Learning Objectives

- Discuss general considerations about salivary gland neoplasia
- Highlight selected new diagnoses
- Present clinical and management considerations
- Develop criteria for when to obtain additional studies in an evaluation of these lesions

General Considerations

- 1% of all tumors (considered under-reported)
- Most common in adults
- Increased frequency in females with Warthin tumor (papillary cystadenoma lymphomatosum)
- Fine needle aspiration first line screening test
- Little known about etiology
- Clinic stage is important
- Molecular techniques slow to catch on

Genetics

- Adenoid cystic carcinoma
  - MYB-NFIB: t(6;9)(q22-23;p23-24)
- Mammary analogue secretory carcinoma
  - ETV6-NTRK3: t(12;15)(p13;q25)
- Mucoepidermoid carcinoma
  - CRTC1-MAML2: t(11;19)(p11;q13)
  - About 70% of low grade tumors
- Pleomorphic adenoma
  - PLG1: 8q12 (40%) (increased PLG1)
  - HMG2A: 12q14-15 (8%)

Tumor Site Distribution

- Parotid 70%
- Submandibular 10%
- Minor 20%
- Subling 5%
Tumor Site Distribution
Minor Salivary Glands Only

- Palate: 55%
- Upper Lip: 10%
- Other: 10%
- Tongue: 10%
- Cheek: 10%

Tumor Type Distribution
MAJOR GLANDS

- Pleomorphic Adenoma: 80%
- Mucoepidermoid Ca: 20%
- Adenoid Cystic Ca: 10%
- Others: 10%

Tumor Type Distribution
MINOR GLANDS

- Pleomorphic adenoma: 40%
- Mucoepidermoid Ca: 20%
- Adenoid Cystic Ca: 10%
- Others: 30%

Benign versus Malignant

As a general rule:
The smaller the involved salivary gland . . .
The higher the possibility of the tumor being malignant

Benign versus Malignant

- Rate of growth
- Relationship with surrounding structures
- Circumscription
- Cytological atypia
Benign versus Malignant

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<thead>
<tr>
<th>Rate of growth</th>
<th>Relationship with surrounding structures</th>
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<tr>
<td></td>
<td>Circumscription</td>
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<tr>
<td></td>
<td>• Benign: Encapsulated; Well circumscribed</td>
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<td>• Malignant: Poorly circumscribed; infiltrative</td>
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... BUT — Be aware of multifocality and minor salivary gland location

Cytological atypia

Multifocal, Multilobular, and Without a Capsule

• Pleomorphic adenoma
• Basal cell adenoma
• Canalicular adenoma
• Warthin tumor
• Cystadenomas
• Oncocytic lesions
  • Oncocytoma vs. nodular hyperplasia
Cribriform Adenocarcinoma of the Minor Salivary Glands

Carcinoma usually affecting the tongue (base) morphologically like thyroid papillary carcinoma

- Age: 21 – 85 (mean 57 years)
- Sex: Male > Female (2:1)
- Location: Tongue >>> buccal, lip, FOM
- Symptoms: Mass lesion
  - >50% have lymph nodes metastasis at time of presentation
- Management: Surgery, follow-on radiation
- Follow-up: NED (mean 4.3 years)
Cribriform Adenocarcinoma of the Minor Salivary Glands

- Gross: Unencapsulated, hard, white-tan
- Intact squamous epithelium
- Invasive periphery of unencapsulated tumor
- Cribriform, microcribriform, tubular, solid
  - Clefting results in glomeruloid appearance
  - Psammoma bodies may be seen
- Fibrous septa separate into nodules
  - Mucinous-myofibroblastic stroma
- Nuclei: Large, overlapped, pale, optically clear (monotonous: Thyroid papillary carcinoma); cytoplasm is cleared in some
Case #8

- 72 year old
- Female
- Presented with difficulty breathing and sinusitis
- During evaluation, a mass was noted along the maxilla-palate region

**Polymorphous Adenocarcinoma**

**Clinical**
- A malignant epithelial tumor characterized by morphological diversity, cytological uniformity, and a low metastatic potential
- PAC/PLGA exclusively in minor glands
- Age: 50-70 years
- Sex: F > M (2:1)
- Site: Palate (60%), junction of hard & soft
  Upper lip, buccal mucosa, retromolar, and posterior tongue
- Slow growing mass
  - Ulceration, bleeding and pain uncommon

**Macroscopic**
- 2nd most common intraoral salivary gland malignancy
- Circumscribed but not encapsulated
- Size:
  - Up to 4 cm
  - Mean: 2 cm
- Firm to solid, ovoid masses
- Close to surface epithelium
  - Creates roughened or corrugated folds
Polymorphous Adenocarcinoma
Microscopic

- Intact surface
- Prominent “targetoid” perineural infiltration
- Fat invasion
- Normal salivary gland incarcerated by tumor
- Background “slate-grey” myxoid degenerated stromal hyalinization
Polymorphous Adenocarcinoma
Microscopic

- **Wide variety of patterns**
  - Lobules, nests, tubules
  - Linear, single cell (Indian filing), concentric targetoid pattern around a nerve
  - Swirling, “Eye-of-the-storm” appearance

- **Cytologically bland**
  - Small to medium polygonal cells
  - Abundant pale cytoplasm without distinct border
  - Round nuclei with “vesicular” open nuclear chromatin
  - Mitotic figures are nearly absent
Polymorphous Adenocarcinoma Immunohistochemistry

- Positive:
  - Cytokeratin
  - S100 protein
  - CK5/6
  - p63
  - Glial fibrillary acidic protein (GFAP)
  - Actin
  - bcl-2
  - CD117 (variably positive)

Polymorphous Adenocarcinoma Differential Diagnosis

- Small, incisional biopsy and frozen artifacts make separation difficult
- Pleomorphic adenoma
  - Circumscribed (but palate tumors are often unencapsulated)
  - Plasmacytoid appearance
  - Chondroid matrix
- Adenoid cystic carcinoma
  - Destructive growth
  - Smaller cells with hyperchromatic, angular nuclei
- Canalicular adenoma
Polymorphous Adenocarcinoma
Prognosis and Management

- Excellent (>95% 10-year survival)
- Local recurrence (around 10%)
  - Higher frequency in palate tumor
  - Women develop recurrences more often than men
- Regional lymph node metastases up to 15%
- Complete, but conservative surgery
  - May be more extensive due to neural invasion
- Neck dissection for proven regional metastases
Acinic Cell Carcinoma

Malignant epithelial salivary gland neoplasm comprised of neoplastic acinar cells
- Is not exclusively, nor even necessarily predominantly, serous type cells
- Salivary ductal cells are also part of this neoplasm
- AKA: Acinic cell adenocarcinoma
- Incidence
  - ~6% of salivary gland tumors (2nd to MEC)
  - ~10-12% of all malignant salivary gland tumors

Epidemiology
- Sex: Female > Male (1.5:1)
- Age: Wide range
  - Mean: 5th decade
  - 2nd most common malignant salivary gland tumor in children (after MEC)
- Presentation:
  - Slowly growing mass
  - Vague pain – usually for years

Site
- Parotid gland most common (95%)
  - Parotid is largest salivary gland, comprised nearly exclusively of serous type acini
- Minor salivary glands 2nd most common site (but in doubt: may be MASC, CATMSG)
  - Intraoral, buccal mucosa, upper lip, and palate specifically (5%)
- Most common bilateral salivary gland malignancy
  - Dwarfed by bilateral Warthin tumor and pleomorphic adenoma
Macroscopic

- Circumscribed, solitary oval to round masses
  - Occasionally ill defined with irregular periphery
  - Not usually encapsulated
- Cut surface is lobular and tan to red
- Solid to cystic (hemorrhagic)
- Size: Mean: 1 – 3 cm

Microscopic Findings

- Specific pattern is the dominant or only finding
  - Solid, microcystic, papillary-cystic, follicular
  - However, combinations and spectrum are common
- Frequent extension into the adjacent normal parenchyma
**Patterns of Growth**

- **Solid, lobular or nodular pattern**
  - Blue dot tumor: Basophilic, granular cytoplasm

- **Small spaces in microcystic pattern**
  - Yields lattice-like or sieve-like appearance

- **Large cysts with papillary projections**
  - Complex papillae within cystic spaces
  - Vascular and hemorrhagic with cytoplasmic hemosiderin
  - “Hobnail” or “tombstone row” luminal cells

- **Follicular pattern**
  - Cystic spaces filled with eosinophilic proteinaceous material
### Cell types

- **Serous acinar cells**: Large, polygonal cells with abundant lightly basophilic, granular cytoplasm
  - Strong resemblance to normal serous acini cells
  - Dense, gray to blue to purple, fine to coarse zymogen granules

- **Intercalated duct type cells**: Surround luminal spaces and tend to be smaller, eosinophilic to amphophilic cells with central nuclei

- **Nonspecific glandular cells**: Round to polygonal, often syncytial, and smaller than acinar cells
  - Amphophilic to eosinophilic cytoplasm without granules

- **Clear cells** have nonstaining cytoplasm with prominent cell borders (no glycogen)

- **Vacuolated cells** have clear, large cytoplasmic vacuoles
  - PAS and mucicarmine negative

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<thead>
<tr>
<th>Image 1</th>
<th>Image 2</th>
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<th>Image 3</th>
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<tr>
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<td><img src="image4.jpg" alt="Image" /></td>
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</table>
Microscopic Findings

- Lymphoid infiltrate, sometimes prominent with germinal center formation, can be seen
  - “Tumor-associated lymphoid proliferation” (TALP)
  - May simulate a lymph node (not metastasis)
  - Very difficult on frozen section: can be confused with metastatic disease
  - DO NOT DIAGNOSE metastatic tumor unless level III or IV lymph nodes
- Stromal fibrosis or desmoplasia is uncommon
- High-grade transformation (dedifferentiation) into high-grade carcinoma (including small cell carcinoma) heralds poor prognosis

Special Studies

- PAS(+), diastase-resistant zymogen granules
  - Reaction can be patchy and limited
  - No glycogen identified
- Immunohistochemistry
  - DOG-1 and SOX-10 reactive
- EM shows round, electron dense secretory granules
  - Rough endoplasmic reticulum usually present
Management and Prognosis

- Complete surgical excision
  - Radiation only for incompletely excised tumors or advanced stage disease
- Recurrences in ~35% of cases (within 5 years)
- Generally, excellent prognosis
  - 20-year survival is 90%
- Poor prognosis:
  - Large size, deep lobe involvement, incomplete resection, multiple recurrences, lymph node metastasis
  - High grade transformation (40 vs. 125 months)

Differential Diagnosis

- Normal salivary gland
  - Lobular, with striated and interlobular ducts, acini, and adipocytes
  - Very well-differentiated tumors may be difficult to diagnose on core needle biopsy specimens
- Cystadenocarcinoma
  - Arranged in papillary and microcystic pattern
  - Lacks zymogen granules (acinar cells), vacuolated cells, and intercalated ductal differentiation
- Secretory carcinoma
  - Similar to papillary-cystic pattern
  - Positive: Mammaglobin; S100 protein; MUC1; MUC4; STAT5a

Case #9 (3032)

- 77 year old
- Female
- A 6 month history of a slowly growing mass in the parotid gland
- Noted increased size recently

Secretory Carcinoma

- Where did the tumor come from?
  - Acinic cell carcinoma
    - 12% on re-review were MASC
  - Adenocarcinoma, NOS
    - 38% on re-review were MASC
  - Other ductal derived tumors
Secretory Carcinoma

Secretory carcinoma is a generally low-grade salivary carcinoma characterized by morphologic resemblance to its mammary counterpart and an ETV6 associated gene fusion.

- **Mammary Analogue Secretory Carcinoma**
- Resembles acinic cell carcinoma but lacks well developed acinar differentiation
- **Age:** Middle aged (mean, 46 years)
- **Sex:** Equal distribution
- **Site:** Major salivary glands (71% parotid)
  Oral cavity (19%); Submandibular (7%)

- **Lobulated growth**
- Possible invasion into parenchyma
- Microcystic to glandular appearance
- Eosinophilic, homogenous or bubbly secretory (colloid-like) material in the lumen
- Vesicular nuclei with finely granular chromatin but distinct centrally placed nucleoli
- Ample pale pink, granular or vacuolated cytoplasm
- Pleomorphism is limited
- Mitoses are rare
- Lacks serous acinar differentiation

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23rd Seminar in Pathology-Allegheny Health Salivary Gland
Secretory Carcinoma

- **Positive:** Mammaglobin, S100 protein, CK7, STAT5a, MUC1, MUC4
- **Variable:** GCDFP-15, EMA, CD117
- **Negative:** DOG1, p63, calponin, CK14, smooth muscle actin, CK5/6

- **Ki-67 index:** Usually 5% (up to 30%)
Secretory Carcinoma: Molecular Findings

- **Definitional** specific recurrent balanced chromosomal translocation
  - \( ETV6-NTRK3 \) fusion transcript at \( t(12;15)(p13;q25) \)
    - \( ETV6 \) on chromosome 12
    - \( NTRK3 \) on chromosome 15
    - Transcriptional regulator fuses with membrane receptor kinase, activates kinase through ligand independent dimerization, promoting cell proliferation and survival
  - Chimeric tyrosine kinase identical to secretory breast carcinoma (triple negative, basal phenotype), mesoblastic nephroma and infantile fibrosarcoma

How to Detect Translocations

- DNA based PCR testing
- RNA based RT-PCR testing
- Fluorescent in situ hybridization (FISH)

Expression of \( ETV6-NTRK3 \) fusion transcript detected by RT-PCR (2: + case; 3: + control)

Sequence analysis of \( ETV6-NTRK3 \) fusion transcript (translocation breakpoint)
Green and Red show break apart
[VYSIS LSI ETV6 (Tel) (12p;13)]

Secretory carcinoma
Prognosis and Predictive Behavior

- Lymph node metastases in about 20%
- Local recurrence is about 18%
- Distant metastases in about 4%
- Disease free survival: 7.5 years
  - Only about 6% have died with disease
- Clinical stage and high grade transformation are poor prognostic markers

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WHO histological classification of tumours of the salivary glands

<table>
<thead>
<tr>
<th>Benign epithelial tumours</th>
<th>Carcinoma ex pleomorphic adenoma</th>
<th>Carcinosarcoma</th>
<th>Metastasizing pleomorphic adenoma</th>
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</thead>
<tbody>
<tr>
<td>Pleomorphic adenoma</td>
<td>8941/0</td>
<td>8990/3</td>
<td>8940/1</td>
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<tr>
<td>Myoepithelioma</td>
<td>8920/0</td>
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Pleomorphic Adenoma
Clinical

- Most common salivary gland neoplasm
- Age: 30 – 60 years
- Sex: F = M
- Site: Parotid most common site
  - 75% superficial lobe; 25% deep lobe
  - Palate next most common
- Tumor may be multinodular
- Tumor has “pseudopods” that bulge outwards
- Margins are difficult to assess
  - Tumor without parotid tissue surrounding it
  - The capsule may rest on the nerve(s)
Case #10 (3157)

- 73 year old
- Male
- A neck mass for the past 6 years
- Recently thought it was larger and bothered him while shaving
Carcinoma Ex-Pleomorphic Adenoma Demographics

- About 6 – 10% of PA develop carcinoma
  - Represents about 12% of all salivary malignancies
  - About 4% of all salivary gland tumors
- Must have pre-existing PA
  - Only clinical history is some cases
  - Long history of PA or frequent recurrences
    - Risk of 1.5% at 5 years
    - 10% at 15 years

Carcinoma Ex-Pleomorphic Adenoma Clinical

- Age: Elderly (usually >60 yrs.)
- Sex: M = F
- Site: Majority in major glands
  - 2/3 in parotid
- Sudden enlargement, with/without nerve symptoms

Carcinoma Ex-Pleomorphic Adenoma Pathology

- Large tumors
  - Must have adequate sampling
- Malignant component adjacent to benign
- Often poorly differentiated carcinoma
  - Salivary duct carcinoma common
- Infiltrative pattern
- Remarkable cytological atypia
- Scarring and sclerosis is common
  - Presence in PA requires additional evaluation

Courtesy Dr. Roman Carlos
<table>
<thead>
<tr>
<th>Classification</th>
<th>\textbf{Carcinoma Ex-Pleomorphic Adenoma}</th>
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<tbody>
<tr>
<td>\textbf{Subclassified (prognostic significance)}</td>
<td>\textbf{Classification}</td>
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<td>\item Non-invasive</td>
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<tr>
<td>\item Intracapsular, \textit{in situ}, dysplastic PA</td>
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<tr>
<td>\item Minimally invasive ($&lt; 1.5$ mm)</td>
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<tr>
<td>\item Invasive ($&gt; 1.5; 3; 6; 8$ mm)</td>
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**Recurrences:**
- Up to $70\%$ show regional and/or distant metastases
- Lungs, bone, brain or liver

**Histological Images:**
- Images of tissue sections showing various stages and types of lesions.
Salivary Duct Carcinoma (SDC) Definition

- Aggressive malignant epithelial neoplasm histologically resembling high-grade mammary ductal carcinoma
- Approximately 10% of malignancies
- Age: Older, with peak in 7th decade
- Sex: Male > Female (2-4:1)
- Site: Parotid gland >>> other sites (rare in minor salivary glands)
- Presentation: Recent rapid growth
- Nerve issues: Facial nerve paresthesia, pain, paresis, paralysis

Salivary Duct Carcinoma (SDC) Macroscopic Features

- Unencapsulated and poorly circumscribed
  - Extraglandular spread
  - Infiltration of adjacent parenchyma
- Multinodularity is common
- Cysts and foci of necrosis are frequently seen
- Fibrosis is often prominent
- Concurrent/preexisting pleomorphic adenoma may be seen
- Size: Average: 3.5 cm (up to 12 cm)

Carcinoma Ex-Pleomorphic Adenoma

- Pathologic stage
- Size
- Histologic grade and type
- Proportion of carcinoma
- Extent of invasion
- Ki-67 labeling index
Salivary Duct Carcinoma (SDC) Histologic Features

- Comedonecrosis is conspicuous
- Perineural invasion (60%); Vascular invasion (31%)
- Marked, dense, desmoplastic (hyalinized) fibrosis
- High mitotic index
- Small tumor nests infiltrate between larger nodules
  - Nonneoplastic glandular parenchyma is absent between nodules
- Variably sized, rounded, solid or cystic nodules resembling ductal carcinoma of the breast
- Cells are arranged in cribriform, band-like solid, and papillary patterns
  - "Roman bridge" architecture is classic
Salivary Duct Carcinoma (SDC)

**Histologic Features**

- Variably sized, rounded, solid or cystic nodules of tumor resembling ductal breast carcinoma
- Cells are arranged in cribriform, band-like solid, and papillary patterns
  - "Roman bridge" architecture is classic
- Moderate to marked pleomorphism
- Cuboidal to polygonal
- Ample eosinophilic, granular, oncocytic cytoplasm
- Large, prominent nucleoli and hyperchromatic chromatin
Variants

- Sarcomatoid
  - Biphasic neoplasm composed of both SDC and sarcomatoid (spindle cell) elements
  - Invasive Micropapillary
    - Invasive micropapillary architecture, apocrine snouts or globules
- Mucin-rich
  - SDC with malignant cell nests floating in pools of extracellular epithelial mucin
- Osteoclast-type giant cell
  - Osteoclast-like giant cells resembling giant cell tumor of bone
- Intraductal carcinoma (low grade)

### Micrographs

1. Sarcomatoid neoplasm
2. Invasive micropapillary architecture
3. Mucin-rich SDC
4. Osteoclast-type giant cell
5. Intraductal carcinoma
6. p63 staining
Immunohistochemistry

- **Positive:**
  - Epithelial markers (including CK7)
  - Androgen receptor, HER-2/neu (40-50%)
  - GCDFP15
- **Negative:**
  - p63
  - CK5/6

[Images of CK-pan, CK7, AR, Her-2/neu, p63]
Differential Diagnosis

- **Cystadenocarcinoma:**
  - Predominantly papillary, cystic tumor, with low-grade cytologic features, absent comedonecrosis and lacks infiltration

- **Oncocytic Carcinoma**
  - Abundant, granular eosinophilic cytoplasm, but lacks cystic, papillary, and cribriform patterns, usually absent comedonecrosis

- **Mucoepidermoid Carcinoma, High Grade**
  - Lacks prominent papillary or cribriform patterns, shows goblet cells, epidermoid and transitional cells; positive with p63, CK5/6, p40

- **Metastatic Squamous cell Carcinoma**
  - Prominent lymphoid reaction, squamous differentiation, keratinization, lacks comedonecrosis; positive with p63, CK5/6, p40

Treatment and Outcome

- Aggressive multimodality therapy required
- Surgery (including lymph node dissection)
- Radiation
- Androgen deprivation therapy and chemotherapy
- Poor prognosis overall (< 35% 5-year survival)
  - Local recurrences in up to 50%
  - High lymph node and distant metastases (up to 70%)