# Histological Classification of Salivary Gland Tumors (WHO)

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While the clinical presentation of a salivary gland tumor (SGT) is usually an asymptomatic mass that may occasionally be ulcerated or cause pain, the histologic presentation is far more complex. The tumor spectrum is vast, and yet repetitive features may be seen in a variety of neoplasms with differing biologic behavior.

Developing salivary glands arise from the stomodeum as ectodermal buds that proliferate as cords into the underlying mesenchyme. The ends thicken to form terminal bulbs. These undergo branching, followed by continued advancement into the mesenchyme. This process repeats itself, all the while maintaining continuity with the oral epithelium. This branching process gives rise to the lobular architecture of the gland. The terminal tubular elements differentiate into acinar cells, & between the acinar cells & basal lamina (BL) MECs form. These are basket-shaped & stellate cells, which may appear as clear cells prior to the development of myofilaments. Intercalated & smaller striated ducts also differentiate from this area. The original cords & their branches become the excretory ducts.

The Histogenesis of SGTs has been controversial. Some suggested that SGTs arise from the reserve cell of intercalated duct or reserve cell (basal cell) of excretory duct (bi-cellular reserve cell hypothesis). Others however, propose that any of all cell types in normal salivary gland, including luminal/acinar as well as basal/MECs, have the potential to give rise to a variety of tumors differing in both morphology and biologic behavior (multi-cellular theory of tumor histogenesis). The complexity of SGTs is due in part to the fact that in most instances more than one cell type is involved. These may be acinar, luminal, MEC, basal, or squamous. Adding to this diversity, extracellular substances---BL, collagen fibers, elastic fibers, and glycosaminoglycans (GAG)---are a striking component of many SGTs. It is believed that these substances are probably secreted by the neoplastic basal/MECs. The cribriform variant of Adenoid cystic CA provides the prime example.

SGTs may involve major or minor glands. The largest number of cases is found within the parotid. While most types of tumors may be found in both sites, relative frequency can vary. Thus approximately 80% of parotid tumors are benign. In minor salivary glands, however, the benign-malignant ratio is closer to 1:1, while in the sublingual gland, an uncommon site for neoplasms, the majority is malignant.

The PA is the most common tumor both in major & minor salivary glands. Warthin tumors, basal cell adenomas, oncocytomas, ACAs, & sebaceous tumors have a strong predilection for the major gland, but the PLGA has a marked predilection for the minor glands. While most intraoral SGTs favor the palate, the canalicular adenoma favors the upper lip.

SGTs are predominantly of epithelial origin. However, it should be appreciated that non-epithelial neoplasms also may arise within the glands that are not actually of salivary gland or ductal origin. Most of these are found in the parotid gland. Among the more common benign tumors is the hemangioma, which is the most frequently occurring tumor in the parotid gland in children. Lipomas & neurogenic tumors also may be seen. Hodgkin and non-Hodgkin lymphomas & most infrequently, soft tissue sarcomas may develop. Metastatic tumors such as renal cell CA, thyroid CA, & melanoma may also occur.
1. Adenoma

1.1: Pleomorphic adenoma

A tumor of variable capsulation characterized microscopically by architectural rather than cellular pleomorphism. Epithelial & modified myoepithelial elements intermingle with tissue of mucoid, myxoid or chondroid appearance. The epithelial and myoepithelial components form ducts, strands, sheets or structures resembling a swarm of bees. Squamous metaplasia is found in about 25% of Pleomorphic adenoma.

The Pleomorphic adenoma (PA) is the most common neoplasm involving both the major and minor salivary glands. There is now universal agreement that the salivary gland PA is entirely of epithelial origin.

Clinical Features according to various studies, PA account for about 50 to 70% of all parotid neoplasms, 40 to 60% of all submandibular tumors, and 40-70% of minor salivary gland tumors.

The sublingual gland is seldom the site for salivary tumors. PA may develop in patients from a wide range of ages, but these tumors are most commonly diagnosed in patients between the ages of 30 and 50 years. (Means: 41.2 years) PAS are generally stated to be somewhat more common in females, with male-to-female ratios ranging from 1:3 to 1:4. The usual clinical presentation is that of a painless, slowly growing, firm mass. In the parotid gland, this tumor most often presents in the lower pole of the superficial lobe as a mass over the angle of the mandible, below and in front of the ear. In early development, parotid PAs are usually movable, but with continued growth, the tumor becomes more nodular and less movable. Recurrent PAs of the parotid gland are usually multi-nodular and appear clinically as multiple small nodules that may seem fixed on palpation.

Although PAs may arise in all sites where minor salivary gland tissue is present, the palate (54%), upper lip (18%), and buccal mucosa (11%) are the sites of most tumors occurring in the intra-oral salivary glands. Because the mucosa of the hard palate is tightly bound to the palatal bone, PAs of the hard palate are not movable; however, those in other sites generally are mobile. Palatal PAs usually are located laterally on the palate and seldom cross the midline. The majority of intra-oral PAs are less than 3 cm in diameter when they are excised. Most intra-oral PAs are surfaced by normal-appearing oral mucosa.

Gross Pathology

PAs appear as well-circumscribed, round to ovoid massed with smooth surfaces. The tumor is usually surrounded by a fibrous capsule of varying thickness, & clear demarcation between the tumor and the adjacent salivary gland tissue is present. (In the major salivary glands the tumors are usually encapsulated but in the minor glands they usually are not.) Cut section is usually solid and white, so-called cut potato surface & may contain variable areas of firmer, somewhat translucent, bluish tissue that correspond to the cartilage-like material seen microscopically. Sections from these tumors that are predominantly myxoid demonstrate a soft, somewhat gelatinous tissue.
Microscopic Findings

All PAs demonstrate combinations of gland-like epithelium and mesenchyma-like tissue, but the proportions of each vary widely. Some are predominantly myxoid with a scant epithelial-appearing component. Other lesions are chiefly cellular, and the characteristic myxochondroid tissue is present only in limited areas.

The epithelial-appearing component of a PA may take the form of ducts, small cellular nests, solid sheets of cells, anastomosing cords, and foci of either keratinizing squamous cells. Studies indicate that myoepithelial cells (MEC) is responsible for development of the characteristic myxoid and chondroid stroma. The modified MEC are usually polygonal in the solid sheets and may be spindle-shaped, or plasmacytoid. Ductal structures present in PAs resemble normal salivary gland intercalated ducts with lumina that are lined by a single layer of ductal epithelium surrounded by darker staining, angular MECs. The cartilaginous areas that are often present in PAs are the result of more extensive accumulation of mucoid material around individual MECs.

It has been suggested that cell-rich variants have a higher risk of malignant transformation and that cell-poor tumors have a higher risk of recurrence. The risk of recurrence is probably due to a variety of reasons, mainly related to the anatomical features of the tumor. Some are easily rupture during removal or extend into the surrounding tissue or others may show intra-capsular invasion.

1.2 Myoepithelioma (myoepithelial adenoma)

A rare tumor of MEC; several growth patterns occur; solid, myxoid & reticular. The cellular components are spindle-shaped, plasmacytoid (hyaline), and clear cells or combinations of these.

Tumors composed entirely or almost exclusively of MECs probably representing one end of the spectrum of PA and having a similar biologic behavior. It is uncommon, accounting for less than 1% of all salivary gland tumors. Unlike pleomorphic adenoma, it does not show (or very little) ductal differentiation. The parotid (40%) and palate (20%) are the sites of predilection. The histogenesis from myoepithelioma cells is reflected in their most frequent location, that is, the parotid gland, where MECs are more common. The age and sex distribution of myoepitheliomas is similar to that of PA. Similar to most other salivary gland tumors myoepitheliomas present as asymptomatic, slowly growing masses, and an intact overlying mucosa.

Macroscopically, myoepitheliomas appear as well-circumscribed, frequently encapsulated tumors that show no features distinct from PAs except for the absence of grossly myxochondroid or chondroid areas. Microscopically, they show three morphologic patterns. The spindle cell pattern (70%) is the most common and consists of a proliferation of spindle-shaped cells with eosinophilic cytoplasm. These may be arranged in diffuse sheets or interlacing fascicles. Little intercellular fibrous stroma of ground substance is present. The plasmacytoid pattern (17%), having a predilection for the palate, shows group of round
cells with eccentric nuclei and eosinophilic, often hyaline-appearing cytoplasm resembling plasma cells. A myxoid stroma may be present. The third and least common pattern (13%) shows a combination of plasmacytoid and spindle-shaped cells. The immunohistochemical demonstration of, cytokeratine, S-100 protein, actin or myosin is of practical value in defining MEC.

There is a close relationship between myoepithelioma and PA as both contain MECs. A criterion that may be used to separate the two lesions is that if the tumor contains less than a 5% of ducts and glands, it should be called a myoepithelioma.

1.3 Basal Cell Adenoma

A tumor of isomorphic basaloid cells with a prominent basal cell layer, a distinct basement membrane-like structure and no mucoid stromal component as in PAs. Four cellular patterns occur; solid, trabecular, tubular and membranous.(1% to 2%)

Basal cell adenomas are benign SGT that derives its name from the basaloid appearance of tumor cells. They are more common in the parotid gland (70%) than in oral mucosal sites. When they do occur in oral mucosa, they have a predilection for the upper lip and rarely occur in the palatal mucosa, in contrast to the PA, which frequently occurs within palatal mucosa and uncommonly in the upper lip. The lesions are painless, well-circumscribed masses that tend to be smaller (1 to 3cm) than most PAs. Equal sex distribution or more common in females, with some studies showing as high as a 2:1 and most occur in older adults (average age, 60 years).

Characteristic signs of basal cell adenoma

Pattern
---solid
---trabecular
---tubular
---membranous

Unicellular, isomorphic cell type
Prominent basal cell layer
Distinct basement membrane-like structures
Basisquamous whorling in globular ends of epithelial islands
Absence of mucoid stromal component

Age Peak: 7th decade
Frequency: 1-2 % of all salivary gland adenomas

Location
---parotid gland (70%)
---minor salivary glands (30%)
  --upper lip (80%)
  --palate (10%)
  --buccal mucosa /lower lip (10%)

Malignant transformation to basal cell adenocarcinoma
Characteristics of the membranous variant (dermal anlage type) of basal cell adenoma

Membranous pattern
- Palisade fashion of peripheral cell layers
- Excessive hyaline basal membranes
- Focal squamous metaplasia
- Intercellular hyaline deposits
- No infiltrative growth
- Multi-focal and multi-nodular development with ductal hyperplasia and micro-adenomas
- Common occurrence with dermal cylindroma / trichoepithelioma

Solid: It consists of uniform-appearing, generally small cells arranged in large compact aggregates in which the outer layer often is palisaded. In addition, intercellular deposits occur, as do focal squamous differentiation and basisquamous whorls in the epithelial islands.

Trabecular / Tubular: Have a major component of basaloid cell arranged in narrow, anastomosing bands or on the outer aspect of ductal structures. Combinations of both growth patterns to varying degrees are common. Even in the trabecular form glandular differentiation, i.e. an inner layer of slightly larger luminal cell, may be evident. Palisading of the epithelial nuclei along the stromal interface is less frequently than in the solid type and small dark cells are typically fewer. Many small lumens are evident within the trabecular cords of basaloid cells in this type and termed tubulo-trabecular type.

Membranous (dermal anlage type): is characterized by palisading of peripheral cells and an excessive hyaline basal membrane. Multi-focal and multi-nodular tumors may develop in parotid or also in the submandibular in the same patient, & also can association with dermal cylindroma, trichoepithelioma.

1.4 Papillary cystadenoma lymphomatosum (Warthin Tumor)

A tumor composed of glandular and often cystic structures, sometimes with a papillary cystic arrangement, lined by characteristic eosinophilic epithelium. The stroma contains a variable amount of lymphoid tissue with follicles.

Warthin’s tumor is a benign neoplasm that occurs almost exclusively in the parotid gland. (the 2nd most common benign parotid tumor, accounting for 5% to 14% of all parotid neoplasms.) The pathogenesis of these tumors is uncertain. The traditional hypothesis suggests that they arise from heterotopic salivary gland tissue found within parotid lymph nodes. However, it also has been suggested that these tumors may develop from a proliferation of salivary gland ductal epithelium that is associated with secondary formation of lymphoid tissue. Warthin’s tumor remains one of the most histologically recognizable salivary gland tumors, and is a classical example of those neoplasms in which both luminal
and non-luminal tumor cells differentiate. Smokers have an eightfold greater risk for Warthin’s tumor than do nonsmokers.

Male is predominantly and vast majority in parotid gland. Some early studies demonstrating a M-to-F ratio up to 10 to 1. (but now decreased to about 3 : 1 )The age peak is in the 6th and 7th decades. Warthin tumors are known to occur bilaterally (synchronously or metachronously) in about 4% to 6% of cases, or two or more tumors are known to occur simultaneously in the same gland (also synchronous tumors). The term papillary cystadenoma lymphomatosum is accurate but cumbersome. The surgical specimen is usually a spherical or oval mass that is covered by a thin capsule. Tumor consistency varies from fluctuant in specimens with a single large cystic space to firm and rubbery in more solid tumors with small multicystic. Solid white homogenous tissue and multiple white nodules throughout are corresponded to the lymphoid component. The lunina may contain clear, mucoid, or semisolid often brownish material.

Microscopically, the lining epithelium shows multiple papillary projections into cystic spaces and larger cystic spaces consist of epithelial cells covering fibrovascular cores, some of which contain variable numbers of lymphocytes. It is double-layered with the inner cells (near the luminal space) being high columnar resting on a layer of cuboidal cells. The cytoplasm in both layers has abundant finely granular acidophilic cytoplasm (oncocytic in nature, due to extensive production of mitochondria stained with PTAH). The epithelium is supported by a lymphoid stroma that frequently shows germinal center formation. Ultrastructural (EM) studies confirm that Warthin’s tumor contains luminal and basal cells. Cytoplasm of luminal & basal cells is virtually completely occupied by mitochondria. It is proposed that the Warthin tumor arise from the reserve precursor cells which are normally present in the striated ducts.

Surgical removal is the treatment of choice for patients with Warthin’s tumor.

1.5 Oncocytoma (Oxyphil Adenoma)

A rare tumor composed of a well-demarcated mass of polyhedral eosinophilic cells with small, dark nuclei. It has a solid, trabecular or tubular pattern and frequently contains both light and dark cells.

The oncocytoma is a benign salivary gland tumor composed of large epithelial cells known as oncocytes. It is a rare neoplasm, representing approximately 1% of all salivary tumors. It occurs predominantly in the parotid gland (Table) of older adults, with a peak prevalence in the eighth decade of life, and a thin capsule which may be incomplete. The intensely eosinophilic granular cytoplasm is due to large numbers of MITOCHONDRIA which was staining with phosphotungstic acid-hematoxylin (PTAH). Microscopically, it is composed of sheets of large polyhedral cells (oncocyes), with abundant granular, eosinophilic cytoplasm. The cells have centrally located nuclei that can vary from small and hyperchromatic to large and vesicular. Little stroma is present, usually in the form of
thin fibrovascular septa.

Clear cell oncocytoma,—Immunohistochemical and ultrastructural (EM) studies confirm that it contains mitochondria. Staining with phosphotungstic acid-hematoxylin (PTAH) may show the granular positivity of mitochondria. Variable amounts of glycogen may be detected within cells, positive with PAS stain but negative after digestion with diastase, while mucous stains are negative.

Oncocytes are normally found as age-related change in the intralobular ducts of the parotid gland, it is suspected that they represent a limited proliferation of striated duct origin. Oncocytoma may also originate from multi-focal oncocytic adenomatous hyperplasia or a diffuse oncocytsis. (Oncocytosis refer to both the proliferation and accumulation of oncocyes within salivary gland tissue.) Diffuse oncocytsis of the parotid gland is a very rare non-neoplastic lesion due to complete oncycytic metaplasia (is the transformation of ductal and acinar cells to oncocytes.) of the gland lobules affecting both the ductal and acinar epithelium. This is an intracellular metabolic disorder with mitochondriopathy. It is almost always unilateral and occurs in older age groups. Multifocal oncocytic adenomatous hyperplasia is a non-encapsulated, partly micro-nodular & partly macro-nodular hyperplasia of oncocytic buds from the ductal epithelium. It is assumed that oncocytoma can arise by confluent growth and later formation of a capsule. Oncocytomas are best treated by surgical excision. The prognosis after removal is good, with a low rate of recurrence.

1.6 Canalicular Adenoma

A tumor of columnar epithelial cells which are arranged in anastomosing bilayered strands that form a beading pattern. The stroma is loose, highly vascular and not fibrous.

The most common site of occurrence of canalicular adenoma is the upper lip (73.5 %). There is a dramatic peak in the canalicular adenoma's occurrence in the seventh decade. It presents as non-ulcerated, non-painful nodules that exhibit gradual enlargement. They range in size from 0.4 to 2.0 cm, with a mean of 1.7cm. The overlying mucosa may be normally colored or slightly bluish. They are often freely movable and unattached to the underlying skin, or somewhat fluctuant to palpation. In some instances, the lesion has been noted to be multifocal, with multiple separate tumors discovered in the upper lip or buccal mucosa. It represents the second most common tumor (PA is the most) of the upper lip. The gross appearance of canalicular adenomas varies from a discrete encapsulated nodule to lesions that are circumscribed but unencapsulated. The microscopic features of canalicular adenoma are fairly characteristic. The cells are remarkably isomorphic & cuboidal or columnar. Epithelium composed only of luminal cells with considerable
cytologic uniformity. For the most part, the low-magnification appearance reveals columns or cords of columnar & cuboidal epithelial cells in a single layer (resembling the ICD). These single-layered cords are arranged in duct-like structures with intermittent widening and narrowing of the lumen-like zone between the two rows, arrow, appear as one double row of cells) of luminal cells leading to a "bead-on-string" form. In many areas, the single rows of cells are parallel, forming long “canals” with central lumina; hence the term canicular is used. Multiple, smaller cystic dilatations can give the neoplasm a microcystic appearance, and larger cysts may result in a prominent cystic presentation, both microscopically & grossly. The remarkable features of the stroma are the sparse fibrillarity, the lack of cellularity, and the prominent vascularity. The tumor is distinguished from the trabecular type of basal cell adenoma, which has a fibrous rather than a loose, vascularized stroma. There is no association with dermal cylindroma. Ultra-structurally (EM), canalicular adenomas are composed of orderly rows of columnar cells arranged so that the base rests on a layer of basal lamina & apical regions converge to form a lumen. Note the absence of a second cell type interposed between the columnar cells & the basal lamina confirming the differentiation of only luminal type cells in this form of adenoma.

2. Carcinomas

2.1 Acinic Cell Carcinoma
A malignant epithelial neoplasm that demonstrates some cytological differentiation toward acinar cells.

Because many of these tumors act in a non-aggressive fashion and are associated with a good prognosis, this neoplasm was formerly called acinic cell tumor, a non-specific designation that did not indicate whether the lesion was benign or malignant. However, because some of these tumors do metastasize or recur and cause death, it is generally agreed today that acinic cell adenocarcinoma (ACA) should be considered a low-grade carcinoma. The ACA is located most common in the parotid gland (85%). About 9% of all ACA develop in the oral minor salivary glands, with the buccal mucosa, lips, and palate being the most common sites. The tumor occurs over a broad age range, with a relatively even peak prevalence stretching from the 2nd to 7th decades of life; the mean age is in the mid-40s. Women are affected more frequently than men in a ratio of 3 to 2 in AFIP files. It usually presents as a slowly growing mass, and the lesion is often present for many months or years before a diagnosis is made. Up to 3% found bilaterally, which means that it ranks 2nd only to Warthin tumors in bilateral occurrence. It may appear to be encapsulated, but microscopically usually found to be incomplete.

The individual cell characteristics can be categorized as acinar, intercalated duct-like, vacuolated, clear and non-specific glandular.
Acinar cells: are usually identified by relatively large size, round to polygonal shape, basophilic to amphophilic cytoplasm & dark staining cytoplasmic granules similar to those of normal acinar cells. Cytoplasmic granules: PAS (+) before & (-) after diastase digestion, amylase (+), mucin (-)

Intercalated duct-like cells: are smaller than acinar cells and cuboidal in shape and often surround small lumina. Their cytoplasm is amphophilic to acidophilic. The nuclei are centrally placed and about the same size as the acinar cells, so that the N/C ratio is increased.

Vacuolated cells: are peculiar & seem unique to ACA among salivary gland neoplasms. These cells are typically about the size of the well-differentiated acinar cells. There may be several vacuoles or a single large vacuole. Stains for lipids & glycogen demonstrate no material in the vacuoles, but there may be some mucopolysaccharides.

Clear cells: In only a small number & a small part of ACA. They have the shape and morphology of acinar or intercalated duct-like cells that have lost their cytoplasmic staining due to hydropic degeneration or artifact (post-fixation defect).

Non-specific glandular cells are defined by the absence of features characteristic of the other four cell types. The nuclei are typically larger, more vesicular and more pleomorphic than those of the other cell types.

Four growth patterns may be seen.

Solid growth pattern: is the most easily recognized morphological variant of ACA because it usually contains large numbers of well-differentiated acinar cells & most closely resembles the normal parotid gland parenchyma.

Microcystic pattern: shows numerous small cystic spaces which are bout three to ten times the size of acinar cells. Well-differentiated acinar cells are still quite frequent & dominant but vacuolated and intercalated duct-like cells can also be prominent. Microcystic spaces may result from the coalescence of intra-cellular vacuoles or ruptured cells.

Papillary cystic growth pattern: is characterized by one or more cystic structures that contain proliferations of epithelium. Intercalated duct-like & non-specific glandular cells usually predominate.

Follicular pattern: is the least often & has a definite thyroid-like appearance. Ovoid to round cystic spaces contain an eosinophilic proteinaceous material that simulates the appearance of colloid. The inter-cystic areas are usually occupied by epithelial cells that are mostly non-specific glandular cells, with some vacuolated and acinar type cells.

Treatment and Prognosis:

The ACA is associated with one of the better prognoses of any of the malignant salivary gland tumors. Approximately one third of patients have recurrences locally, and metastases develop in 10% to 15% of patients. From 6% to 26% of patients die of their disease. The prognosis for minor gland tumors is better than that for tumors arising in the major glands. The facial nerve may need to be sacrificed if it is involved by tumor.


2.2 Mucoepidermoid Carcinoma

A tumor characterized by the presence of squamous cells, mucus-producing cells and cells of intermediate type.

It is the most common malignant salivary gland tumors with relatively uniform (evenly) age distribution between 2nd to 7th decades. The mucoepidermoid CA. (MC) is most common in the parotid gland (about 47% ) and pain or facial nerve palsy may develop. The minor glands constitute the second most common site, especially the palate. Minor gland tumors also typically appear as asymptomatic swellings, which are sometimes fluctuant and have a blue or red color that can be mistaken clinically for a mucocele. Although the lower lip, floor of mouth, tongue, & retromolar pad areas are uncommon locations for salivary gland neoplasia, the MC. is the most common salivary tumor in each of these sites. Central MC seems to arise from dentigerous cyst or ectopic salivary gland tissue in bone.

The gross appearance varies with grade, but most tumors are poorly circumscribed and usually show cyst formation in low-grade tumors. The cyst frequently contains viscid mucoid material that is blood-tinged hemorrhagic. In solid tumors epidermoid and intermediate cells usually predominate, whereas in mainly cystic tumors mucous cells tend to be more conspicuous.

Traditionally, MCs have been categorized into one of three histopathologic grades based on the following: 1. Amount of cyst formation 2. Degree of cytologic atypia 3. Relative numbers of mucous, epidermoid, and intermediate cells

Mucous Cells: are cuboidal, columnar or more goblet-like and form solid masses or line cysts. They may form a single layer or be multi-layered, particularly where they cover papillary projections into the cyst lumen. Mucin can be visualized with Mucicarmine or PAS stain.

Epidermoid cells : usually have identifiable intercellular bridges but keratinization is very rare. They may be arranged as solid masses or form part of the cyst lining.

Intermediate cells : are small with dark-staining nuclei and is believed to be a progenitor of the mucous and epidermoid cells.

Clear cells are containing glycogen with strong PAS (+) before & (-) after diastase digestion and occasionally these are the predominant features.

Well-differentiated type or low-grade: is usually less than 4 cm in diameter, circumscribed but non-encapsulated and predominantly cystic. More than 50% of the tumor consists of mucusproducing cells and well-differentiated epidermoid cells. Microscopy shows well-differentiated mucous cells, epidermoid cells and intermediate cells with absent or occasional mitoses and minimal nuclear pleomorphism.

Poorly differentiated or high-grade: is usually more than 4 cm in diameter. Have a
macroscopically ill-defined margin, tend to be solid & may show focal areas of hemorrhage or necrosis. Cystic areas are usually smaller than in low-grade. Microscopy shows high mitotic frequency, nuclear pleomorphism and infiltrative margins. It consists of undifferentiated intermediate cells or poorly differentiated epidermoid cells (often difficult to see the intercellular bridges). Mucous cells are less than 10% & not readily identified without special stains.

Intermediate-grade tumors show features that fall between those of the low-grade and high-grade neoplasms. Cyst formation occurs but is less prominent than that observed in low-grade tumors. All three major cell types are present, but the intermediate cells usually predominate. Cellular atypia may or may not be observed.

**Cell origin: Ductal unit (including MEC /Basal cell) of all levels**

The prognosis depends on the grade and stage of the tumor. Patients with low-grade tumors generally have a good prognosis. For most primary sites, local recurrences or regional metastases are uncommon, and around 90% to 95% of patients are cured. The prognosis for those with intermediate-grade tumor is slightly worse than that for low-grade tumors. The out-look for patients with high-grade tumors is guarded, with only 25%-30% of patients surviving within 5 years.

### 2.3 Adenoid Cystic Carcinoma

An infiltrative malignant tumor having various histological features with three growth patterns: cribriform (glandular), tubular or solid. The tumor cells are of two types: duct-lining cells and cells of myoepithelial type. Perineural or perivascular spread without stromal reaction is very characteristic. All structural types of ACC can be associated in the same tumor.

**Cell Origin: derived from ICD and MEC. (Intercalated duct complex)**

**Site:** even distribution in parotid, submandibular and palate. (About 50% develop within the minor salivary glands.)

**Age:** often adult, 5th-7th decades is the most. Pain is a common and important finding, occasionally occurring early in the course of the disease before there is a noticeable swelling. Facial nerve paralysis may develop with parotid tumors. Palatal tumors can be smooth surfaced or ulcerated.

**Histopathologically,** the adenoid cystic CA. (ACC) is composed of a mixture of myoepithelial cells & intercalated ductal (ICD) cells that can have a varied arrangement. Three major patterns are recognized and usually a combination of these is seen, and the tumor is classified based on the predominant pattern.

**Glandular (cribriform) type:** consists of epithelial cells nests filled by numerous cylindrical spaces, so-called Swiss-cheese appearance. Most of these are pseudocysts containing
proteoglycans and basal membrane-like material. The cells surrounding the pseudocysts resemble modified MECs of a flat, spindle-like shape with scanty cytoplasm. The true lumen with usually inconspicuous lumens contains secretory material and is surrounded by ICD-like cuboidal cells with broader, eosinophilic cytoplasm. Cribriform type is the most common and classic and best recognized appearance.

**Tubular type**: consists of epithelial ductal structures or strands surrounded by hyaline desmoplastic stroma. Tubular lumens are lined by ICD-type cells, which in turn surrounded by one or more peripheral layers of modified MECs. The tubular lumina can be lined by one to several layers of cells, and sometimes both a layer of ductal cells and MECs can be discerned.

**Solid type**: is characterized by solid epithelial strands, nest which contain few gland-like spaces & often central necrosis. The tumor cells are small and basophilic with hyperchromatic dense nuclei. Mitoses are few. Between the cell nests there are narrow areas of stromal tissue.

All ACC regardless of their histological types, are biologically aggressive, able to metastases. **Peri-neural invasion (neurotropism)**, peri-vascular spread, mitotic activity and pleomorphism appear to have no exact correlation to prognosis. The perineural invasion probably corresponds to the common clinical finding of pain in these patients. Sometimes the cells appear to have a swirling arrangement around nerve bundles. However, perineural invasion is not pathognomonic for ACC; it also may be seen in other salivary malignancies, especially polymorphous low-grade adenocarcinoma.

**Cribriform or tubular type has better prognosis** than that of solid type. Local extension into bone, adequacy of the margin of excision and the size of the tumor will influence the prognosis. Fifty per cent of patients are alive & well at 10 years with tumors of 2 cm and under. Death usually results from local recurrence or distant metastases. Tumors of the palate or maxillary sinus eventually may invade upward to the base of the brain.
2.4 Polymorphous low grade adenocarcinoma (Terminal duct carcinoma)

A malignant epithelial tumor characterized by cytological uniformity, morphological diversity and a low metastatic potential.

Features of the polymorphous low-grade adenocarcinoma PLGA (terminal duct carcinoma)
-----------------------------------------------------------------------------------------------
Minor salivary glands (palate)  
Varied histologic pattern  
--cords, tubules, papillae  
--glandular and adenoid structures  
--solid aggregates  
Cytologic uniformity  
--myoepithelial cells  
--luminal epithelial cells  
Immunohistochemistry  
--S-100-protein and EMA (more than 90%)  
--keratin (75-90%)  
--muscle-specific antigen (10-65%)  
--CEA  
Infiltrative growth pattern  
Almost no recurrence or metastases
-----------------------------------------------------------------------------------------------

The PLGA is a recently recognized type of salivary malignancy that was first described in 1983. Cell population contains terminal duct epithelium (intercalated duct) and MEC.

Age: The most frequently in 6th –7th decades.
Location: exclusively in oral cavity, esp. palate (60%). (almost in minor gland).
The tumor most often appears as a painless mass that may have been present for a long time with slow growth. Occasionally, it is associated with bleeding or discomfort. The tumor can erode or infiltrate the underlying bone.

The main microscopic patterns are:

(1) Cells are often pale like under-staining. The nuclei are small to medium sized and oval, pale. Mitoses are uncommon.
(2) Cells are isomorphic & uniform, & growth pattern is polymorphous (different growth patterns).
(3) cribriform areas, sometimes closely resembling those in ACC.
(4) papillary or papillary-cystic
(5) trabeculae or small, duct-like structures.
(6) Indian file, Tagetoid appearance.

Neurotropism may be a conspicuous feature and is easily misinterpreted as indicative of ACC. The nuclei in PLGA are slightly larger, rounder, and more uniform than the angular hyperchromatic nuclei in ACC. The tumor appears to arise only in the minor salivary glands,
esp. palate. Prognosis is good, despite the microscopic evidence of invasion. There is local recurrence in about 20% of cases but regional and distant metastases are uncommon. It should be differentiated from papillary cystadenocarcinoma, ACC, & CA in PA.

2.5 Epithelial-Myoepithelial Carcinoma
A tumor composed of variable proportions of two cell types which typically form duct-like structures. There is an inner layer of duct lining cells and an outer layer of clear cells.

It is essentially a tumor confined to the major glands, particularly to parotid (80%), most prevalent in older individuals, with a peak incidence in 7th decades.

The cell origin of epithelial-myoeopithelial CA. is intercalated duct complex and is a rare biphasic type of low-grade salivary gland CA. that constitutes less than 1 % of salivary gland neoplasms.

The tumor is usually multi-nodular, may be encapsulated, or incomplete capsule, or nodules often extend through it. This neoplasm was classified as a CA. based on a locally infiltrative and destructive growth pattern. The inner layer of the duct-like structures consisting of small, dark-staining, cuboidal cells is thought to be an intercalated duct origin. The outer clear cells stain strongly for glycogen and positive for S-100 protein and myosin. E.M shows features of a MEC origin. Mitoses are rare and the tumor is cytologically bland; indeed, it has previously been classified as a type of adenoma. However, perineural and vascular invasion may be present and recurrence and metastasis are not uncommon.

2.12 Adenocarcinoma, NOS, (Not Otherwise Specified)
A carcinoma with glandular, ductal or secretory differentiation that does not fit into the other categories of carcinoma.

Subclassification of adenocarcinomas

2.14 Carcinoma in PA (Malignant mixed tumor)

Tumors showing definitive evidence of malignancy, such as cytological and histological characteristics of anaplasia, abnormal mitoses, progressive course and infiltrative growth and in which evidence of PA can still be found.

Clinically: It composes of 3-4% of all PAs and occurs most in parotid gland and older age, 6-7th decade. First of all, the mean age of patients with this tumor is about 15 y/o than that of benign mixed tumor (42ys). The presenting symptoms are variable. The tumors are characteristically present for long periods of time, up to 50 years. The most frequent symptom is a painless mass, 15% of patients note recent rapid growth, occasionally with ulceration.
Grossly: encapsulated to poor circumscribed, hemorrhage, necrosis. There are 3 subtypes of Malignant Mixed Tumors:

(1) Carcinoma Ex PA: CA ex PA.
also known as “CA. arising in a benign PA”, is a benign PA in which a second neoplasm develops from the epithelial component that fulfills the criteria for malignancy. These criteria include invasiveness, destruction of normal tissues, cellular anaplasia, and atypical mitoses. The most common histologic pattern of this second neoplasm is poorly differentiated CA,(106 Lower) or adenocarcinoma, but squamous cell carcinoma, mucoepidermoid CA, ACC, and PLGA have also been described.
The term “non-invasive CA” refers to circumscribed malignant areas in a PA without infiltration of the surrounding tissue. This term is preferred to “intracapsular CA.” or “CA. in situ ”. Patients with non-invasive CA have an excellent prognosis if the tumor is completely removed surgically.
In "invasive CA" the extent of invasion as measured in millimeters is a valuable guide to prognosis and biological behavior; CA invading less than 8 mm carry a 5-year survival of 100%, invading more than 8 mm a 5-year survival of less than 50%.
(2) Metastatic mixed tumor: A histologically benign tumor that inexplicably manifests distant metastases.
(3) Carcinosarcomas--Both Epithelial and mesenchymal components are malignant changed. It shows mostly a chondrosarcomatous pattern. 5-year survival of 0%

3 Non-epithelial Tumors

Make up 5% of all tumors of the salivary glands. About 90% of non-epithelial tumors are benign. The most common type of benign mesenchymal tumor is angioma (45%), esp. hemangioma or lymphangioma. Lipomas represent about 20% of all benign mesenchymal tumors of the salivary tumor, as do neural tumors.

4.Malignant Lymphomas
5. Secondary tumors

Salivary tumors with clear cells

<table>
<thead>
<tr>
<th>Benign tumors</th>
<th>Malignant tumors</th>
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<tbody>
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<td>PA Primary</td>
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</tr>
<tr>
<td>Oncocytoma</td>
<td>--Mucoepidermoid carcinoma</td>
</tr>
<tr>
<td>Multifocal nodular</td>
<td>--Acinic cell carcinoma</td>
</tr>
<tr>
<td>Oncocytic hyperplasia</td>
<td>--Epithelial-myoepithelial CA.</td>
</tr>
<tr>
<td>Sebaceous adenoma</td>
<td></td>
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Secondary

--Renal clear cell carcinoma
--Thyroid clear cell carcinoma

a. Clear cell renal CA. Containing abundant glycogen and lipid.
b. Thyroid CA.
   Negative for glycogen and lipid.  Positive for thyroglobulin staining
   CT scanning, urography is necessary.

**Clear cells in Salivary gland:**
The histogenesis (cell origin) of the clear cells in salivary gland neoplasms may be from a variety of cells, including myoepithelial cells, intercalated duct cells, mucous cells, sebaceous cells, and acinar cells. They are attributed to one of the following three causes (1) a minimal degree of cellular differentiation with a deficiency of cytoplasmic organelles; (2) an increase in the degree of cellular differentiation with a marked accumulation of cytoplasmic glycogen, mucin, lipid, or clear secretory granules, or (3) tissue fixation and/or processing artifact. Clear cells attributed to post-surgical fixation artifact are seen occasionally in oncocytic lesions and acinic cell adenocarcinoma.

1. Oncocytoma------Mitochondria, PTAH (+), some glycogen, E.M.
2. Mucoepidermoid CA---few mucin, sometimes glycogen, MEC.
3. Acinic cell Ca.---artifact or hydropic degeneration of Acinar or intercalated duct cells
4. Epithelial-myoepithelial Ca--MEC. Glycogen
5. Renal cell Ca, Meta.---glycogen and lipid
6. Sebaceous adenoma--lipid,
7. Thyroid CA. ---thyroglobulin

6. Unclassified tumors
7. Non-neoplastic lesions:

(1). Mucocele: (Pseudocyst.)
--Is a clinical term, to refer to both Mucus extra-vasation Phenomenon and Mucus Retention Cyst.
--Result from rupture of gland duct (esp. minor duct), spillage of mucin to the CT.
--Dome-shaped swelling, anywhere in oral cavity, 75% in lower lip.
--All age, most common in children and young adults
--Bluish translucent hue (surface lesion (deep lesion-normal color),
--Fluctuant to firm, few days to several years,
--History of a recurrent swelling (periodically rupture)
--Superficial mucocele is created by the superficial nature of the mucin spillage, which causes a separation of the epithelium from the connective tissue.
*Histology:
Pooling of mucin, spilled mucin, elicit a granulation tissue response containing foamy histiocytes.

(2). Ranula:
A clinical term that is used to designate a retention mucocele that occurs specifically in floor of mouth. It may represent either Mucus extra-vasation phenomenon or Mucus Retention Cyst.-
Name from Latin—Rana, which means frog, because the swelling may resemble the appearance of a frog’s translucent underbelly.

* Etiology:--Obstruction of sublingual duct

* Clinically --Only occurs in mouth floor, Bluish color.
--Larger than mucocele, many cm. in size even elevate the tongue.
--Dome-shaped, fluctuant swelling,
--Lateral to midline,

* Histology----Pseudocyst, but contains duct lining epithelium.
● Other mucous retention cyst:

(3). Sialolithiasis (salivary stone):
Sialolith: A stone develop within the salivary duct system.-
---Arising from deposition of calcium salts around a Nidus of debris within the duct lumen. This debris may include inspissated mucin, bacterial, duct epithelial cells or foreign body.
* Clinically--often within ductal system.
  --occurs more common in long, tortuous duct of submandibular gland.
  --young and middle age,
  --pain or swelling, especially, at meal time,
  --severity depending on degree of obstruction,
  --terminal portion of duct may be palpable,
  --white to yellowish to yellowish brown color
  --round to ovoid shape, smooth or irregular.

X-ray--R-O mass occurs anywhere along the duct or within gland itself. (Occlusal view)
  --Panex or periapical view may be superimposed on mandible may confuse with other intra-bony lesion.

* Micro---shows concentric lamination surrounding a nidus of amorphous substance.
  ---duct demonstrates squamous, oncocytic or mucous metaplasia.
  ---acute or chronic sialadenitis.

(4). Sialadenitis--inflammation of salivary gland.

Can arise from (A) infection (B) Non-infection

(A) Infection;  
  (1) Virus
    (i) paramyxo-virus → mumps
    (ii) Coxsackie A
    (iii) Cytomegalo-virus → neonate,
    (iv) HIV → AIDS
  
(2) Bacteria---as a result of
    (i) Ductal obstruction.----stone, strictures, tumors,
    (ii) salivary flow decreased,--dehydration,
        --debilitation
        --medication
    (iii) recent surgery--NPO, atropine etc.

* staphylococcus aureus
  *Allowing retro-grade spread of bacteria.

(B) Non-infectious---Sjogren’s Syndrome

---Sarcoidosis--non-caseous necrosis granulomatous inflammation
  ---Radiation treatment

* Clinical and X-ray findings:
  --Swelling, pain,
  --Overlying skin—erythematous
  --lower grade fever
  --trismus,
--purulent discharge from the duct orifice.
--Sialography--Sialectasia ( ductal dilatation ) proximal to the area of obstruction.

* Micro--acute--accumulation of PMN
--Chronic----a. lymphocyte and plasma cells infiltration scattered throughout the parenchyma,
   b. Acinic atrophy--destructed and replaced by fibrous tissue,
   c. Duct → dilatation.

(5). Xerostomia----Dry Mouth
   (1) Gland aplasia
   (2) Aging, smoking, mouth breathing,
   (3) Radiation → Treatment of head and neck malignancy
   (4) BLL, Sjogren’s Syndrome
   (5) HIV
   (6) Medication---antihistamine
       ---reserpine (anti-hypertension )
       ---atropine ( anti-cholinergics)

* Clinicall findings:
   (1) residual saliva → thick
   (2) mucosa → dry
   (3) tongue → filiform papilla → atrophy & fissured.
   (4) prevalence of oral candidiasis ( due to anti-microbial activity ↓ )
   (5) caries → Rampant caries, cervical and root.

* Treatment:
   (1) artificial saliva
   (2) continuous drinking water throughout the day
   (3) sialagogue---pilocarpine
   (4) if side-effect of drug occurs → stop medication
   (5) caries----------------→ fluoride topical

(6). Benign Lymphoepithelial Lesion (B.L.L.) ( Mukulicz’s Disease)

It is an Auto-immune disease---patient's own salivary gland tissue becomes antigen. The disease affects older women almost exclusively and is characterized by a recurrent painful swelling mostly of the parotid glands. It may be observed as a local disorder of the salivary gland or a manifestation of Sjogren syndrome.

The histopathological appearance of this lesion is made up of a triad of parenchymatous atrophy, interstitial lymphocytic infiltration, and so-called epi-myoepithelial islands.
B.L.L. + Xerophthalmia (lacrimal gland) → sicca or primary Sjogren's syndrome.

* Clinically
  ---adult, mean age = 50
  ---60-80% women
  ---firm, diffuse swelling of parotid gland,
  ---may be asymptomatic or only mild pain,
  ---xerostomia.

* Micro:
  ---Heavy lymphocyte infiltration with or without follicle,
  ---acinic destruction
  ---ductal epithelium → persist
  ---ductal cell and surrounding MEC → proliferation forming Epi-myoepithelial islands.

* Mukulicz's syndrome: salivary enlargement accompanied specific diseases, such as T.B, lymphoma.

* Treatment → Surgical removal.

(7). Sjogren's syndrome (SS):
Patient has rheumatoid arthritis (connective tissue disorders), keratoconjunctivitis sicca and xerostomia.

Sicca Syn. + Connective Tissue disease (collagen disease, such as rheumatoid arthritis, scleraderma, or polymyositis)
→ 2nd Sjogren's syndrome.

* Triad of SS:
  1. Xerostomia
  2. Xerophthalmia (keratoconjunctivitis sicca)
  3. Collagen disease

---male: female = 1 : 10 (middle age women)
---painful burning sensation of oral mucosa (xerostomia)
---parotid gland enlargement
---same histological pictures of BLL.

* Sialography ---cheery blossom of branchless tree, (fruit-laden tree)
---Suggests that the contrast material extra-vasates through the weakened gland ducts to produce the sialographic features.
(8). Necrotizing Sialometaplasia:

---An uncommon locally destructive inflammatory condition of salivary gland.
---Unknown etiology \(\rightarrow\) may be the result of ischemia\(^1\)
  \(\rightarrow\) lead to local infarction.
---Mimics a malignant process both clinically and micro.

* Clinically
  ---75\% of all cases on post. palate (hard palate > soft palate)
  ---May occur in parotid
  ---Most common in adult, mean: 46 y/o.
  ---Present initially as a non-ulcerated swelling associated with pain,
  ---Within 2-3 weeks \(\rightarrow\) crater-like ulcer, 1-5 cm. painless,
  ---5-6 weeks \(\longrightarrow\) self-healing of the ulceration.

* Micro:
  ---Acinar necrosis in early followed by squamous metaplasia of duct epithelium.
  ---Necrotic acini and inflammatory cell infiltrates are found peripherally.
  ---Mimics SCC.

D.D.--S.C.C., mucoepidermoid Ca.

Need not Treatment. self-limited within 6 weeks.--------------------------------------------END