

**Cytopathology Competency / Milestone Assessment**

***Salivary Gland Cytopathology***

Michelle R. Pramick, MD  
Zubair W. Baloch, MD, PhD

Department of Pathology & Laboratory Medicine  
University of Pennsylvania, Perelman School of Medicine  
3400 Spruce Street, 6 Founders  
Philadelphia, PA. 19104  
Emails: [Michelle.Pramick.uphs.upenn.edu](mailto:Michelle.Pramick.uphs.upenn.edu); [baloch@mail.med.upenn.edu](mailto:baloch@mail.med.upenn.edu)

## TABLE OF CONTENTS

1. Fine Needle Aspiration Biopsy of Salivary Gland Lesions
2. Normal Salivary Glands
3. The Cells
  - a. Acinic Cells
  - b. Ductal Cells
  - c. Myoepithelial Cells
  - d. Oncocytes
  - e. Miscellaneous
  - f. Lymphoid Tissue
4. Diseases of the Salivary Gland
  - a. Sialadenosis
  - b. Cysts
  - c. Non-neoplastic Cysts
  - d. Neoplastic Cysts
  - e. Sialadenitis
  - f. Chronic Sialadenitis
  - g. Radiation Sialadenitis
  - h. Granulomatous Sialadenitis
  - i. Necrotizing Sialometaplasia
  - j. Adenomatoid Hyperplasia
  - k. Autoimmune Sialadenitis
  - l. Benign Lymphoepithelial Lesion
  - m. Benign Lymphoepithelial Cyst
  - n. Parotid Gland in HIV infection
5. Salivary Gland Neoplasms
6. Benign Salivary Gland Tumors
  - a. Pleomorphic Adenoma
  - b. Monomorphic Adenoma
  - c. Warthin's Tumor
  - d. Oncocytoma
7. Malignant Salivary Gland Tumors
  - a. Adenoid Cystic Carcinoma
  - b. Mucoepidermoid Carcinoma
  - c. Acinic Cell Carcinoma
  - d. Malignant Mixed Tumor
8. Other Salivary Gland Tumors
  - a. Adenocarcinoma
  - b. Primary squamous cell carcinoma
  - c. Undifferentiated Carcinoma
  - d. Small Cell Carcinoma
  - e. Malignant Myoepithelioma
  - f. Clear Cell Tumors
  - g. Malignant Lymphoma
  - h. Mesenchymal Tumors

- i. Metastasis
- 9. Salivary Gland Masses in Children
- 10. System Based Practice Monitors

**The 6 ACGME Competencies**

*Medical Knowledge*

*Practice Based Learning*

*System based practice*

*Interpersonal and communication skills*

*Patient care*

*Professionalism*

## **1. Fine Needle Aspiration Biopsy of Salivary Gland Lesions**

### *a. Medical Knowledge*

- i. Understand the clinical questions that can be answered by a fine needle aspiration biopsy of a salivary gland
- ii. Understand the potential risks associated with a fine needle aspiration biopsy of a salivary gland
- iii. Understand the advantages of a fine needle aspiration biopsy of a salivary gland over a frozen section
- iv. Know the primary indication for fine needle aspiration of a salivary gland
- v. Know the relative sensitivity and specificity of a fine needle aspiration biopsy of salivary gland lesions
- vi. Understand the potential causes of false positive and false negative diagnoses

### *b. Practice Based Learning*

- i. Understand that a fine needle aspiration biopsy of a salivary gland should be correlated with clinical findings, and follow-up procedures performed as indicated

## **2. Normal Salivary Glands**

### *a. Medical Knowledge*

- i. Understand that salivary glands are exocrine secretory organs specialized for the production of saliva
- ii. Recognize that there are major and minor salivary glands
  1. major = parotid, submandibular, and sublingual glands
- iii. Know the relative size distribution of the major salivary glands
- iv. Recognize that the incidence of neoplasms roughly parallels the relative size of the salivary glands
- v. Understand the embryologic origin of the of the salivary glands
- vi. Understand that the parotid gland is the only salivary gland with intraglandular lymph nodes
- vii. Recognize the normal anatomy of the salivary glands and their relationship to other vital structures in the head and neck.
- viii. Understand the distribution of minor salivary glands
- ix. Understand that ectopic salivary gland tissue is relatively common in cervical lymph nodes
- x. Know that rare sites of ectopic salivary gland tissue include: middle and external ear, neck, mandible, and pituitary gland
- xi. Identify the normal histology of a salivary
- xii. Understand the configuration of ducts regarding the flow of saliva in the major salivary glands
- xiii. Understand the type of secretion produced by the major salivary glands

## **3. The Cells**

### *a. Acinic Cells*

#### *i. Medical Knowledge*

1. Recognize the architectural arrangement and key nuclear and cytoplasmic features of various forms of acinic cells

2. Understand the function of the acinic cell secretions
- ii. *Practice Based Learning*
  1. Know that mucinous acinic cells produce acid sialomucins (alcian blue and mucicarmine positive) and neutral sialomucins (PAS positive)
- b. Ductal Cells
  - i. *Medical Knowledge*
    1. Recognize the architectural arrangement and key nuclear and cytoplasmic features of ductal cells
- c. Myoepithelial Cells
  - i. *Medical Knowledge*
    1. Recognize the architectural arrangement and key nuclear and cytoplasmic features of myoepithelial cells
    2. Understand the function of myoepithelial cells
- d. Oncocytes
  - i. *Medical Knowledge*
    1. Recognize the architectural arrangement and key nuclear and cytoplasmic features of oncocytes
    2. Know that oncocytes appear with age in the normal salivary gland and some lobules as they undergo focal oncocytic metaplasia
    3. Understand that oncocytic metaplasia begins in the patient's forties
- e. Miscellaneous
  - i. *Medical Knowledge*
    1. Understand that adipose tissue is normal in the salivary gland, and that it increases with age, and may be massive in alcoholic or malnourished patients
    2. Recognize that ciliated respiratory-type glandular cells can occasionally be seen in salivary gland ducts
    3. Recognize that the parotid gland may have sebaceous cells
    4. Understand that squamous metaplasia can occur due to chronic inflammation, ischemia, radiation, or neoplasia
    5. Know that psammoma bodies are seen in a variety of benign and neoplastic conditions and are nonspecific
    6. Know that crystals of various types can be identified in salivary gland aspirate biopsies
      - a. tyrosine-rich and collagen-rich crystals in pleomorphic adenoma
      - b. sulfur-rich crystals in cysts
      - c.  $\alpha$ -amylase-rich crystals in sialadenitis
- f. Lymphoid Tissue
  - i. *Medical Knowledge*
    1. Recognize the architectural arrangement and key nuclear and cytoplasmic features of lymphocytes
    2. Understand that lymphoid tissue may be aspirated from intraparotid or adjacent cervical lymph nodes

#### 4. Diseases of the Salivary Gland

##### a. Sialadenosis

###### i. *Medical Knowledge*

1. Understand the clinical characteristics, presentation, pathogenesis, and prognosis of sialadenosis
2. Recognize that sialadenosis is usually caused by a metabolic derangement (malnutrition, alcoholism, endocrine disease) or medications (antihypertensive and sympathomimetic drugs)
3. Recognize the architectural arrangement, cellular components, and key nuclear and cytoplasmic features of sialadenosis in an aspirate biopsy
4. Know the differential diagnosis of bilateral salivary gland enlargement and the key features to differentiate these entities

###### ii. *Practice Based Learning*

1. Understand that fine needle aspiration of sialadenosis can be painful for the patient

##### b. Cysts

###### i. *Medical Knowledge*

1. Understand that salivary gland neoplasms are frequently cystic
2. Know that any salivary gland can develop a cyst and that they can occur at any age

###### ii. *Practice Based Learning*

1. Know that the general principles of the aspiration of cystic masses
  - a. Drain the cyst
  - b. Re-aspirate any residual mass
  - c. Excise the lesion if it recurs more than once
2. Understand that correct classification of a cystic lesion can be difficult due to low cellularity of the aspirate
3. Understand that a cytologic report of a poorly cellular fluid does not exclude the presence of a neoplasm, clinical correlation is critical
4. Know that appropriate follow-up for a patient diagnosed with a non-neoplastic cyst (should be reexamined in 2 to 4 weeks to confirm that the cyst has receded)

##### c. Non-neoplastic Cysts

###### i. *Medical Knowledge*

1. Know the most common types of non-neoplastic cysts
2. Know the most common locations of non-neoplastic cysts
3. Know the pathogenesis of retention cysts
4. Recognize the cellular and non-cellular components present in an aspirate biopsy of a non-neoplastic cyst
5. Understand the causes for the possibility of a false positive or false negative diagnosis
6. Understand the differential diagnosis of macrophages with mucin (with possible reactive atypia) is low-grade mucoepidermoid carcinoma

##### d. Neoplastic Cysts

###### i. *Medical Knowledge*

1. Know the various neoplasms that can give rise to cystic masses
- e. Sialadenitis
- i. *Medical Knowledge*
    1. Understand the clinical characteristics and presentation of sialadenitis (acute versus chronic)
    2. Know that sialadenitis occurs more commonly in children
  - ii. *Practice Based Learning*
    1. Understand that a patient with a classic clinical history of sialadenitis is probably not a good candidate for fine needle aspiration biopsy (painful, usually yields little diagnostic information)
    2. Know that a portion of the aspirated material should be sent for culture if an aspiration is performed on acute sialadenitis
  - iii. Acute Sialadenitis
    1. Know that acute sialadenitis is not an indication for fine needle aspiration biopsy (although occasionally viral changes or bacteria can be seen)
    2. Know the causes of acute viral sialadenitis
    3. Know the most common bacteria associated with acute purulent sialadenitis
    4. Understand the pathogenesis and clinical associations of acute sialadenitis
    5. Recognize the cellular and non-cellular components seen in an aspirate biopsy of acute sialadenitis
- f. Chronic Sialadenitis
- i. *Medical Knowledge*
    1. Understand the clinical characteristics, presentation, pathogenesis, and prognosis of chronic sialadenitis
    2. Recognize that chronic sialadenitis is usually associated with duct obstruction and can be patchy in distribution
    3. Recognize the cellular components of chronic sialadenitis in an aspirate biopsy
    4. Know the differential diagnosis of salivary gland lesions with lymphocytes and the key features to differentiate these entities
- g. Radiation Sialadenitis
- i. *Medical Knowledge*
    1. Recognize chronic radiation change in an aspirate biopsy
    2. Understand that a scant specimen with cohesive clusters favors a benign process (in contrast to a highly cellular specimen with single atypical cells favoring a malignancy)
- h. Granulomatous Sialadenitis
- i. *Medical Knowledge*
    1. Recognize a granuloma in an aspirate biopsy
    2. Know that differential diagnosis of granulomatous sialadenitis and the key features to differentiate these entities
  - ii. *Practice Based Learning*

1. Understand that a vigorous biopsy technique may be required to obtain adequate material in a fine needle aspiration biopsy (due to reticulin fibrosis)
  2. Know that if enough material is obtained for diagnosis of granulomatous inflammation, a portion of the biopsy should be sent for culture
- i. Necrotizing Sialometaplasia
- i. *Medical Knowledge*
    1. Know that necrotizing sialometaplasia is a benign process that mimics malignancy
    2. Know the most common distribution of necrotizing sialometaplasia
    3. Understand the clinical settings in which necrotizing sialometaplasia usually occurs
    4. Recognize the cellular components and key nuclear and cytoplasmic features of necrotizing sialometaplasia in an aspirate biopsy
- j. Adenomatoid Hyperplasia
- i. *Medical Knowledge*
    1. Understand the clinical characteristics and presentation of adenomatoid hyperplasia
    2. Recognize the cellular and non-cellular components of adenomatoid hyperplasia in an aspirate biopsy
- k. Autoimmune Sialadenitis
- i. *Medical Knowledge*
    1. Know that two forms of autoimmune sialadenitis are recognized:
      - a. Mikulicz's disease
      - b. Sjogren's syndrome
    2. Understand the clinical characteristics, presentation, and prognosis of each of these entities
    3. Understand that Sjogren's syndrome refers to the presence of sicca syndrome *and* a systemic autoimmune connective tissue disease
  - ii. *Practice Based Learning*
    1. Know that patients with Sjogren's syndrome have an increased risk of lymphoma and poorly differentiated squamous cell carcinoma
- l. Benign Lymphoepithelial Lesion
- i. *Medical Knowledge*
    1. Understand the clinical characteristics and presentation of benign lymphoepithelial lesion
    2. Know that it benign lymphoepithelial lesion is also known as myoepithelial sialadenitis
    3. Know that disease entities that are associated with benign lymphoepithelial lesion
    4. Recognize the architectural arrangement, cellular components, and key nuclear and cytoplasmic features of benign lymphoepithelial lesion in an aspirate biopsy
    5. Know the differential diagnosis of benign epithelial lesion and the key features to differentiate these lesions

m. Benign lymphoepithelial Cyst

i. *Medical Knowledge*

1. Recognize the clinical setting in which benign epithelial cysts arise
2. Recognize the cellular and non-cellular components of benign lymphoepithelial cyst in an aspirate biopsy
3. Know the differential diagnosis of benign lymphoepithelial cyst and the key features to differentiate these entities

n. Parotid Gland in HIV infection

i. *Medical Knowledge*

1. Understand the clinical features and presentation of HIV-associated salivary gland disease
2. Recognize that parotid cysts or lymphadenopathy may be the presenting symptom of HIV
- 3.

**5. Salivary Gland Neoplasms**

a. *Medical Knowledge*

- i. Understand that most salivary gland neoplasms are benign
- ii. Know the clinical features of a benign salivary gland neoplasm
- iii. Understand that each segment on the tubulo-acinar unit is associated with a specific neoplasm:
  1. Acinus – acinic cell carcinoma
  2. Intercalated duct – pleomorphic and monomorphic adenoma and adenoid cystic carcinoma
  3. Striated duct – Warthin’s tumor and oncocytoma
  4. Excretory duct – mucoepidermoid carcinoma, squamous cell carcinoma, and adenocarcinoma
- iv. Understand that there is a relationship between the length of the intercalated duct and incidence of neoplasms in the major salivary
- v. Recognize that there is an inverse relationship between the size of the gland and relative incidence of malignancy
- vi. Understand that minor salivary gland neoplasms are more likely to be malignant than major salivary gland neoplasms
- vii. Know that pleomorphic adenoma is the most common neoplasm

b. *Practice Based Learning*

- i. Know that any salivary gland lesion that causes a facial nerve deficit is considered malignant until proven otherwise

**6. Benign Salivary Gland Tumors**

a. Pleomorphic Adenoma (Benign Mixed Tumor)

i. *Medical Knowledge*

1. Understand the clinical characteristics, presentation, and prognosis of pleomorphic adenoma
2. Recognize the variable architectural arrangements, cellular and non-cellular components, and key nuclear and cytoplasmic features of pleomorphic adenoma in an aspirate biopsy

3. Understand that pleomorphic adenoma can undergo malignant degeneration
4. Know the differential diagnosis of pleomorphic adenoma and the key features to differentiate these neoplasms
5. Identify the characteristic metachromatic stroma of pleomorphic adenoma on a Diff Quik stained slide (usually transparent on a Papanicolaou stained slide)

*ii. Practice Based Learning*

1. Know that pleomorphic adenomas are prone to recur if not adequately excised (due to small finger-like projections); cannot be enucleated
2. Know the clinical presentation of malignant degeneration of a pleomorphic adenoma

b. Monomorphic Adenomas

*i. Medical Knowledge*

1. Understand the clinical characteristics, presentation, and prognosis of monomorphic adenomas
2. Know the various types of monomorphic adenomas and recognize the architectural arrangements and key nuclear and cytoplasmic features of each type of monomorphic adenoma in an aspirate biopsy:
  - a. Basal cell adenoma
  - b. Trabecular adenoma
  - c. Tubular adenoma
  - d. Canalicular adenoma
  - e. Clear cell adenoma
  - f. Sebaceous adenoma
  - g. Myoepithelioma
3. Know the differential diagnosis of each type of monomorphic adenoma and the key features to differentiate these lesions
4. Understand the differential diagnosis of entities where sebaceous cells can be seen (neoplasms and normal)
5. Know that myoepithelioma tends to be more aggressive and may convert to malignant myoepithelioma

c. Warthin's Tumor (Papillary Cystadenoma Lymphomatosum)

*i. Medical Knowledge*

1. Understand the clinical characteristics, presentation, and prognosis of Warthin's tumor
2. Recognize the architectural arrangements, cellular and non-cellular components, and key nuclear and cytoplasmic features of Warthin's tumor in an aspirate biopsy
3. Know the differential diagnosis of Warthin's tumor and the key features to differentiate these entities

d. Oncocytoma

*i. Medical Knowledge*

1. Understand the clinical characteristics, presentation, and prognosis of oncocytoma

2. Recognize the architectural arrangements, cellular components, and key nuclear and cytoplasmic features of oncocytoma in an aspirate biopsy
3. Understand that oncocytoma may display marked cytologic atypia and oncocytic carcinoma may have benign appearing cells, therefore evidence of invasion or metastasis provides definitive proof of malignancy
4. Know the differential diagnosis of oncocytoma and the key features to differentiate these entities

## 7. Malignant Salivary Gland Tumors

### a. Adenoid Cystic Carcinoma

#### i. Medical Knowledge

1. Understand the clinical characteristics, presentation, and prognosis of adenoid cystic carcinoma
2. Recognize the architectural arrangements and key nuclear and cytoplasmic features of adenoid cystic carcinoma in an aspirate biopsy
3. Understand that adenoid cystic carcinoma can dedifferentiate into a high grade lesion with anaplastic cytology
4. Know the differential diagnosis of neoplasms in which hyaline globules can be seen
5. Know the differential diagnosis of adenoid cystic carcinoma and the key features to differentiate these neoplasms

### b. Mucoepidermoid Carcinoma

#### i. Medical Knowledge

1. Understand the clinical characteristics, presentation, and prognosis of mucoepidermoid carcinoma
2. Recognize the cellular components and key nuclear and cytoplasmic features of mucoepidermoid carcinoma in an aspirate biopsy
3. Understand the clinical and prognostic significance of a low grade mucoepidermoid carcinoma compared to a high grade mucoepidermoid carcinoma
4. Recognize the key findings seen in an aspirate biopsy to differentiate a low grade from a high grade mucoepidermoid carcinoma
5. Know the differential diagnosis of mucoepidermoid carcinoma and the key features to differentiate these neoplasms

### c. Acinic Cell Carcinoma

#### i. Medical Knowledge

1. Understand the clinical characteristics, presentation, and prognosis of acinic cell carcinoma
2. Recognize the cellular components (present and absent) and key nuclear and cytoplasmic features of acinic cell carcinoma in an aspirate biopsy
3. Know the differential diagnosis of acinic cell carcinoma and the key features to differentiate these entities (including benign salivary gland)

#### ii. Practice Based Learning

1. Know that the cytoplasmic zymogen granules in acinic cells are PAS positive
- d. Malignant Mixed Tumor
  - i. *Medical Knowledge*
    1. Know the three categories of malignant mixed tumors
      - a. Carcinoma ex Pleomorphic Adenoma
      - b. True Malignant Mixed Tumor (carcinosarcoma)
      - c. Benign metastasizing mixed tumor
    2. Understand the clinical characteristics, presentation, and prognosis of each type of malignant mixed tumor
    3. Recognize the cellular components, architectural arrangement, and key nuclear and cytoplasmic features each type of malignant mixed tumor in an aspirate biopsy
    4. Know the differential diagnosis of each type of malignant mixed tumor and the key features to differentiate these entities

## 8. Other Salivary Gland Tumors

- a. Adenocarcinomas
  - i. *Medical Knowledge*
    1. Understand that this category includes adenocarcinomas of the salivary gland that do not fit into other recognized entities
    2. Recognize the cellular components, architectural arrangement, and key nuclear and cytoplasmic features of adenocarcinomas present in salivary gland tissue
      - a. Mucous producing carcinoma
      - b. Papillary adenocarcinoma
      - c. Salivary duct carcinoma
      - d. Polymorphous low grade carcinoma
      - e. Epithelial-myoepithelial carcinoma
      - f. Basal cell adenocarcinoma
    3. Understand the clinical characteristics, presentation, and prognosis of each of these malignancies
    4. Know the differential diagnosis of each of these malignancies and the key features to differentiate these entities
- b. Primary Squamous Cell Carcinoma
  - i. *Medical Knowledge*
    1. Understand the clinical characteristics, presentation, and prognosis of squamous cell carcinoma
    2. Recognize the architectural arrangements and key nuclear and cytoplasmic features of squamous cell carcinoma in an aspirate biopsy
    3. Know the differential diagnosis of squamous cell carcinoma and the key features to differentiate these entities
  - ii. Practice Based Learning
    1. Understand that metastatic squamous cell carcinoma is more common than primary squamous cell carcinoma
- c. Undifferentiated Carcinoma

*i. Medical Knowledge*

1. Recognize that undifferentiated carcinoma is a subtype of salivary gland carcinoma with lymphoid stroma
2. Understand the clinical characteristics, presentation, and prognosis of undifferentiated carcinoma
3. Know that undifferentiated carcinoma is associated with Epstein-Barr virus
4. Recognize the cellular components, architectural arrangements, and key nuclear and cytoplasmic features of undifferentiated carcinoma in an aspirate biopsy
5. Know the differential diagnosis of undifferentiated carcinoma and the key features to differentiate these entities

d. Small Cell Carcinoma

*i. Medical Knowledge*

1. Understand that small cell carcinoma is a type of non-pulmonary poorly differentiated neuroendocrine carcinoma
2. Understand the clinical characteristics, presentation, and prognosis of small cell carcinoma
3. Recognize the cellular components, architectural arrangements, and key nuclear and cytoplasmic features of small cell carcinoma in an aspirate biopsy
4. Know the differential diagnosis of small cell carcinoma and the key features to differentiate these neoplasms

e. Malignant Myoepithelioma

*i. Medical Knowledge*

1. Know that the key characteristics that differentiate malignant myoepithelioma from myoepithelioma
2. Understand the clinical characteristics, presentation, and prognosis of malignant myoepithelioma

f. Clear Cell Tumors

*i. Medical Knowledge*

1. Understand that clear cell tumors can be benign or malignant
  - a. Myoepithelial adenoma/carcinoma
  - b. Acinic cell carcinoma
  - c. Mucoepidermoid carcinoma
  - d. Sebaceous neoplasms
  - e. Oncocytomas
  - f. Metastatic carcinoma (frequently renal)
2. Understand the clinical characteristics, presentation, and prognosis of clear cell tumors
3. Recognize the cellular components, architectural arrangements, and key nuclear and cytoplasmic features of each type of clear cell tumor in an aspirate biopsy
4. Know the differential diagnosis of each clear cell tumor and the key features to differentiate these entities

g. Malignant Lymphoma



3. Pleomorphic adenoma
4. Mucoepidermoid carcinoma
5. Rhabdomyosarcoma

**10. System Based Practice Monitors for the Salivary Gland Cytopathology Curriculum.**

**The Practitioner Should:**

- a. Achieve an understanding of the organization and function of the various technical sections of the laboratory processing and diagnosing salivary gland cytology specimens.
- b. Practice cost-effective laboratory utilization and resource allocation that does not compromise quality care.
- c. Develop an awareness of how cytopathology services and other professional practices affect other health care professionals and organizations managing patients based on results of salivary gland cytopathology reports.
- d. Develop clear understanding of the government regulations for State, CLIA, CAP, JCAHO, HIPPA/patient data security requirements for practice management.
- e. Demonstrate an awareness of basic billing requirements (ICD-9 & CPT-codes) and re-imburement policies in compliance with Medicare and Medicaid.
- f. Develop an understanding of quality assurance and quality control issues associated with salivary gland pathology. This includes but not limited to:
  - i. Using appropriate controls for each test performed; molecular, IHC, in-situ hybridization, etc.
  - ii. Histopathologic correlation of atypical and malignant cases

**References:**

1. The Art & Science of Cytopathology. R. M. DeMay. ASCP Press, 2<sup>nd</sup> Edition. 2011.
2. Cytology : diagnostic principles and clinical correlates . Edmund S. Cibas, Barbara S. Ducatman. Saunders Elsevier, 3<sup>rd</sup> Edition. 2009.