Salivary Gland FNA: The Milan System

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Objectives

• Introduce the Milan System for reporting salivary gland cytopathology
• Define cytologic features of benign, malignant, and indeterminant salivary gland lesions
• Emphasize differential diagnostic considerations in the indeterminant category

Role of Salivary Gland FNA

• Neoplastic versus non-neoplastic
• Salivary vs. non-salivary origin
• Type specific benign neoplasms
• Differentiate low and high grade carcinomas
• Approximately one third of patients spared surgery
Role of Salivary Gland FNA

- 81-98% accuracy benign versus malignant
- Specific diagnosis in 60-75%
  - Variety of tumor types
  - Complex histologic patterns
  - Rarity of lesions increases difficulty

Specific Problem Areas

- Cellular inflammatory lesion versus neoplasm
- Benign neoplasm versus low grade malignancy
- Malignancies difficult to distinguish from one another (usually low grade)
- Cystic neoplasms are the source of most false negative aspirates

Specific Problem Areas

- Cystic neoplasms are the source of most false negative aspirates due to sampling
- False negative interpretive error
  - Low grade mucoepidermoid carcinoma
  - Adenoid cystic carcinoma
  - Low grade NHL
- False positive interpretive error
  - Warthin tumor
  - Pleomorphic adenoma
Milan System for Reporting Salivary Gland Cytopathology

Six (6) diagnostic categories:
1. Non-diagnostic
2. Non-neoplastic
3. Atypia of undetermined significance (AUS)
4. Neoplasm
5. Suspicious for malignancy
6. Malignant

Goals of the Milan System

- Effective communication between pathologist and clinician
- Cytologic-histologic correlation
- Data evaluation and comparison between institutions
Risk of Malignancy

• 20-25% parotid gland
• 40-50% submandibular gland
• 50-81% sublingual and minor salivary gland

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>% Risk of Malignancy</th>
<th>Management</th>
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</thead>
<tbody>
<tr>
<td>Non-diagnostic</td>
<td>25</td>
<td>Repeat FNA</td>
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<tr>
<td>Non-neoplastic</td>
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<td>Clinical F/U</td>
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<tr>
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<td>Repeat FNA or surgery</td>
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<td>Benign</td>
<td>&lt;5</td>
<td>Surgery or f/u</td>
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<tr>
<td>SUMP</td>
<td>35</td>
<td>Surgery</td>
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<td>60</td>
<td>Surgery</td>
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<tr>
<td>Malignant</td>
<td>90</td>
<td>Surgery</td>
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</table>

I. Non-Diagnostic

• Insufficient cellular material for a cytologic diagnosis
• Low cellularity (< 60 lesional cells)
• Poorly prepared slides
• Normal salivary gland in presence of a mass
• Non-mucinous cyst fluid without epithelium
• Necrotic debris only
• Estimated rate of non-diagnostic FNA <10%
Normal acini

Normal acini and ducts

Non-mucinous cyst contents
Excess blood
Necrosis only

Non-Diagnostic
Exceptions

- Presence of cytologic atypia
- Mucinous cyst fluid lacking epithelium
- Abundant inflammatory cells without epithelium
- Matrix component without neoplastic cells

Management

- Repeat FNA
- Clinical and radiologic correlation

II. Non-Neoplastic

- Benign entities
  - Sialolithiasis
  - Sialadenitis
  - Granulomas
  - Infection
  - Benign lymphoepithelial lesion
  - Benign (including reactive) lymph node
Management

- Clinical follow up
- Repeat imaging
- Any change in clinical or radiologic appearance should prompt repeat sampling

Most Common Problems

- Pleomorphic adenoma and Warthin tumor placed in non-neoplastic category
- Lymphoma, mucoepidermoid carcinoma and squamous cell carcinoma are the most common malignancies
III. Atypia of Undetermined Significance (AUS)

- Limited cytologic atypia
- Indefinite for neoplasm
- Should represent <10% of salivary gland FNA results
- Reactive atypia or poor sampling in the majority

Atypia of Undetermined Significance: Scenarios

- Reactive atypia indefinite for neoplasm
- Metaplasia indefinite for neoplasm
- Low cellularity sample
- Preparation artifacts
- Mucinous cysts lacking epithelium
- Lymphoid samples indefinite for lymphoma

Mucinous Cyst without Epithelium

Mucin stain
AUS

Management

• Repeat FNA under ultrasound guidance, biopsy or excision
• Flow cytometry if lymphoid

Neoplasm

• Benign neoplasm
• Salivary gland neoplasm of uncertain malignant potential (SUMP)
Benign Neoplasm

- Pleomorphic adenoma and Warthin tumor most common (>80% of salivary gland tumors)
- Includes less commonly encountered benign mesenchymal neoplasms (schwannoma)
- Prior literature: majority (95.5%) benign; 3% malignant; 1.5% non-neoplastic
- Classic morphologic features should be present or an alternate category considered

Management

- Surgery or clinical follow up

Pleomorphic Adenoma

- Account for 50% of salivary gland neoplasms
- Biphasic tumor: epithelial cells, myoepithelial cells and chondromyxoid matrix
- Chondromyxoid matrix is unique
Matrix Matters!

- Fibrillary matrix material
- Admixed with cells
- Magenta on DQ
- Light blue/pink on Pap

Pleomorphic Adenoma Challenges

- Stroma may be limited
- May have unusual metaplasia (oncocytic/clear cell/ mucinous)
- Stroma may appear more basement membrane like
- If not classic or if atypical features are present should be considered “SUMP”
Differential Diagnosis

- Other matrix producing tumors
- Cellular basaloid neoplasms ("SUMP")

Other Matrix Producing Tumors

- Aside from adenoid cystic carcinoma, rare and/or rarely FNA’d
- Usually have matrix with basement membrane-type appearance
  - Basal cell adenoma/adenocarcinoma
  - Epithelial myoepithelial carcinoma
  - (Polymorphous low grade adenocarcinoma)
Basement Membrane:
- Dense, sharply demarcated
- Not interspersed with cells
- Metachromatic on DQ

Cellular Basaloid Neoplasms
- Basal cell adenoma
- Solid Adenoid Cystic Ca
- Cellular pleomorphic adenoma
Basaloid Neoplasms IHC

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>IHC</th>
<th>p63</th>
<th>p40</th>
<th>SMA</th>
<th>C抹cin</th>
<th>S100</th>
<th>C-kit</th>
<th>LIT1-1</th>
<th>PLAG1</th>
<th>HMG2</th>
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Basaloid Neoplasms IHC

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<td>Adenoid cystic CA</td>
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Warthin Tumor

- Second most common salivary gland neoplasm
- Significant association with smoking
- Nearly exclusively parotid
- Classic features required for definitive diagnosis
Warthin Tumor
- Three part histologic and cytologic appearance
  - Papillary architecture with cystic spaces
  - Bilayered oncocytic epithelium
  - Background lymphocytes

Differential Diagnosis
- Oncocytic neoplasms
- Cystic neoplasms
- Intraparotid lymph node and lymphoid lesions
- If not classic Warthin tumor, then should be considered “SUMP”
Oncocytic Tumors

- Oncocytoma
- Acinic cell carcinoma
- Salivary duct carcinoma
- Metastasis

Oncocytic Neoplasms IHC

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<th>Diagnosis</th>
<th>p63</th>
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<th>MGB</th>
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### Oncocytic Neoplasms IHC

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### Salivary Gland Neoplasm of Uncertain Malignant Potential (SUMP)

- Aspirate is diagnostic of neoplasm
- Specific diagnosis cannot be rendered
- Malignant neoplasm is possible
  - Cellular basaloid neoplasms
  - Cellular oncocytic neoplasms
  - Clear cell neoplasms

### SUMP Prior Literature

- Most common follow up diagnoses:
  - Pleomorphic adenoma
  - Mucopidermoid carcinoma
- Benign: 48.4%
- Malignant: 37.5%
- Non-neoplastic: 14.1%
Clear Cell Neoplasms

- Uncommon tumors
- Broad differential diagnosis
- Cells with clear or vacuolated cytoplasm
- Most are low grade malignancies on follow up

Clear Cell Neoplasms

Acinic Cell Ca

Met Renal Cell Ca

Salivary Duct Ca

Clear Cell Neoplasms IHC

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<td>q/-</td>
<td>q/+</td>
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Clinical Management

• Benign neoplasms
  – Complete surgical excision
  – Nerve preservation

• “Uncertain malignant potential”
  – Preoperative imaging (extent of lesion, status of neck)
  – Nerve preservation
  – Intra-operative frozen section may be helpful

Suspicious for Malignancy

• An aspirate with features highly suggestive but not unequivocal for malignancy
• Type of malignancy favored or differential diagnosis should be noted
• Primary versus secondary versus lymphoma specified when possible
• Majority are high grade carcinoma on resection
Management

- Not equivalent to “malignant”
- Repeat FNA, biopsy or excision may be considered
- Consider ancillary studies if repeat FNA is performed (cell block, flow cytometry)
- Intraoperative frozen section can be considered

Malignant

- Diverse group of primary and secondary neoplasms
- Parotid and submandibular glands
- For primary malignancies:
  - Low grade carcinoma
  - High grade carcinoma
- Cell blocks for immunohistochemistry
- Prior literature: positive predictive value 92%; likely related to diversity of malignancies and overlap with benign entities
Low Grade Carcinomas

- Acinic cell carcinoma
- Secretory carcinoma
- Epithelial – myoepithelial carcinoma
- Management: Superficial parotidectomy

Acinic Cell Carcinoma

- 10-15% of salivary gland malignancies
- 33% of malignant tumors in children
- Predominantly parotid
- Asymptomatic and slow growing
- Can metastasize to cervical lymph nodes
- 35% recurrence rate
Acinic cell carcinoma

- Acinar-microcystic
- Zymogen granules

Acinic Cell CA

Secretery Carcinoma

- Recently described by Skalova et al in 2010
- Most likely considered acinic cell carcinoma prior to description
- A malignancy that shares overlapping features with juvenile secretory carcinoma of the breast
  - including an identical translocation leading to ETV6-NTRK3 fusion oncogene
Secretory Carcinoma

PAS

DOG-1

GATA3

mammoglobin

S-100

Acinic Cell CA

+  

+  

+  

+  

+  

Secretery CA

+/-  

-  

+  

+  

+  

Immunohistochemistry

Molecular Alterations

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Gene Fusion/s</th>
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<tr>
<td>Pleomorphic adenoma</td>
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<td>MYB-NFIB</td>
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<td>Secretery CA</td>
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High Grade Carcinomas

- Salivary duct carcinoma
- Lymphoepithelial carcinoma
- High grade transformation
- Metastasis

Specific diagnosis of a high grade salivary gland carcinoma is often not possible without immunohistochemical stains

High Grade Carcinomas

- Specific diagnosis of a high grade salivary gland carcinoma is often not possible without immunohistochemical stains
- Salivary gland primaries treated aggressively: total parotidectomy sacrificing the facial nerve +/- lymph node dissection

Salivary Duct Carcinoma
Salivary Duct Carcinoma

- Immunohistochemical stains needed
  - Androgen receptor positive
  - GATA3 positive
  - GCPIF-15 positive >80%
  - P63/ p40 negative

Carcinoma ex pleomorphic adenoma

Intermediate or Multiple Grade Tumors

- Mucoepidermoid carcinoma
- Adenoid cystic carcinoma
- Myoepithelial carcinoma
- Carcinoma ex pleomorphic adenoma
- Hematolymphoid tumors
Mucoepidermoid Carcinoma

Low grade

High grade

Adenoid cystic carcinoma

Metastatic small cell carcinoma

Basal cell adenoma
Take Home Points

- Milan System provides a framework for diagnosis of salivary gland neoplasms
- Particularly helpful in unifying terminology of the indeterminant lesions
- Hopes to allow rapid implementation of future diagnostic and therapeutic refinements

Indeterminant Categories

- Atypia of undetermined significance
- Salivary gland neoplasm of uncertain malignant potential
- Atypical, suspicious for malignancy

Special Thanks

- Tarik Elsheikh MD
- Deborah Chute MD