Time to Standardize the Cytology Reporting of Salivary Glands: 
Introduction of the Milan System

W.C. Faquin, M.D., Ph.D.
Director Head and Neck Pathology
Massachusetts General Hospital
Harvard Medical School
Boston, MA

Salivary gland tumors are among the most heterogeneous group of neoplasms.

ACCME/Disclosure

DR. Faquin has nothing to disclose

Salivary Gland FNA

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• The diversity of salivary gland tumors creates a challenge for cytology:
  – Effectiveness & Utility of FNA
  – Diagnosis & Reporting

Effectiveness of Cytomorphology alone:
  » Sensitivity: 86-100%
  » Specificity: 48-94%
  » Accuracy:
    • Benign/low grade vs HG malignant: 81-98%

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
Increasing Availability of Molecular Markers For Salivary Gland Tumors

- Mammary analogue secretory carcinoma:
  - ETV6-NKRT; t(12:15)
- Pleomorphic adenoma & Ca ex PA:
  - PLAG1; t(3;8)
  - HMGA2 rearrangement
- Clear cell carcinoma:
  - EWSR1-ATF1; t(12:22)
- Mucoepidermoid carcinoma:
  - MECT1/MAML2; t(11:19)
- Cribriform Adenocarcinoma:
  - PRKD rearrangement
- Adenoid cystic carcinoma:
  - MYB-NFIB; t(6:9)

Anchored Multiplex PCR (AMP)

- ~190 target amplicons across 39 genes and 50+ rearrangements
- High-quality sequence:
  - Staggered start sites
  - >100X target coverage
  - Molecular indexing
  - Bi-template coverage
  - ~2% analytical sensitivity
- Fast turn-around (~2 weeks)
- Cost-effective (<$500)
- Small tissue amounts (5-10 ng)

FISH Analysis:

- t(6:9) MYB oncogene-NFIB transcription factor

NORMAL SALIVARY GLAND
Immunohistochemical Markers

- Ker 7, 19, CAM 5.2, EMA
- Ker 7, CAM 5.2, DOG1
- Ker 5/6, S-100, p63, calponin, SM actin

NGS-SNaPshot Panel

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Adenoid Cystic Carcinoma:
MYB Translocation

FISH contributed by Dr. Joaquin Garcia, Mayo Clinic
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

The Milan System for Reporting Salivary Gland Cytopathology

- Sponsored by the ASC and the IAC
- Our goal is to produce a practical classification system that will be user-friendly and internationally accepted.
- The system will be evidence-based, and will provide a useful & uniform format for clinicians who treat salivary gland disease.
- The classification system and ROM for the diagnostic categories will be further refined as more data is available in the literature.

The Milan System for Reporting Salivary Gland Cytopathology

Core Group
- Co-Chairs: Bill Faquin, MD, PhD & Diana Rossi, MD
- Zubair Baloch, MD, PhD
- Guliz Barkan, MD
- Maria Pia Foschini, MD
- Daniel Kurtycz, MD
- Marc Pusztaszeri, MD
- Philippe Vielh, MD

Proposed Classification Scheme
- 1) Non-Diagnostic
- 2) Non-Neoplastic
- 3) Atypical
- 4) Neoplasm:
  - a) Benign
  - b) Other
- 5) Suspicious for Malignancy
- 6) Malignant
Participants:
37 Members from 12 Countries
Cytopathologists, Surgical Pathologists, Molecular Pathologists, ENT Surgeons

• Overview of Diagnostic Terminology and Reporting:
  - Core group: Bruce Wenig, Raja Seethala
  - 2. Non-diagnostic:
    - Mariapia Foschini (lead), Laszlo Vass, Esther Diana Rossi, Jhala Nirag, Philippe Vielh, Kayoko Higuchi
  - 3. Non-neoplastic:
    - Bill Faquin (lead), Massimo Bongiovanni, Sule Canberk, Marc Pusztaszeri, Tarik Elsheik, Dan Kurtycz, Fabiano Callegari
  - 4. Atypical:
    - Marc Pusztaszeri (lead), Zubair Baloch, Bill Faquin, Diara Rossi
  - 5. Neoplasms (benign & other):
    - Zubair Baloch (lead), Jeff Kraner, Lester Layfield, Marc Pusztaszeri, Jerzy Kijianski, Ritu Nayar, Celeste Powers, Piero Nicolai, Guido Fadda
  - 6. Suspicious for malignancy:
    - Diana Rossi (lead), Syed Ali, Ashish Chandra, Zarha Maleki, Bo Ping, He Wang
  - 7. Malignant:
    - Gül 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 – MGH), Piero Nicolai (Italy)

The Benefits of a Uniform Reporting System for Salivary Gland Cytopathology

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

The Milan System for Reporting Salivary Gland Cytopathology

ONLINE SURVEY

• Dr. Dan Kurtycz was key in the implementation
• Survey Results – LOTS OF DATA!:
  - 49 questions
  - 284 participants
  - 54% academic, 46% private practice
  - 82% use U/S guided FNA/ 62% use ROSE
  - Other info: Dividing ND into cyst and non-cyst; Dividing neoplasms into Benign and Indeterminate; use of individual terms (e.g. basaloid neoplasm) controversial; subsite important etc.
  - There will be an additional online open comment period soon for pathologists and clinicians.

The Milan System for Reporting Salivary Gland Cytopathology

• Due date for the Atlas: Summer 2017
• Collaborative publications to enhance the literature and provide better ROM
The Milan System for Reporting Salivary Gland Cytopathology

We look forward to your input as we work to develop and refine the Milan system – Thank You!