplasm
Atypia of Undetermined Significance:

Indefinite for a lymphoproliferative disorder

Mixed population of lymphocytes with increased numbers of larger lymphocytes. A lymphoma cannot be excluded, particularly in the absence of flow cytometry.
Atypia of Undetermined Significance:

Low cellularity specimens suggestive of, but not diagnostic of a neoplasm

Groups of basaloid appearing epithelium that are indefinite for a neoplastic process
Atypia of Undetermined Significance: Sample Report

Example 1:
Evaluation limited by scant cellularity
ATYPIA OF UNDETERMINED SIGNIFICANCE
Histiocytes ± scant epithelial cells in a background of abundant mucin. See Note.
Note: The differential diagnosis of mucin-containing cysts includes mucocele, mucus retention cysts, and low-grade mucoepidermoid carcinoma. Clinical and radiological correlations are needed. Aspiration of a residual mass, if present, may help to achieve a more specific diagnosis.
Atypia of Undetermined Significance:

Sample Report:

Example 2:
Evaluation limited by scant cellularity
**ATYPIA OF UNDETERMINED SIGNIFICANCE**
Few clusters of basaloid cells with mild atypia. See note.
Note: While the aspirate may represent chronic sialadenitis with metaplasia and reactive changes, a salivary gland neoplasm with basaloid features cannot be completely excluded. Recommend clinical and radiologic correlations and additional sampling if clinically indicated.
The Milan System for Reporting SGC

Diagnostic Categories

1) Non-Diagnostic
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4) **Neoplastic:**
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Neoplasm

Benign Neoplasm:
• Reserved for clear-cut benign neoplasms
• This category will include classic cases of PA, WT,…
• The ROM is < 5%

Salivary Gland Neoplasm of Uncertain Malignant Potential:
• Diagnostic of a neoplasm; however, a diagnosis of a specific entity cannot be made. A malignant neoplasm cannot be excluded.
• Most malignant tumors included in this diagnostic category will be low-grade carcinomas.
Table 5.1  Definitions and entities included in the diagnostic category “Neoplasm” [5–25]

<table>
<thead>
<tr>
<th>Neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benign</strong></td>
</tr>
<tr>
<td>FNA specimens showing cytomorphic features of a benign epithelial or mesenchymal neoplasm</td>
</tr>
<tr>
<td>1. Epithelial origin^a^</td>
</tr>
<tr>
<td>a. Pleomorphic Adenoma</td>
</tr>
<tr>
<td>b. Warthin Tumor</td>
</tr>
<tr>
<td>c. Oncocytoma</td>
</tr>
<tr>
<td>2. Mesenchymal origin</td>
</tr>
<tr>
<td>a. Lipoma</td>
</tr>
<tr>
<td>b. Schwannoma</td>
</tr>
<tr>
<td>c. Lymphangioma</td>
</tr>
<tr>
<td>d. Hemangioma</td>
</tr>
<tr>
<td><strong>Salivary Gland Neoplasm of Uncertain Malignant Potential (SUMP)</strong></td>
</tr>
<tr>
<td>FNA specimens showing cytomorphic features diagnostic of a neoplastic process, but a malignant neoplasm cannot be excluded</td>
</tr>
<tr>
<td>3. Cellular basaloïd neoplasm</td>
</tr>
<tr>
<td>4. Cellular oncocytic/oncocytoid neoplasm</td>
</tr>
<tr>
<td>5. Cellular neoplasm with clear cell features</td>
</tr>
</tbody>
</table>

^aDue to overlapping cytomorphic features with malignant tumors, most cases of benign neoplasm classified as basal cell adenoma, myoepithelioma, and cystadenoma on histopathologic examination will be diagnosed as SUMP on FNA (under the subheading of cellular basaloïd neoplasm or cellular neoplasm with clear cell features) (see Tables 5.2 and 5.3)
Neoplastic: Benign
Pleomorphic Adenoma

Matrix-rich types of PA are the easiest.
Neoplastic: Benign

**Warthin Tumor**

Oncocytes, chronic inflammation, and cystic debris

WT occurs almost exclusively in the parotid gland and the **tripartite appearance** is essentially diagnostic.
Neoplastic: Benign

Sample Report

Example 1:
Satisfactory for evaluation

**NEOPLASM: BENIGN**
Pleomorphic adenoma.
Salivary Gland Neoplasm of Uncertain Malignant Potential (SUMP)

- SUMP is a diagnostic category reserved for FNA specimens that are **diagnostic of a neoplasm**; however, a **definitive diagnosis** of a specific entity cannot be made.

- This diagnosis should be used for cases in which a **malignant neoplasm cannot be excluded**.

- The ROM is 35%
Salivary Gland Neoplasm of Uncertain Malignant Potential (SUMP)

- A majority of these cases will include neoplasms with monomorphic lesional cells:
  - Basaloid neoplasms
  - Oncocytic/oncocytoid neoplasms
  - Neoplasms with clear cell features

- Neoplasms with atypical features
Neoplastic: SUMP

oncocytic/oncocytoid subcategory

- Cellular aspirate
- Neoplastic cells with oncocytic or oncocytoid features that cannot be classified further
- Neoplastic cells lack high-grade cellular features such as marked nuclear atypia, high mitotic activity, and necrosis.
Differential diagnosis of cases classified as “SUMP: cellular oncocytic/oncocytoid”

<table>
<thead>
<tr>
<th>Cytomorphologic features</th>
<th>Differential diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cellular oncocytic/oncocytoid neoplasm with</strong></td>
<td></td>
</tr>
<tr>
<td>1. Cystic background (histiocytes, proteinaceous debris, ± inflammatory cells)</td>
<td>• Warthin tumor(^a)</td>
</tr>
<tr>
<td></td>
<td>• Cystadenoma, oncocyctic</td>
</tr>
<tr>
<td>2. Mucinous background</td>
<td>• Mucoepidermoid carcinoma, oncocytic variant</td>
</tr>
<tr>
<td></td>
<td>• Rare case of Warthin tumor with focal mucinous metaplastic change(^b)</td>
</tr>
<tr>
<td>3. Blood or non-specific background</td>
<td>• Oncocytoma</td>
</tr>
<tr>
<td></td>
<td>• Myepithelioma(^c)</td>
</tr>
<tr>
<td>4. Granular (usually coarse)/vacuolated cytoplasm</td>
<td>• Acinic cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>• Secretory carcinoma / Mammary analogue secretory carcinoma (MASC)</td>
</tr>
<tr>
<td></td>
<td>• Metastatic renal cell carcinoma</td>
</tr>
<tr>
<td>5. Appreciable focal nuclear atypia(^d)</td>
<td>• Salivary duct carcinoma</td>
</tr>
<tr>
<td></td>
<td>• High grade mucoepidermoid carcinoma</td>
</tr>
<tr>
<td></td>
<td>• Metastatic carcinoma</td>
</tr>
</tbody>
</table>
Neoplastic: SUMP
oncocyctic/oncocytoid subcategory

On histologic follow-up this case was diagnosed as myoepithelioma
Neoplastic: SUMP

Basaloid Neoplasm

DDX basal cell adenoma, cellular PA, AdCC

On histologic follow-up this case was diagnosed as solid variant of adenoid cystic carcinoma
Differential diagnosis of cases classified as “basaloid neoplasm”

<table>
<thead>
<tr>
<th>Cytomorphologic features (^a)</th>
<th>Differential diagnosis (^b)</th>
</tr>
</thead>
</table>
| 1. Cellular basaloid neoplasm *with* fibrillary stroma | • Cellular pleomorphic adenoma  
• Epithelial-myoepithelial carcinoma  
• Basal cell adenoma/adenocarcinoma |
| 2. Cellular basaloid neoplasm *with* hyaline stroma | • Basal cell adenoma/adenocarcinoma  
• Adenoid cystic carcinoma  
• Epithelial-myoepithelial carcinoma  
• Polymorphous adenocarcinoma\(^c\) |
| 3. Cellular basaloid neoplasm *with* mixed/other stroma | • Adenoid cystic carcinoma  
• Polymorphous adenocarcinoma\(^c\) |
| 4. Cellular basaloid neoplasm *with* scant to no stroma | • Cellular pleomorphic adenoma  
• Canalicular adenoma  
• Myoepithelioma  
• Myoepithelial carcinoma  
• Adenoid cystic carcinoma |
Example 2:
Satisfactory for evaluation

**NEOPLASM: SALIVARY GLAND NEOPLASM OF UNCERTAIN MALIGNANT POTENTIAL (SUMP)**

Cellular basaloid neoplasm. See note.

Note: The specimen shows a *monomorphically populated* population of basaloid cells with minimal nuclear atypia associated with fibrillar matrix. *No mitoses or tumor necrosis is seen.* The findings are suggestive of a cellular pleomorphic adenoma; however, other matrix-producing basaloid tumors such as basal cell adenoma, basal cell adenocarcinoma, and epithelial-myoeipithelial carcinoma cannot be completely excluded.
The Milan System for Reporting SGC

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4) Neoplastic:
   a) Benign
   b) Uncertain malignant potential
5) **Suspicious for Malignancy**
6) Malignant
Suspicious for Malignancy

- Aspirates which are highly suggestive of malignancy but not definitive.
- Often high grade carcinomas with limited sampling or other limitation.
- The ROM is 60%.
Suspicious for Malignancy

- 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., ACC or MEC) in an otherwise sparsely cellular aspirate
Suspicious for Malignancy

Markedly atypical cells suspicious for high-grade carcinoma, but obscuring blood limiting the assessment
Suspicious for Malignancy

Hypocellular but contains occasional small groups of markedly atypical cells suspicious for carcinoma. The corresponding resection showed a high-grade MEC
Suspicious for Malignancy
Sample Report

Example 1:
Satisfactory for evaluation
SUSPICIOUS FOR MALIGNANCY
Rare markedly atypical cells, suspicious for high-grade carcinoma.
Example 3:
Evaluation limited by scant cellularity
SUSPICIOUS FOR MALIGNANCY
Atypical cells in a mucinous background, suspicious for low-grade mucoepidermoid carcinoma.
The Milan System for Reporting SGC

Diagnostic Categories

1) Non-Diagnostic
2) Non-Neoplastic
3) Atypia of undetermined significance
4) Neoplastic:
   a) Benign
   b) Uncertain malignant potential
5) Suspicious for Malignancy
6) **Malignant**
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
Low-Grade Carcinomas

Acinic cell carcinoma

Cytologic Criteria:
• Cellular smears
• Monotonous population of epithelial cells
• Loosely cohesive groups
• Low nuclear–cytoplasmic (N:C) ratio
• Abundant delicate vacuolated cytoplasm
• Cells adherent to a delicate capillary meshwork
• No mitotic activity or necrosis
Malignant

High-Grade Carcinomas

Salivary Duct Carcinoma

Undifferentiated Carcinoma (LEC)
Malignant
Indeterminate or Multiple Grades

Mucoepidermoid Carcinoma
Malignant:

Adenoid Cystic Carcinoma
Malignant

HG B-Cell Lymphoma
Example 3: Satisfactory for evaluation
MALIGNANT
High-grade carcinoma. See note.
Note: The aspirate is cellular and shows pleomorphic cells arranged in cribiform and papillary groupings with prominent nucleoli and background necrosis. The cytomorphologic findings are suggestive of salivary duct carcinoma; however, ancillary testing could not be performed due to a paucity of tumor cells in the corresponding cell block sections.