*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 annual incidence 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 region.

Among these cases, the distribution is as follows: approximately 80% of these tumors occur within the parotid glands, while 15% take root in the submandibular glands. The remaining 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. Additionally, the basal cells of the excretory duct are responsible for the development of all other salivary elements.

***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, any of the various cell types present in a normal salivary gland could potentially give rise to the different types of tumors that occur in these tissues. Hubner and colleagues have suggested that myoepithelial cells are responsible 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 differentiate into both duct and myoepithelial cells. Furthermore, myoepithelial cells can undergo mesenchymal metaplasia.

***Gross Pathology:***

The gross appearance of pleomorphic adenoma 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.

Except in large and long-standing lesions, we may rarely see Cystic degeneration or tumor infarction and necrosis .

* Smooth
* Well-demarcated
* Solid
* Cystic changes
* Myxoid stroma
* Intra-oral accessory glands not >1 to 2 cm in size
* Difficulties in mastication, speech,

Microscopic Characteristics:

Microscopically, pleomorphic adenoma is characterized by varying proportions 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 known as Papillary Cystadenoma Lymphomatosum or Adenolymphoma, constitutes 5-14% of parotid neoplasms, positioning it as the second most common benign tumor. Its exact pathogenesis remains uncertain, but it is thought to arise either from heterotrophic salivary gland tissue within the parotid lymph nodes or from the proliferation of salivary gland ductal epithelium that prompts secondary formation of lymphoid tissue. Notably, smokers exhibit an eightfold greater risk of developing this tumor, and it's associated with the Epstein Barr Virus (EBV).

- Clinical Features:

Warthin's tumor typically presents as a painless, 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.

- Histology:

Histologically, the tumor displays epithelial cells forming papillary projections into cystic spaces intertwined with lymphoid stroma. The epithelium comprises a double cell layer, with tall columnar cells lining the cystic spaces and cuboidal cells adjacent to the basement membrane. The nuclei of the columnar cells face the cystic space, while the cuboidal cell nuclei align with the basement membrane. Additionally, the stroma features mature lymphoid follicles boasting germinal centers, and focal areas of metaplasia may appear.

- 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 preferred treatment 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 uniform 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 predilection 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 most 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, myoepitheliomas exhibit a benign behavior.

The recommended treatment is complete surgical excision.

**Malignant Neoplasms:**

Malignant salivary tumors are outnumbered 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 in order of frequency: 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 strongly influenced 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.

***Gross pathology***

* Well-circumscribed to partially encapsulated to unencapsulated
* Solid tumor with cystic spaces

On gross examination, some mucoepidermoid carcinomas appear well-circumscribed and may be partially encapsulated or unencapsulated while others are poorly defined and infiltrative. The cut surface of the tumor may contain solid areas or cystic areas or both. The cystic spaces comprehend viscous or mucoid material.

***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

**SALIVARY GLAND NEOPLASMS OF PARAPHARYNGAEL SPACE.**

Tumors in the Parapharyngeal Space:

The most prevalent tumors emerging within the parapharyngeal space (PPS) typically originate from salivary glands, encompassing 40-50% of PPS lesions. These specific tumors are generally situated in the prestyloid PPS region. The source of these tumors may include the deep lobe of the parotid gland, ectopic salivary gland nests, or even the minor salivary glands located within the lateral pharyngeal wall. Intriguingly, while the occurrence rate of tumors in the deep lobe of the parotid gland is comparable to that in the superficial lobe, only a small fraction of deep lobe parotid tumors extend into the parapharyngeal space.

Common Prestyloid PPS Lesion: Pleomorphic Adenoma

Pleomorphic adenoma stands out as the predominant lesion within the prestyloid parapharyngeal space, constituting about 80-90% of salivary neoplasms in this region. Other benign salivary lesions, such as Warthin's tumor and oncocytomas, are also found in the prestyloid PPS, alongside malignant salivary lesions.

Malignant Salivary Lesions:

Malignancies affecting the prestyloid PPS include notable entities like carcinoma ex pleomorphic adenoma, wherein carcinoma develops atop a preexisting pleomorphic adenoma, and adenoid cystic carcinoma. These two malignancies are among the most frequently reported within the PPS. In fact, approximately 20% of all salivary lesions identified in the PPS demonstrate malignant characteristics.

The figure below showing MRI imaging of the deep lobe of the parotid tumor.

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*Axial T1W (a) and T2W (b) MR scans show a slightly dumbbell-shaped left deep lobe parotid begin mixed tumor. The mass lies anterior to the internal carotid artery (arrow-head). Note that there is no fat plane between the posterolateral margin of the tumor and the parotid gland*

**Malignant Mixed Tumors:**

Malignant mixed tumors represent the malignant counterparts of their benign counterparts. These tumors comprise a modest 2-6% of all salivary tumors, falling into three primary categories: Carcinoma Ex Pleomorphic Adenoma, Carcinosarcoma, and Metastasizing Mixed Tumor.

**Carcinoma Ex Pleomorphic Adenoma:**

The most prevalent within these categories is Carcinoma Ex Pleomorphic Adenoma, characterized by the transformation of the epithelial component of a benign pleomorphic adenoma into a carcinoma. The other two tumors in this class, carcinosarcoma and metastasizing mixed tumor, are relatively rare. In carcinosarcoma, both stromal and epithelial elements are present in metastatic lesions, differing from carcinoma ex pleomorphic adenoma where only epithelial elements are found in metastases. Carcinoma Ex Pleomorphic Adenoma accounts for about 3.6% of all salivary neoplasms. Typically, it occurs in the 6th to 8th decade of life, primarily in the parotid, followed by the submandibular gland and palate. Clinical presentation often involves a painless mass, sometimes with recent rapid enlargement of a long-standing nodule. Pain, skin adherence, and facial weakness are common. The risk of malignant change in pleomorphic adenoma rises from about 1.5% in the first five years to 9.5% for adenomas exceeding 15 years. Grossly, carcinoma ex pleomorphic adenoma appears as a poorly circumscribed, infiltrative, hard mass. Microscopically, malignant cells are found adjacent to a typical pleomorphic adenoma. The malignant portion can take the form of various epithelial malignancies, excluding acinic cell carcinoma. Most frequently, undifferentiated carcinoma (30%) or adenocarcinoma (25%) are observed. Around 25% of patients exhibit lymph node metastasis. The preferred treatment involves radical surgical resection often coupled with neck dissection and postoperative radiation therapy, with prognosis tied to disease extent and histologic variation.

**Carcinosarcomas:**

Carcinosarcomas, true malignant mixed tumors, are exceedingly rare, constituting only 0.05% of salivary gland neoplasms. Typically presenting around age 60, men and women are affected equally. The parotid gland is the primary site. Microscopically, these tumors encompass both sarcomatous and carcinomatous components. Sarcoma dominates, frequently as chondrosarcoma, while carcinoma often manifests as undifferentiated or high-grade ductal adenocarcinoma. This is an aggressive tumor type, often displaying distant metastasis. Treatment typically involves radical surgery, neck dissection for palpable nodes, and postoperative XRT, with potential chemotherapy due to high rates of distant metastasis.

**Squamous Cell Carcinoma:**

Primary squamous cell carcinoma of the salivary gland is incredibly rare, accounting for about 1.6% of salivary gland neoplasms. It's crucial to distinguish this diagnosis from high-grade mucoepidermoid carcinoma and exclude metastatic squamous cell carcinoma or direct extension of a squamous cell carcinoma. Generally presenting in individuals over 60, these tumors are typically firm, enlarging masses adhering to surrounding tissues, often accompanied by pain or facial weakness. Grossly and microscopically, they resemble squamous cell carcinoma of other primary sites, ranging from well-differentiated with keratinization to poorly differentiated without keratinization. Rapid growth and regional lymph node spread characterize these tumors, leading to surgical resection, neck dissection, and postoperative radiation in the treatment protocol.

**Clear Cell Carcinoma:**

Clear cell carcinoma, also known as glycogen-rich carcinoma, is rare, mostly found in minor salivary glands of the palate and the parotid. Generally, it presents in the 6th to 8th decades of life and equally affects males and females. Microscopically, these tumors exhibit uniform round or polygonal cells with clear cytoplasm and peripherally displaced dark nuclei. Tumors may grow in nests, cords, or solid sheets separated by fibrous stroma, often displaying local infiltrative growth. Being low-grade tumors, they are treated with complete local excision.

**Polymorphous Low-Grade Adenocarcinoma:**

Polymorphous low-grade adenocarcinoma (PLGA) is the second most common malignancy in minor salivary glands, often appearing in the palate, lip, and buccal mucosa. Typically emerging in the seventh decade of life, it is more prevalent in women (67%) than men. These tumors present as painless submucosal swellings that gradually enlarge, possibly causing ulceration and bleeding. On microscopic examination, PLGA displays a variety of growth patterns (solid, tubular, trabecular, glandular, cribriform, cystic), which can be observed within the same lesion or among different lesions. Although PLGA shows perineural and perivascular invasion tendencies, it follows a rather indolent course. Treatment primarily involves complete local excision, often without the need for postoperative radiation or neck dissection, as distant metastasis is rare.

**Epithelial-Myoepithelial Carcinoma:**

Epithelial-myoepithelial carcinoma comprises less than 1% of salivary gland neoplasms, primarily affecting those in their 6th and 7th decades of life, with a higher incidence in women. Predominantly located in the parotid gland, patients with these tumors seem to carry an increased risk of a second primary malignancy in the salivary glands or elsewhere (e.g., breast, thyroid). These tumors appear as well-circumscribed, multinodular firm masses with irregular cystic spaces upon gross examination. Microscopically, they exhibit a biphasic character with outer clear myoepithelial cells, inner cuboidal epithelial cells lining small duct-like structures, and a surrounding thickened basement membrane. Complete surgical resection is the primary treatment, as little is known about the potential benefits of adjuvant radiotherapy or chemotherapy due to the rarity of this tumor.

**Undifferentiated Carcinoma:**

Undifferentiated carcinomas are infrequent yet aggressive malignancies with poor prognoses, similar to other salivary gland tumors. Lymphoepithelial carcinoma of salivary glands is most prevalent in North American and Greenland Eskimos and Asians. Eskimos predominantly experience parotid gland involvement, often in a familial pattern, while Asians see a higher incidence in the submandibular gland, affecting men more frequently. Undifferentiated large-cell carcinoma typically affects individuals in their 6th and 7th decades or their 9th decade. Undifferentiated small-cell carcinoma mainly occurs in the parotid of individuals aged 50-70, with a male-to-female ratio of 1.6:1. All these malignancies have potential for local recurrence, regional, and distant metastasis. Treatment involves complete surgical excision, with neck dissection for palpable disease and consideration for postoperative radiation therapy and, in select cases, chemotherapy.

In sum, while the various malignant mixed tumors encompass rare and distinct entities within salivary gland neoplasms, a common thread is the imperative for thorough surgical resection and, in certain cases, adjuvant therapies to effectively manage the aggressive nature and recurrence potential of these malignancies.