*Navigating the Landscape of Salivary Tumors: Unraveling Complex Entities*

**Introduction**

A diverse array of neoplasms originates within the salivary glands, which are known for displaying the most intricate and varied histopathology among all organs in the body. These types of tumors, however, remain relatively uncommon. Specifically, their yearly frequency in the United States hovers around 2.2 to 2.5 cases per 100,000 people. To put this into perspective, they constitute merely 2% of all neoplasms found in the head and neck area.

Among these cases, the distribution is as follows: approximately 80% of these tumors arise within the parotid glands, while 15% take root in the submandibular glands. The outstanding 5% are found in the sublingual and minor salivary glands combined. Furthermore, when it comes to the nature of these neoplasms, roughly 80% of parotid gland tumors are benign, along with 50% of submandibular gland tumors. In contrast, benign neoplasms account for less than 40% of sublingual and minor salivary gland tumors.

**BENIGN NEOPLASMS**

***PLEOMORPHIC ADENOMA***

* Name derived Greek term *pleos =* many; *morphus=* form.
* Benign mixed tumor of salivary glands because of heterogeneous nature of its histologic appearance

Term suggested by Willis

* Accounts for 2/3 of all salivary tumors.
* It affects parotid - 90% are superficial to facial nerve.

Grossly this tumor has well defined capsule macroscopically



***Histogenesis***

1971, Eversole proposed two theories:

* Pluripotential unicellular theory
* Semipluripotential bicellular theory.

Darkick proposed;

Multicellular theory.

***Pluripotential Unicellular Theory:***

According to the pluripotential unicellular theory, the excretory duct reserve cell possesses the ability to generate squamous or epidermoid elements, as well as intercalated-like cells.

***Semipluripotential Bicellular Theory:***

The semipluripotential bicellular theory proposes that the basal cells of the excretory duct and the luminal progenitor cells of these basal cells primarily drive the development of intercalated, striated, and acinar units. The intercalated duct units are formed by the basal cells, and the luminal progenitor cells of these basal cells contribute to the creation of intercalated duct units.

***Multiple Cellular Theory:***

Under the multiple cellular theory, various cell types present in a typical salivary gland could potentially give rise to the different types of tumors that occur in these tissues. Hubner and colleagues have proposed that myoepithelial cells are accountable for the diverse morphology of the tumors, including the formation of fibrous, mucinous, chondroid, and osseous areas. Regezi and Batsakis proposed that the intercalated duct reserve cell can distinguish into both duct and myoepithelial cells. Furthermore, myoepithelial cells can undergo mesenchymal metaplasia.

***Gross Pathology:***

It typically manifests as a smooth or lobulated mass. This well-encapsulated tumor exhibits distinct demarcation from the surrounding normal salivary gland tissue. Typically, these tumors present a solid consistency and may contain regions of gelatinous myxoid stroma.

Microscopic Characteristics:

Microscopically, pleomorphic adenoma is characterized by variable extents of gland-like epithelium and mesenchymal stroma. Within the epithelial component, a range of growth patterns can be observed, spanning from small nests and solid sheets to ductal structures and anastomosing trabeculae. The stromal component, on the other hand, can exhibit myxoid, chondroid, fibroid, or osteoid characteristics. A defining microscopic feature of pleomorphic adenoma is the presence of incomplete encapsulation and the growth of tumor pseudopods that extend beyond the tumor's boundaries.

Macroscopic Presentation:

Grossly, these tumors are encapsulated, but they might display finger-like projections, often referred to as "pseudopodia." These projections are associated with a heightened recurrence rate. The tumors are essentially a mix of epithelial and mesenchymal components, earning them the term "mixed tumor." Notably, the epithelial component showcases remarkable diversity, potentially exhibiting combinations of ductal, squamous, clear, spindled, oncocytic, and mucous cells. This remarkable diversity is what lends the tumor its "pleomorphic" designation. Meanwhile, the mesenchymal components can take on various characteristics, including hyalinized, myxomatous, chondromatous, and even osseous features.

***Diagnostic dilemmas***

* Distinctive histopathology pleomorphic nature.

Chondroid syringoma which is a mixed tumor of the skin, is a firm nodule and has predilection for head and neck area. If occurs over salivary glands mimic salivary tumor.

* Cribriform areas on histology mimic tumor as adenoid cystic carcinoma but with adequate tissue specimen. Pleomorphic areas are distinctive
* Development of carcinoma in pleomorphic adenoma is another diagnostic concern but focal areas of malignant degeneration are usually evident.

***Management***

Treatment of Pleomorphic Adenomas:

The primary treatment for pleomorphic adenomas involves complete surgical excision, ensuring a margin of normal tissue around the tumor. This typically entails superficial parotidectomy while preserving the facial nerve in cases of parotid tumors. For submandibular gland tumors, excision is performed, and a wide local excision is undertaken for minor salivary gland tumors. It's worth noting that previous instances of simple enucleation have demonstrated high rates of local recurrence, making this approach something to be avoided. Additionally, recurrence might stem from capsule rupture and tumor spillage, thus underscoring the importance of meticulous dissection to prevent such occurrences.

Warthin's Tumor:

- Overview:

Warthin's tumor, also recognized as Papillary Cystadenoma Lymphomatosum or Adenolymphoma, comprises a notable proportion, ranging from 5% to 14%, of parotid neoplasms, thereby establishing it as the second most prevalent benign tumor in this anatomical region. The precise pathogenesis of this tumor remains a subject of ongoing investigation; however, current theories propose that it may originate either from heterotrophic salivary gland tissue located within the parotid lymph nodes or from the proliferation of ductal epithelial cells of the salivary gland, subsequently leading to the secondary development of lymphoid tissue. Importantly, individuals who smoke exhibit an eightfold elevated risk of developing this tumor, and it has also been associated with the Epstein-Barr Virus (EBV).

- Clinical Features: Warthin's tumor typically manifests as asymptomatic, slow-growing nodular mass. It can manifest as either firm or fluctuant. The tail of the parotid gland is a common site for its occurrence. One unique characteristic is its bilateral presence (5-14%), while it's relatively rare in submandibular or lingual glands. It predominantly affects older Caucasian males in their 6th to 7th decade of life.

- Gross Pathology:

Grossly, Warthin's tumor is encapsulated with a smooth or lobulated surface. It often contains cystic spaces of varying sizes, housing turbid fluid, caseous debris, and tenacious mucoid material accompanied by shaggy epithelium. Solid areas with white nodules representing lymphoid follicles can also be observed.

- Management: Surgical excision is the mainstay of management for Warthin's tumors. While malignant transformation is rare, studies indicate instances of squamous metaplasia at 7.5%. Notably, recurrence rates have been demonstrated at 12% by Synodeman and Johnson. The ideal conduct is superficial parotidectomy with facial nerve preservation, but in select cases, enucleation of the tumor may also be considered.

***Oncocytoma***

* Composed of large epithelial cells known as ONCOCYTES
* Constitutes 1-2% of all salivary tumors.

***Clinical Features***

* Tumor of elderly - 8th decade
* Female predilection.
* Major salivary glands = parotid⎝80-90%
* Firm, slow growing, painless mass. Rarely >4cm.

***Gross***

* Encapsulated
* Homogeneous, smooth
* Orange/rust color

Grossly, it is a homogenous tumor with smooth surface which may be divided into lobules by fibrous tissue septae.

***Histology***

Well circumscribed, with Large sheets of polyhedral cells.

* Granular, eosinophilic cytoplasm.
* Granular appearance is due to abundance of mitochondria.
* Cords of even cells and thin fibrous stroma
* Distinct cell membrane
* Central, round, vesicular nucleus.

Special staining procedures such as the Bensley’s aniline-acid fuchsin or phosphotungstic acid hematoxylin stain, or Luxol-fast-blue reaction are helpful in making the diagnosis of oncocytoma. Electron microscopy can also be done.

***Management***

* Best treated by surgical excision.
* Partial parotidectomy (lobectomy) and for submandibular gland ⎝ total gland removal.
* Minor salivary gland oncocytomas may be excised with small margin of normal tissue.
* Good prognosis and low recurrence rate.

There are examples of malignant oncocytoma, which though are very rare and have poor prognosis.

**Myoepithelioma:**

Myoepithelioma constitutes an exceedingly rare portion, accounting for less than 1% of all salivary gland neoplasms. These tumors are primarily observed in the minor salivary glands, parotid glands, palate, and occasionally in the submandibular glands. Much like pleomorphic adenomas, myoepitheliomas tend to manifest around the 5th decade of life, with a preference for females. Clinically, they present as asymptomatic, slow-growing masses that are well-circumscribed. Grossly, myoepitheliomas resemble pleomorphic adenomas but lack the myxoid stroma.

Microscopic Features:

Three distinct patterns have been identified in myoepitheliomas: the spindle cell pattern, the plasmacytoid pattern, and a combination of both spindle cell and plasmacytoid patterns. The spindle cell pattern is the maximum prevalent and is particularly common in parotid myoepitheliomas. The plasmacytoid pattern, on the other hand, is less frequent but is encountered most often in palate tumors. The third pattern is uncommon. Generally, m

yoepitheliomas exhibit a benign behavior.

The recommended treatment is complete surgical excision.

**Malignant Neoplasms:**

Malignant salivary tumors are outstripped by benign tumors at a ratio of about three to one. However, this generalization might not hold true for site-specific descriptions; for instance, parotid tumors are typically benign (75%), while sublingual tumors tend to be malignant (75%).

There are four primary types of malignant salivary gland tumors: mucoepidermoid carcinoma, adenocarcinoma (NOS), acinic cell carcinoma, and adenoid cystic carcinoma.

Clinically, the malignant nature of these tumors is not readily apparent, and they, too, often produce asymptomatic swellings.

Prognostic guidelines for salivary malignancies are sturdily predisposed by the stage of the tumor. Generally, higher stages correlate with worse prognoses.

High-grade carcinomas tend to be more aggressive compared to low-grade carcinomas.

The location of the tumor often influences clinical outcomes. For instance, submandibular gland carcinomas generally have a worse prognosis than parotid tumors.

Extended follow-up is essential to assess the potential for recurrence, which may require monitoring for up to 20 years.

**Adenoid Cystic Carcinoma**

* Term coined by Foote & Frazell in 1953. Originally called as cylindroma
* 2nd most salivary malignancy, 5-10% of major & 35% of minor
* 40-60% of sublingual gland.
* M=F, mean age of occurrence 45yrs.

Painless mass with 20% cases of paresthesia, & 30% CN VII palsy.

Tumor has highest propensity for neural invasion.hallmark of this tumor.

***Gross Pathology:*** Typically well-circumscribed. Mainly solid in nature, occasionally with cystic spaces. Can display infiltrative characteristics.   
Clinical Behavior:

Paradoxical clinical behavior: Slow tumor growth, but relentless and progressive clinical course. Surgical intervention is often feasible, yet multiple local recurrences are the norm.

Lymph node metastasis is uncommon, whereas distant spread occurs frequently.

Five-year survival rates seem optimistic, but 10 to 20-year survival rates are disappointingly low.

Histology - Cribriform Pattern:

Most common histological pattern.

Presents a "Swiss cheese" appearance.

Histology - Tubular or Trabecular Pattern:

Exhibits a more glandular architecture.

Features layered cells forming duct-like structures.

Presence of basophilic mucinous substance.

Histology - Solid Pattern:

Characterized by solid nests of cells lacking cystic or tubular spaces.

Minimal or no luminal spaces.

Management:

Lymphatic spread is rare, occurring in only 17% of cases.

Recurrence can manifest even up to 20 years later.

The tumor's nature is unrelenting, prone to recurrence, and predisposed to distant metastasis, with the lungs being the most common site.

Wide surgical excision is the preferred treatment.

The prognosis varies based on histological subtype:

Tubular variety tends to have a favorable prognosis.

Solid subtype has a worse prognosis.

According to Eneroth et al., the 10-year survival rate is zero for the solid type and 62% for the cribriform type.

Neural invasion can occur in an antegrade or retrograde manner.

***Acinic Cell Carcinoma***

It was classified as benign adenoma until 1953.

* Many authors now believe this tumor as malignant but with low potential,
* Vast majority occur in parotid- 2nd most common site in oral cavity.
* 2-5% of all salivary tumors.
* In 3% of cases shows bilateral involvement
* 30-60yrs of age with M:F ratio = 1:2.

***Gross pathology:***

* Uncapsulated,
* Well-demarcated
* Most often homogeneous
* Cut surface = britlle, gray-white color,
* May be solid or cystic.

Microscopically seven variety of patterns are described;

* 1. acinar-lobular, 2. microcystic, 3. follicular, 4. papillary cystic,
* 5. medullary, 6. ductoangular, and 7. primitive tubular.
* 30% of histologic component⎝ lymphoid, and hence like Warthin’s tumor appears to arise from lymphnodes in the glands.
* Calcifications may be seen.

Composed entirely of serous elements.

***Histology***

* Solid sheets
* Numerous small cysts
* Polyhedral cells
* Small, dark, eccentric nuclei
* Basophilic granular cytoplasm

***Management***

* Complete local excision.
* +/- postoperative RT (doubtful benefits following RT)

***Mucoepidermoid Carcinoma***

***Clinical Features:***

* 10% of all major salivary tumors & 10-15% of minor salivary tumors.
* Occurs at all ages but rare in first decade.
* Most common malignancy of children,
* Asymptomatic swelling.
* High grade tumors⎝CN VII palsy & pain.
* Affects minor glands in palate.
* May be fluctuant, bluish to red color.

***Histology***

* + - * Mucous-producing cells and epidermoid cells.
  + Mucous cells - foamy cytoplasm.
* Epidermoid cells - squamoid features, polygonal cells, with intercellular bridges.
* Sometimes third type cells- intermediate cells.
  + Progenetor of mucous & epidermoid cells.
* Also described to have varied six celluar patern
  + 1. maternal cell, 2. intermediate cells, 3. epidermoid cell, 4. clear cell, 5. columnar cell & 6. mucous cell.
* Generally lacks the capsule
* Auclair, Goode & Ellis; in 1992 & 1998; gave ***histologic predictors for prognosis;***
* Cystic component (20% or less=good prognosis)
* Tumor necrosis
* Neural invasion,
* Cellular anaplasia and,
* Mitotic activity.

Histologically tumors are categorized on basis of;

* Amount of cyst formation.
* Degree of cytologic atypia
* Relative numbers of mucous, epidermoid, and intermediate cells.
* Histology - Low-grade
* Mucus cell > epidermoid cells
* Prominent cysts
* Mature cellular elements
* Histology— Intermediate- grade
* Mucus = epidermoid
* Fewer and smaller cysts
* Increasing pleomorphism and mitotic figures
* Histology— High-grade
* Epidermoid > mucus
* Solid tumor cell proliferation
* Mistaken for SCCA

***Management***

* Influenced by site, stage, grade  
  Stage I & II
  + Wide local excision.
  + Parotid = subtotal parotidectomy with CN VII preservation.
  + Submand = total gland removal.
  + Minor glands = wide excision.
  + Margins = low grade min, high grade wide approx. 3mm+
* Stage III & IV
* Radical excision, total parotidectomy, submand gland removal, and bone resection if involved etc.
* +/- neck dissection for suspected metastasis or high grade tumors.

+/- postoperative radiation therapy for more aggressive tumors.