

**VM103 Fine-Needle Aspiration of the Salivary Gland:  
From Common to Exotic**

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This videomicroscopy tutorial will use a series of 6 salivary gland FNA cases to discuss the evaluation and diagnosis of several commonly encountered, yet sometimes diagnostically challenging, salivary gland tumors.

**OBJECTIVES:**

- **Apply cytomorphologic criteria in the diagnosis of key salivary gland tumors**
- **Recognize common problem areas and diagnostic pitfalls in salivary gland cytology**
- **Formulate a focused differential diagnosis using a practical algorithmic approach**

**INTRODUCTION TO SALIVARY GLAND FNA**

Salivary gland FNA is probably the most challenging area of cytopathology. In part, this is due to the fact that there are so many different types of lesions that can occur within the major and minor salivary glands, of which there are over 600 glands within the human body. In addition, there is a significant degree of both histologic and cytologic overlap between many of the neoplasms encountered - this includes overlap between benign and malignant lesions, between various low-grade carcinomas, as well as between high-grade tumors. It is important to remember that FNA has a high accuracy for the specific diagnosis of certain salivary gland tumors (e.g. pleomorphic adenoma, Warthin's tumor, acinic cell carcinoma), while for others (e.g. salivary duct carcinoma, basal cell adenocarcinoma, epithelial-myoepithelial carcinoma), FNA may not be able to specifically subtype the lesion, but it can reliably distinguish low-grade from high-grade neoplasms. For the purposes of clinical management, the latter distinction is the most important. **Key take-home point: When evaluating most salivary gland aspirates, it is very important to have both Papanicolaou-stained as well as Romanowsky-stained slides, otherwise your diagnostic assessment of the case may be compromised!**

In assessing salivary gland aspirates, my approach is to first place the aspirate into one of several general categories (see list below) based upon the predominant features that can usually be appreciated at low magnification. Once the lesion is placed into a general category, careful evaluation of the cytologic features will allow one to narrow the focused differential diagnosis.

**An Algorithmic Approach:**

- **Matrix-containing tumors**
- **Oncocytic lesions**
- **Basaloid tumors**
- **Inflammatory and lymphoid lesions**
- **Cystic and mucinous lesions**
- **High-grade carcinomas**
- **Clear cell tumors**
- **Spindle cell lesions**

**ACCURACY**

Overall, FNAB is fairly accurate in the assessment of salivary gland lesions. In recent studies, sensitivity and specificity for neoplasia is >90%. The distinction between benign and malignant neoplasms has a sensitivity of 80-90% and a specificity of >90%. Diagnostic accuracy is lower for rendering a specific diagnosis.

- **High diagnostic accuracy for neoplastic versus non-neoplastic lesions**
- **High accuracy for low-grade versus high-grade lesions**
- **Variable accuracy depending upon the specific entity**

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It is important to remember that some salivary lesions such as pleomorphic adenoma and Warthin's tumor can be accurately diagnosed using FNA, while others such as adenoid cystic carcinoma can sometimes be definitively diagnosed, while others such as basal cell adenocarcinoma will require a descriptive diagnosis. A Table listing common salivary gland lesions and the general probability of rendering a specific diagnosis is provided:

<u>Usually Specific Diagnosis</u>	<u>Sometimes Specific Diagnosis</u>	<u>Usually Descriptive Diagnosis</u>
Pleomorphic adenoma	Adenoid cystic carcinoma	Basal cell adenoma, tubulotrabeular and solid types
Warthin's tumor	LG mucoepidermoid carcinoma	HG mucoepidermoid carcinoma
Basal cell adenoma, membranous type	Metastasis	Polymorphous low grade adenocarcinoma
Acute and chronic sialadenitis	Carcinoma ex PA	Salivary duct carcinoma
Reactive lymph node	Small cell carcinoma	Basal cell adenocarcinoma
Lymphoma	Mucocele	Epithelial-myoepithelial carcinoma
	Oncocytoma	
	LESA	
	Acinic cell carcinoma	

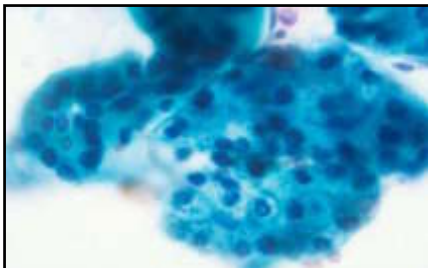
**THE NORMAL SALIVARY GLAND ASPIRATE**

Aspirates of normal salivary gland are hypocellular, comprised of groups of acinar cells, occasional ductal cells, and admixed adipose tissue. Acinar cells are usually present as cohesive polarized grape-like clusters with associated small inconspicuous tubules and honeycomb sheets of cohesive ductal cells. Naked nuclei from crushed acinar cells may be present in the background. The presence of normal salivary gland as the only cytologic finding warrants careful clinical correlation to exclude the possibility of a sampling error. Other explanations for normal-appearing salivary gland elements include a prominent but normal salivary gland, sialadenosis, and lipoma.

**Pitfall:** A pitfall for the diagnosis of normal salivary gland tissue is mistaking it for acinic cell carcinoma (and vice versa).

**Cytologic Features of the Normal Salivary Gland Aspirate**

- Serous and mucinous acinar cells in grapelike clusters ± background naked nuclei
- Admixed small tubules and/or sheets of ductal epithelium
- Adipose tissue



**Normal salivary gland showing ductal cells and acinar cells.**

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**CASES:**

**Case #1.** 55-year-old female with a painless, slowly enlarging 1.5 cm left preauricular mass.

**Diagnosis:** Pleomorphic adenoma (aka benign mixed tumor)

**General Info:** Pleomorphic adenoma is the most common salivary gland tumor in both children and adults. Depending upon the site, between 50% and 80% of salivary gland tumors are pleomorphic adenomas. The most common site is the superficial parotid gland, often the tail of the gland at the angle of the jaw. While benign, these tumors can cause significant morbidity when recurrent, and there is between 5% and 10% risk of malignant transformation (i.e. carcinoma ex pleomorphic adenoma), most often as salivary duct carcinoma.

**Cytologic Features of Pleomorphic Adenoma:**

- **Myoepithelial cells (usually predominant), often plasmacytoid or spindled**
- **Cohesive epithelial cells in honeycomb groups**
- **Chondromyxoid matrix - fibrillar, bright magenta using Romanowsky stains, frayed edges, embedded myoepithelial cells**



**Differential Diagnosis:**

- **Adenoid cystic carcinoma**
- **Basal cell adenoma/adenocarcinoma**
- **Myoepithelioma**
- **Carcinoma ex pleomorphic adenoma**

**Pitfalls:**

- **Cellular specimens with scant matrix**
- **Metaplastic changes: squamous, mucinous, oncocytic**
- **Spindle cell predominance**
- **Cytologic atypia**
- **Focal adenoid cystic-like areas**

**Case #2.** 34-year-old female with enlarging 1.5 cm right parotid mass and right facial paresthesia.

**Diagnosis:** Adenoid cystic carcinoma

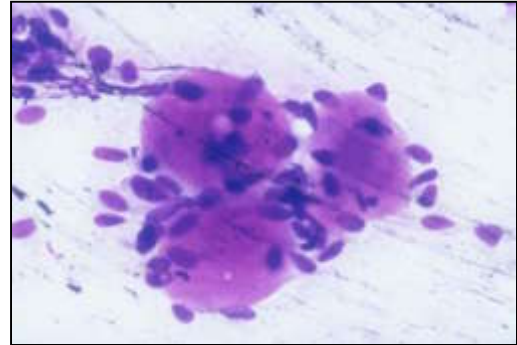
**General Info:** Adenoid cystic carcinomas represent 4-10% of all salivary gland neoplasms. Although the clinical course of adenoid cystic carcinoma is often protracted, long-term (15-20 year) survival is poor; in part this is related to the neurotropism of the tumor. The tendency of these tumors to invade nerves manifests itself clinically as a **painful** mass or as pain during the FNAB, which should increase the clinical suspicion of malignancy. Three variants are recognized and often present in combination: tubular, cribriform, and solid. The most easily recognized form on FNA is the cribriform subtype, while the solid form is by far the most difficult.

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**Cytologic Features of Adenoid Cystic Carcinoma:**

- Basaloid cells with dark angulated nuclei and variable nuclear atypia
- Variable numbers of myoepithelial cells
- Matrix: cookie cutter-like matrix spheres and linear branching structures (acellular with sharp borders), magenta using Romanowsky stains



**Differential Diagnosis:**

- Cellular pleomorphic adenoma
- Basal cell adenoma/adenocarcinoma
- Polymorphous low-grade adenocarcinoma
- Cutaneous basal cell carcinoma

**Pitfalls:**

- Solid subtype (scant matrix)
- Increased numbers of myoepithelial cells
- Pleomorphic adenoma-like areas

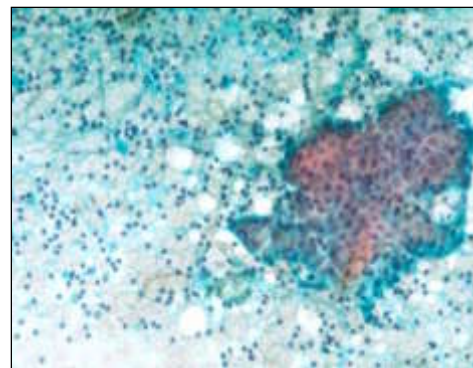
**Case #3.** 69 year-old male with a 1.5 cm left parotid gland mass. The lesion had a doughy feel on palpation. An FNA was performed.

**Diagnosis:** Warthin's tumor

**General Info:** Warthin's tumor (aka papillary cystadenoma lymphomatosum) is the second most common salivary gland tumor, representing 5-10% of all salivary gland neoplasms. It can be bilateral and there is a strong link with cigarette smoking. Previously, it was more common in men, but it is now about equally present in men and women. On clinical examination, it has a "doughy" feel on palpation, and the FNA typically yields thick brown-green opaque fluid.

**Cytologic Features of Warthin's Tumor:**

- Oncocytes in flat 2-D sheets
- Lymphocytes
- Proteinaceous background with cholesterol crystals, degenerate cells, and debris



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**Differential Diagnosis:**

- Reactive lymph node
- Oncocytoma
- Metastatic squamous cell carcinoma
- Mucoepidermoid carcinoma
- Acinic cell carcinoma

**Pitfalls:**

- Predominance of oncocytes or lymphocytes

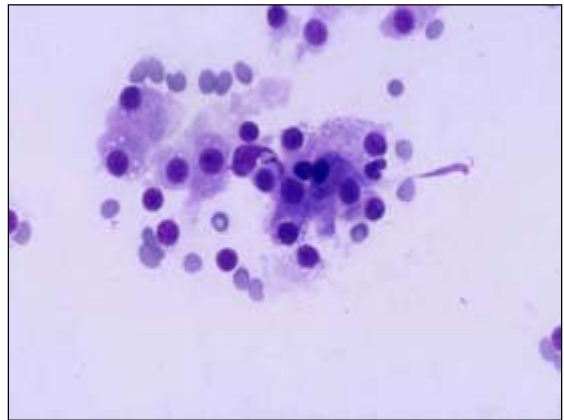
**Case #4.** 45 year-old male with a 2-year history of a right upper neck mass.

**Diagnosis:** Acinic cell carcinoma

**General Info:** Acinic cell carcinoma represents approximately 4-6% of all salivary gland tumors and up to 17% of salivary gland malignancies. It is generally a low-grade tumor although high-grade forms do occur. Acinic cell carcinoma typically presents as a circumscribed, mobile, slowly growing mass which occasionally is painful. Acinic cell carcinomas can be solid or cystic, and may be present for several years before coming to clinical attention.

**Cytologic Features of Acinic Cell Carcinoma:**

- Serous-type acinar cells or intercalated duct cells
- Sheets and dyshesive crowded 3-D clusters
- Cytoplasmic vacuoles (best seen using Romanowsky stains)
- PAS+D resistant cytoplasmic zymogen granules
- Background naked nuclei  $\pm$  lymphocytes



**Differential Diagnosis:**

- Oncocytoma
- Warthin's tumor
- Adenocarcinoma, NOS
- Oncocytic variant of mucoepidermoid carcinoma
- Metastatic renal cell carcinoma

**Pitfalls:**

- Predominance of intercalated duct cells
- Lymphocytes and stripped nuclei in background
- Resemblance to normal acinar cells

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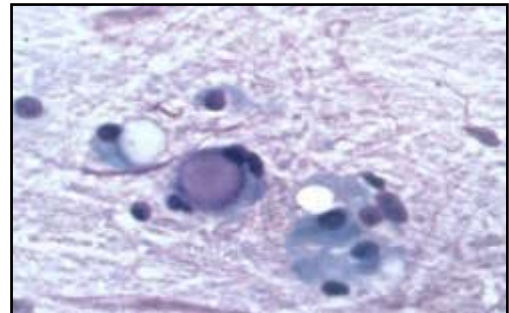
**Case #5.** 70-year-old female with a slowly enlarging 2.0 cm right parotid gland mass.

**Diagnosis:** Low-grade mucoepidermoid carcinoma

**General Info:** Mucoepidermoid carcinoma is the most common salivary gland malignancy in both children and adults. It occurs as low-grade, intermediate grade, and high-grade cancers. The low-grade form is one of the most common causes of false negative FNA diagnoses, often being mistaken as a mucocele!

**Cytologic Features of Low-Grade Mucoepidermoid Carcinoma:**

- Mucus-containing epithelial cells
- Epidermoid cells (squamous features)
- Intermediate cells (squamoid with high N/C ratio)
- Mucinous background



**Differential Diagnosis:**

**Low-Grade Tumors:**

- Mucocele
- Warthin's tumor
- Salivary duct cyst
- Cystic metastatic squamous cell carcinoma

**Pitfalls:**

**Low-Grade Tumors:**

- Hypocellularity
- Foamy histiocyte-like mucus cells
- Bland cytology

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A very rare benign cytologic mimic of low-grade mucoepidermoid carcinoma (and sometimes of oncocytic salivary gland lesions) is **sclerosing polycystic adenosis**. The latter is analogous to fibrocystic disease of the breast, and most indications are that it is non-neoplastic. Aspirates are characterized by flat sheets of epidermoid-appearing cells, ductal cells with oncocytic cytoplasm, occasional vacuolated cells, and scattered cells with apocrine metaplastic changes. The latter is the most useful cytologic feature, which, together with a prolonged benign clinical history, favors sclerosing polycystic adenosis.



**Apocrine metaplastic features in sclerosing polycystic adenosis.**

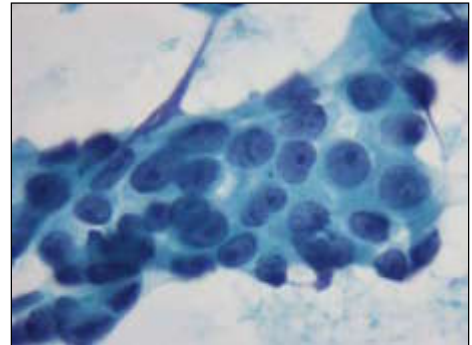
**Case #6.** 84-year-old male with enlarging, 3.0 cm right parotid mass and facial paralysis.

**Diagnosis:** Salivary duct carcinoma

**General Info:** Salivary duct carcinoma is a rare but clinically highly aggressive malignancy. It occurs most commonly in the parotid gland of older to elderly men, and it resembles high-grade comedo-type ductal carcinoma of the breast.

**Cytologic Features of Salivary Duct Carcinoma:**

- High-grade malignant features
- Polygonal cells with vacuolated cytoplasm
- Large hyperchromatic, pleomorphic nuclei with prominent nucleoli
- Background necrosis



**Differential Diagnosis:**

- High-grade mucoepidermoid carcinoma
- Carcinoma-ex-pleomorphic adenoma (malignant mixed tumor)
- Metastatic squamous cell carcinoma

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The diagnostic challenge in assessing aspirates of salivary duct carcinoma is that the overlap among the high-grade carcinomas is significant, and it is often not possible to reliably distinguish between them. For the clinician, the most important information that the cytologist can provide is that the lesion is **high grade**. For clinical management purposes, high-grade carcinomas will often be treated more aggressively than benign and low-grade carcinomas. In many cases this will include a total parotidectomy, possible sacrifice of the facial nerve, and lymph node dissection.

### **References:**

- Abrams AM, Cornyn J, Scofield HH, Hansen LS. Acinic cell adenocarcinoma of the major salivary glands: a clinico-pathologic study of 77 cases. *Cancer* 1965; 18:1145-62.
- Batsakis JG, Sneige N, el-Naggar AK. Fine-needle aspiration of salivary glands: its utility and tissue effects [see comments]. *Ann.Otol.Rhinol.Laryngol.* 1992; 101:185-8.
- Cajulis RS, Gokaslan ST, Yu GH, Frias-Hidvegi D. Fine needle aspiration biopsy of the salivary glands. A five-year experience with emphasis on diagnostic pitfalls. *Acta Cytol.* 1997; 41:1412-20.
- Chan MK, McGuire LJ, King W, Li AK, Lee JC. Cytodiagnosis of 112 salivary gland lesions. Correlation with histologic and frozen section diagnosis. *Acta Cytol.* 1992; 36:353-63.
- Edit D, Pilch BZ, Osgood R, Faquin WC. Fine-needle aspiration biopsy findings in sclerosing polycystic adenosis of the parotid gland. *Diagn.Cytopathol* 2007, in press.
- Ellis GL, Auclair PL. Tumors of the salivary glands. Washington, D.C.: Armed Forces Institute of Pathology, 1996.
- Elsheikh TM, Bernacki EG. Fine needle aspiration cytology of cellular pleomorphic adenoma. *Acta Cytol.* 1996; 40:1165-75.
- Elsheikh TM, Bernacki EG, Pisharodi L. Fine-needle aspiration cytology of salivary duct carcinoma. *Diagn.Cytopathol.* 1994; 11:47-51.
- Eneroth CM, Zajicek J. Aspiration biopsy of salivary gland tumors. II. Morphologic studies on smears and histologic sections from oncocytic tumors (45 cases of papillary cystadenoma lymphomatosum and 4 cases of oncocytoma). *Acta Cytol.* 1965; 9:355-61.
- Eneroth CM, Zajicek J. Aspiration biopsy of salivary gland tumors. III. Morphologic studies on smears and histologic sections from 368 mixed tumors. *Acta Cytol.* 1966; 10:440-54.
- Eneroth CM, Zajicek J. Aspiration biopsy of salivary gland tumors. IV. Morphologic studies on smears and histologic sections from 45 cases of adenoid cystic carcinoma. *Acta Cytol.* 1969; 13:59-63.
- Geisinger KR, Weidner N. Aspiration cytology of salivary glands. *Semin.Diagn.Pathol.* 1986; 3:219-26.
- Granger JK, Houn HY. Malignant mixed tumor (carcinosarcoma) of parotid gland diagnosed by fine-needle aspiration biopsy. *Diagn.Cytopathol.* 1991; 7:427-32.
- Kern SB. Necrosis of a Warthin's tumor following fine needle aspiration. *Acta Cytol.* 1988; 32:207-8.
- Klijanienko J, Vielh P. Fine-needle sample of salivary gland lesions. V: Cytology of 22 cases of acinic cell carcinoma with histologic correlation. *Diagn.Cytopathol.* 1997; 17:347-52.
- Klijanienko J, Vielh P. Fine-needle sampling of salivary gland lesions. III. Cytologic and histologic correlation of 75 cases of adenoid cystic carcinoma: review and experience at the Institut Curie with emphasis on cytologic pitfalls. *Diagn.Cytopathol.* 1997; 17:36-41.
- Klijanienko J, Vielh P. Fine-needle sampling of salivary gland lesions. IV. Review of 50 cases of mucoepidermoid carcinoma with histologic correlation. *Diagn.Cytopathol.* 1997; 17:92-8.
- Krane JF, Faquin WC. Salivary Glands. In: Cibas ES, Ducatman BS, ed. *Cytology: Diagnostic Principles and Clinical Correlates*. Philadelphia: W.B. Saunders Company, 2002.
- Kumar N, Kapila K, Verma K. Fine needle aspiration cytology of mucoepidermoid carcinoma. A diagnostic problem. *Acta Cytol.* 1991; 35:357-9.

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Layfield LJ, Glasgow BJ. Diagnosis of salivary gland tumors by fine-needle aspiration cytology: a review of clinical utility and pitfalls. *Diagn.Cytopathol.* 1991; 7:267-72.

Lee SS, Cho KJ, Jang JJ, Ham EK. Differential diagnosis of adenoid cystic carcinoma from pleomorphic adenoma of the salivary gland on fine needle aspiration cytology. *Acta Cytol.* 1996; 40:1246-52.

Mooney EE, Dodd LG, Layfield LJ. Squamous cells in fine-needle aspiration biopsies of salivary gland lesions: potential pitfalls in cytologic diagnosis. *Diagn.Cytopathol.* 1996; 15:447-52.

Spiro RH, Huvos AG, Strong EW. Acinic cell carcinoma of salivary origin. A clinicopathologic study of 67 cases. *Cancer* 1978; 41:924-35.