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The Milan System 2.0 and Salivary Gland FNA

Disclosure of Relevant Financial Relationships

No financial or other conflicts to disclose.

Information presented includes work by colleagues & collaborators at the MGH as well as work from groups around the globe.

The Milan System 2.0 and Salivary Gland FNA

- Three main take-home messages:
 - 1) There is a significant clinical role for salivary gland FNA to guide patient management
 - 2) The Milan System 2.0 provides a standard means for reporting FNA results
 - 3) Ancillary studies can significantly improve the accuracy of FNA and improve patient care!





SALIVARY GLAND NEOPLASIA

- Tumors:
 - 0.4-13.5 per 100,000 people (uncommon)
 - Older adults, females, parotid gland
 - Approx. 75% are benign
 - Carcinomas include highly aggressive lethal forms
 - Risk of malignancy is inversely proportional to gland size (20% in parotid; 50% in submandibular; 80-89% in oral cavity)



FNA vs Core Biopsy

Major limitation is inability to assess for invasion Preop Dx has significant implications for management.

FNA

Core Biopsy

- Faster TAT; ROSE 1 hr
- Multiple FNA sampling
- Complications are rare
- No risk of needle track seeding or nerve damage
- Material for ancillary studies may be limited
- Used for major SG lesions at MGH
- 1-2 days
 Limited sampling
- Complications are uncommon
- Needle track seeding & nerve injusry are considerations
- More reliable source of material for ancillary studies
 Used primarily for minor SG lesions at MGH

SALIVARY GLAND FNA: How effective is it?

Diagnostic Accuracy of Fine Needle Aspiration Biopsy in Preoperative Diagnosis of Patients With Parotid Gland Masses

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Effectiveness of Cytomorphology alone:

- » Overall Sensitivity: 86-100%
- » Overall Specificity: 48-94%
- » Accuracy based upon grade:
 - » Benign/low grade vs HG malignant: 81-100%
- » Frozen section and FNA are complimentary
 - » Improved accuracy when both are used





Why do we need a new reporting system for salivary gland cytology?





Milan 2nd Edition: Salivary Gland FNA and Imaging

Chapter 9. Drs. Lazor and Garratt, Dept. Radiology, Univ. of Pennsylvania



Imaging of mucoepidermoid carcinoma

Worldwide Publications Related to the Milan System

- Over 100 cytology publications since 2018 related to the Milan System
- Source Countries include: Belgium, China, Czech Republic, England, Finland, France, India, Iran, Italy, Japan, Jordan, Korea, Portugal, USA, and others!
- Most confirm calculated ROMs associated with each diagnostic category





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PH ² Zubair W. Baloch MD, Ph
econd Edition:
15%
11%
30%
<3%
35%
83%
>98%

Some examples of the different Milan 2.0 categories

How would you diagnose this FNA? 50 yo female with a 2 cm right parotid mass.



Milan System for Salivary Gland Cytopathology "Normal" salivary gland elements- likely a sampling error!

- Non-Diagnostic
- Non-Neoplastic
- AUS
- Neoplasm: Benign
- Neoplasm: SUMP
- Suspicious for Malignancy
- Malignant











Milan System for Salivary Gland Cytopathology Metastatic keratinizing SCC (cutaneous) to parotid LN

- Non-Diagnostic
- Non-Neoplastic
- AUS
- Neoplasm: Benign
- Neoplasm: SUMP
- Suspicious for Malignancy
- Malignant



MALIGNANT CATEGORY

- 1) Classic cytologic features of a particular SG cancer (includes selected low-grade cancers)
- 2) Overt malignant features (high-grade cancers)
- 3) IHC or molecular is diagnostic of cancer

An Important Component of the Malignant Category is the GRADE!

- Will influence the extent of surgery
 - Radical resection vs limited resection
 - Frozen sections to confirm NEGATIVE margins
 - Neck dissection
 - Nerve sacrifice







30 yo female with a 1.5 cm right parotid mass.

Milan System for Salivary Gland Cytopathology "Classic" pleomorphic adenoma

- Non-Diagnostic
- Non-Neoplastic
- AUS
- Neoplasm: Benign
- Neoplasm: SUMP
- Suspicious for Malignancy
- Malignant



Neoplasm: Benign

<u>i) Benign:</u> erved for <u>classic benign neoplasms</u> This category will include cases of PA, WT, lipoma, schwannoma, others

Warthin tumo

55 yo female with a 2 cm left parotid mass.



Milan System for Salivary Gland Cytopathology

- Non-Diagnostic
- Non-Neoplastic
- AUS
- Neoplasm: Benign
- Neoplasm: SUMP
- Suspicious for Malignancy
- Malignant



For FNA to be competitive as a diagnostic test, we strive to shift cases from SUMP (Indeterminate) to the Malignant or Benign categories.



Basal Cell Adenoma is a Classic Example of SUMP



Salivary Gland FNA and Ancillary Markers

Salivary Gland FNA: New Markers and New Opportunities for Improved Diagnosis

Marc P. Pusztaszeri, MD¹; Joaquín J. García, MD²; and William C. Faquin, MD, PhD^{3,4}

- Improvements in IHC and molecular testing will
- assist the Milan System 2.0 and salivary gland FNA. It is important that the FNA specimen include adequate material for ancillary studies in difficult
- Used judiciously on a case-by-case basis
- Cell blocks help to address this!





Immunochemistry for Matrix-Producing Tumors

DDX: PA, Basal cell tumor, Epi-myoep carcinoma, AdCC

- One or more myoepithelial markers
 - **p63**
 - **S-100**
 - Keratin 5/6
 - SMA
 - Calponin
- Keratin AE1.3/CAM5.2 or EMA
- Ki-67
- PLAG-1
- HMGA-2
- MYB and CD117
- B-Catenin













Pleomorphic Adenoma

PLAG1 & HMGA2:

Two Useful Immunohistochemical Markers, Especially for Cell Blocks and Core Biopsies





Salivary Gland FNA Case An important entity NOT to miss!

A 38 year-old woman with a slowly enlarging right neck mass medial to the angle of the jaw.For the past 4 months, the mass had been tender to touch. An MRI and FNA were performed.









Cytologic Diagnosis:

SUSPICIOUS FOR MALIGNANCY Highly suspicious for adenoid cystic carcinoma.





Adenoid Cystic Carcinoma

- Second most common salivary gland malignancy
 - 1200 new cases per year in the USA
 <u>4-10% of all salivary gland neoplasms</u>
- Median age 57 years old
- Major salivary glands (66%), Minor glands of oral cavity, sinonasal cavity, other anatomic sites (33%)
- Initial indolent behavior but <u>poor long-</u> term survival
 - 10 year survival of 40-60%; worse prognosis for solid type
 - Metastasis in >50%, especially to lung





FNA Pitfall: Adenoid Cystic Carcinoma vs. Other Basaloid Neoplasms





Adenoid Cystic Carcinoma

Expression of KIT (CD117) in Neoplasms of the Head and Neck: An Ancillary Marker for Adenoid Cystic Carcinoma

M. Mino, M.D., B.Z. Pilch, M.D., W.C. Faquin, M.D., Ph.D. Department of Pathology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

CD117 Immunohistochemistry:

Over 90% are strongly positive for CD117 (KIT)

Protein overexpression but no mutation identified

Useful for all variants including solid form













MYB is overexpressed in >80% of AdCC















Mucoepidermoid Carcinoma:

Among the most useful SG molecular probes for FNA and small biopsies

A Reappraisal of the MECT1/MAML2 Translocation in Salivary Mucoepidermoid Carcinomas

Raja R. Seethala, MD, Sanja Dacic, MD, PhD, Kathleen Cieply, MS, Lindsey M. Kelly, BS, and Marina N. Nikiforova, MD

Cytogenetics:

- t(11:19) translocation
- MECT1/MAML2
- FISH or NGS
- More common in low grade
- Often a better prognosis
 - >75%
 - LG-IG 75%, HG 32%



Mucoepidermoid Carcinoma: 3 FNA examples positive for MAML2 fusion







t(4;9) leading to upregulation of NR4A3 in Acinic Cell Carcinomas:

IHC for NR4A3 is Excellent!

Enhancer hijacking activates oncogenic transcription factor NR4A3 in acinic cell carcinomas of the salivary glands

Florian Haller, J. Matthias Bieg^{2,3}, Rainer Wilf⁴, Cindy Körner⁵, Dieter Weichenhan⁶, Alexander Bott⁵, Naveed Ishaque^{2,3}, Pavlo Lutsik ⁶, Evgeny A. Moskalev¹, Sarina K. Mueller⁷, Marion Bähr⁶, Angelika Woerner⁵, Birgit Kaiser⁴, Claudia Scherl⁷, Marlen Haderlein⁸, Kortine Kleinheinz⁹, Rainer Fietkau⁸, Heinrich Iro⁷, Roland Eils^{2,3,10,11}, Arndt Hartmann¹, Christoph Plass⁶, Stefan Wiemann^{4,5} & Abbas Agaimy¹











Secretory Carcinoma:

Cytogenetics: For difficult cases, test for rearrangement

- ETV6-NTRK3 rearrangement:
- T(12:15)(p13;q25)
- NTRK is therapeutic target
- Detected on histology or cytology using:
 - FISH
 - Next-Gen Sequencing



FISH Contributed by Dr. Joaquin Garcia, Mayo Clinic

CASE

An 80 year-old man presents with right facial paresthesia, and a 3 cm right parotid mass. An FNA of the right parotid mass was performed under U/S guidance in the FNA clinic.













Tumors Where the Molecular Phenotype Can Have Implications Not Only For Diagnostics But Also For Therapeutics

- Role for directed therapies based upon characteristic translocations, mutations, and overexpression
 - MYB expression (adenoid cystic carcinoma)
 - •NOTCH (solid adenoid cystic carcinoma)
 - Her2 expression (salivary duct carcinoma)
 - •NTRK fusions (secretory carcinoma)
 - RET fusions (intraductal carcinoma)

SUMMARY

- FNA can play an important role in the diagnosis of salivary gland lesions.
- Milan 2.0 is useful for uniform reporting!
- New IHC and molecular profiles for various salivary gland tumors can impact the role of FNA:
 - Increased accuracy of salivary gland FNA
 - Important implications for therapeutics
 - Overall improved patient care!

