Neoplastic salivary gland diseases
Benign neoplasms

Incidence:

It's about 3% of all neoplasms, and scattered as 80% in the parotid gland (80% of parotid tumours are benign and 80% of these tumours are Pleomorphic adenoma), 10% in the submandibular gland, and 10% in the sublingual and minor salivary glands.

Aetiology:

It's unknown but the following may be considered:

1. **Polyoma virus.**
2. **Hydrocarbons.**
3. **Low dose radiation.**

Surgical pathology:

Most benign tumors of the parotid seen posteriorly in the retromandibular sulcus and less commonly in the preauricular region or in the deep lobe or the parapharyngeal space. There is no specific site of election in the submandibular gland, and benign tumors are rare in the sublingual gland.

The benign tumors are:

I. **Vascular and lymphatic malformations:**

1. ***Haemangioma*: the congenital type appears at birth as large bilateral bluish spongy swelling which tend to increase in size when the child cries (Fursten Berger sign). It may be associated with haemangioma elsewhere in the body and usually it gets atrophied as the infant grows until the age of 2 years. It differs from the lymphatic type in that it tend to be more confined to the anatomical compartments so their limits are relatively easy to define.**
2. ***Lymphangioma*: it's diffusely infiltrating the temporalis muscle and fascia, the facial nerve, submandibular gland, and sternomastoid muscle. It's difficult to be removed because of indeterminate boundaries, deep seated extensions, and tendency to surround vital structures.**

II. **Pleomorphic adenoma:**

It's a slowly growing benign epithelial tumor which contain both epithelial and myoepithelial elements. It's surrounded by a false incomplete capsule formed by fibrosis and compression of salivary gland parenchyma so tumours may extend through the dehiscence in the capsule to the surrounding glandular tissue and there should be a wide margin as possible during removal of the tumour, because nucleation may be associated with 40% of recurrences.

Pleomorphic adenoma is the most common neoplasm of the salivary glands. It is about ten times more common in the parotid than in the

submaxillary gland, and it is very rare in the sublingual gland. In the parotid gland, most tumors arise within the superficial lobe, from either the tail (50%) or the anterior portion (25%). The remaining 25% arise from the deep lobe and are often present as a pharyngeal mass without external evidence of tumor. Though it is classified as a benign tumor, pleomorphic adenomas have the capacity to grow to large proportions and may undergo malignant transformation (6%), to form carcinoma ex pleomorphic adenoma, a risk that increases with time. Although it is "benign", the tumor can recur after resection, it invades normal adjacent tissue and seen as multiple nodules in the previous scar, subcutaneous tissue parotid gland, facial nerve, or perichondrium of the external auditory meatus .

It is most frequent in women, with a female-to-male ratio of 3:2, in the fourth decade of life, but it can be seen in children and in elderly persons of either sex. White persons have a slightly higher risk of pleomorphic adenomas than that of other races.

III. Warthin's tumor (adenolymphoma):

Warthin's tumors are considered as the second most common neoplasm of the parotid gland. In gross appearance, it is a smooth, soft, *bilateral* parotid mass. They tend to be firm or rubbery in texture and may be nodular. A minority of patients may report rapid enlargement of the tumor with associated pain or pressure. It is well encapsulated when located in the parotid gland and contains multiple cysts.

Although Warthin's tumor can occur elsewhere, it is most commonly found within the parotid gland. In one series, essentially all were located in the parotid. Another series found 90% within the parotid, 7.6% in cervical lymph nodes, and 2.3% in the submandibular glands. The etiology of Warthin's tumors is controversial and whether they are true neoplasms or developmental malformations continues to be debated.

It accounts for 4-15% of salivary gland neoplasms and is more common in men during their 6-7th decades. There is slight male predominance but there has been an increased incidence in women. There is low incidence of this neoplasm in African Americans. Smokers have 8x increased risk of developing this neoplasm.

The presence of lymphoid tissue make it susceptible to inflammation secondary to upper respiratory tract infection leading to pain, tenderness, enlargement, and fluctuation.

All patients with this tumor survive, and the recurrence rate is 5%. Malignant transformation has not been observed.

IV. Oxyphil adenoma (Oncocytoma):

Oncocytoma are rare monomorphic adenomas, which are benign salivary gland tumors accounting for 1% of all salivary gland tumors, the majority of which occurs in the parotid gland (84%). Monomorphic adenomas lack a stromal component.

Oncocytomas are found to be evenly distributed between men and women, usually common in old age (>50). It is also said to have an association with previous radiation exposure, sometimes up to 40 years prior to discovery of the rumor. Most cases are asymptomatic, discovered only incidentally by ultrasound. Oncocytoma are solid, well-circumscribed tumors with a brown lobular cut surface. They are firm, slowly growing, painless masses of < 4 cm. They may also be bilateral. It may become malignant.

V. Myoepithelioma:

Myoepithelial cells are prominent component of pleomorphic adenomas. Tumors derived solely from myoepithelial cells are rare. Myoepitheliomas are considered as a variants of pleomorphic adenomas that are characterized by overwhelming myoepithelial proliferation. A malignant variant is also recognized. The average age of presentation is 40 years but both children and elderly can be affected. There is no apparent predominance in either sex and all salivary glands can be affected.

Clinical features of benign salivary glands tumors:

Symptoms:

1. **Age range 30-70 yrs.**
2. **Slowly growing swelling (if it becomes rapid it's either due to malignant transformation, or infection of Warthin's tumor).**
3. **Pain usually indicate malignancy, infection, or haemorrhage.**
4. **Facial palsy is an indication of malignancy, Tb, or sarcoidosis.**

Signs:

1. **Sub parotid lymph node enlargement (seen during surgery) in benign tumors is due to reactive hyperplasia.**
2. **External swelling seen in the retromandibular sulcus, preauricular region, or over the masseter muscle in parotid gland pathology, and in the submandibular triangle in submandibular gland pathology.**
3. **Non ulcerative swelling in the oral cavity especially on the hard or soft palate.**
4. **Deep lobe parotid tumours usually fill the parapharyngeal space before displacing the lateral pharyngeal wall (the tonsil).**

Investigations:

1. **Radiology:**
   - **CT scan and MRI scan are the investigation of choice because they are quick, precise, and painless.**
   - **Sialography show the exact site of obstruction.**
2. **FNA (fine needle aspiration cytology) negative results are neglected, and the use of open biopsy or wide pore needle biopsy is contraindicated.**

Treatment:

1. **Superficial lobe of the parotid gland: benign tumors are removed with the superficial lobe by superficial parotidectomy to decrease the recurrence rate.**

2. **Deep lobe benign tumors: the two lobes of the parotid gland are removed by total conservative parotidectomy with conservation of the facial nerve.**
3. **Parapharyngeal space tumours: benign tumors are removed without removing the parotid gland by different approaches; submandibular approach, or transmandibular oro-pharyngeal approach.**
4. **Recurrent pleomorphic adenoma: recurrence occur due to:**
   a. **Enucleation without margin of healthy tissue.**
   b. **The tumour is breached accidentally during surgery or biopsy.**
   c. **Spillage of the tumour especially in large tense tumours.**

Recurrences seen as multiple nodules and it may be seen in the parotid gland or in the overlying tissue and treated as follows:

a. ***Salvage surgery*** **by superficial or even total conservative parotidectomy which is difficult without affecting the facial nerve.**

b. ***Radical parotidectomy*** **if the neoplastic nodules are embedded in the facial nerve sheath.**

c. ***Post operative radiotherapy*** **will decrease the recurrence rate to 3-4%.**

5. **Removal of the submandibular salivary gland by submandibular approach.**
6. **Removal of the sublingual salivary gland by intraoral approach.**
7. **Removal of pleomorphic adenoma from the hard palate by Enucleation of the tumor from the bone and the underlying bone should be drilled to prevent recurrence.**

Malignant salivary glands tumors

WHO classification of salivary gland tumors (1991)

1. **Adenomas: pleomorphic adenoma, Warthin's tumor, Oncocytoma.**
2. **Carcinomas: acinic cell carcinoma, mucoepidermoid carcinoma, adenoid cystic carcinoma, Adenocarcinoma, oncocystic carcinoma, carcinoma ex pleomorphic adenoma, undifferentiated carcinoma, and squamous cell carcinoma.**
3. **Non epithelial tumors.**
4. **Malignant lymphoma.**
5. **Secondary tumors.**
6. **Unclassified tumors.**
7. **Tumor like disorders: benign lymphoepithelial lesion, sialadenosis, salivary gland cysts, chronic submandibular sialadenitis (kuttner tumor), cystic lymphoid hyperplasia in AIDs, and Oncocytoma.**

Although the above list is useful, it has no particular relevance in treatment, as it is the clinical behavior of such diseases that tends to predict survival rather better than histology.

Adenocarcinoma:

Adenocarcinomas of the salivary glands represent those malignancies that cannot otherwise be easily classified. These are rare but aggressive tumors. About half of these tumors present in the parotid glands. The minor salivary glands, particularly the palate, lip and tongue are the next most commonly affected sites.

A. ***Etiology and Epidemiology***

According to the bicellular stem cell theory, adenocarcinoma of the salivary gland arises from intercalated stem cells. Risk factors include ionizing radiation and genetic or familial predisposition. Adenocarcinoma is the second most common malignancy of salivary gland tumors. It comprises 9 % of all salivary gland tumors and 16.8 % of all salivary gland malignancies. They tend to present in patients over 40 years of age (range: 10-93 years, average: 58 years) and occur with nearly equal frequency in men and women (almost 1:1 ratio).

B. Clinical Manifestation

Clinical presentation most often involves an enlarging mass. Adenocarcinoma is different from other salivary gland neoplasms in that as many as 25% of patients will complain of pain or facial weakness at presentation.

C. Treatment

Because these are more aggressive tumors, treatment for adenocarcinoma is more aggressive. Complete local excision is the mainstay of therapy. In the parotid this may include facial nerve sacrifice. In the minor salivary glands, a portion of the maxilla or mandible may have to be resected with the tumor. Although the efficacy hasn't been definitely proven, postoperative radiation therapy does seem to be of some benefit. Lymph node metastasis is not uncommon and in patients with palpable neck disease neck dissection is warranted. Elective neck dissection should probably be reserved for patients with extensive local disease or high-grade lesions.

Adenoid cystic carcinoma:

Adenoid cystic carcinoma is a rare form of adenocarcinoma, arising from within secretary glands, most commonly the major and minor salivary glands of the head and neck. AdCC is found mainly in the head and neck, but can occasionally occur in the uterus or other sites in the body. It most commonly occurs in the salivary glands, which consist of clusters of secretary cells scattered throughout the upper aero digestive tract. Therefore, tumors may arise in areas such as the palate, nasopharynx, tongue base, or mucosal lining of the mouth, larynx, or trachea. It may also occur in the major salivary glands (parotid, submandibular, or sublingual). Regardless of where it originates, AdCC has the same basic biologic behavior. AdCC tends to spread along nerves (perineural

invasion) or through the bloodstream. It only spreads to the lymph nodes in about 5% to 10% of cases. The most common place of metastasis is the lung.

A. ***Etiology and Epidemiology:***

AdCC is most often diagnosed in people in their 40s to 60s, but there are documented cases of pediatric AdCC. Women are slightly more likely to be diagnosed with AdCC than men (the female to male ratio is approximately 3 to 2). No strong genetic or environmental risk factors have been identified.

B. Clinical Manifestation:

Signs and symptoms depend largely on the site of origin of the tumor. Early lesions of the salivary glands present as painless, usually slow-growing masses of the mouth or face. Advanced tumors may present with pain and/or nerve paralysis, for this neoplasm has a propensity to invade peripheral nerves. Because there are many salivary glands under the mucosal lining of the mouth, throat, and sinuses, lumps in these locations could be from this type of tumor. Other symptoms may include difficulties in swallowing, hoarseness, dull pain, a bump or nodule in front of the ear or underneath the jaw, paralysis of a facial nerve, numbness of the face or tongue, a lump under the tongue or on the palate (roof of the mouth).

C. Course & prognosis:

The five-year relative survival rate for AdCC is approximately 89%. The 15-year relative survival rate for AdCC is approximately 40%. Tumor progression for AdCC is often slow and patients may live a long time with metastatic disease; however, a late relapse of AdCC is common, and can occur many years after initial treatment. Cancer survival statistics should be interpreted with caution. These estimates are based on data from thousands of cases of this type of cancer in the United States each year, but the actual risk for a particular individual may differ. It is not possible to tell a person how long he or she will live with AdCC. Because the survival statistics are measured in five-year (or sometimes one-year) intervals, they may not represent advances made in the treatment or diagnosis of this cancer. High-grade tumors include adenoid cystic carcinoma. Low-grade tumors have 10-year survival rates of 80-95%, while 10-year survival rates for high-grade tumors range from 25-50%.

For adenoid cystic carcinoma, the distant metastasis rate is nearly 50%. The most common sites are lung and bone. Although patients with metastases from adenoid cystic carcinoma may survive longer than 10 years because of the slow growth of these tumors, their survival with metastatic disease is short. The Dutch group observed the survival rate for patients with adenoid cystic carcinoma with distant metastases is 68% ± 7% in the first year and 32% ± 7% by 5 years. For patients with acinic cell carcinoma, the survival rate with distant metastases is 80% ± 13% at 1 year and 30% ± 14% at 5 years.

Acinic cell carcinoma:

Acinic cell carcinoma is a neoplastic growth of epithelial cells with acinar differentiation. It is a rarely occurring malignancy of the salivary gland. It belongs to the family of Adenocarcinomas and has some similarities with adenoid cystic, mucoepidermoid carcinoma, low-grade adenocarcinomas, and possibly some Breast Cancers. Acinic Cell Carcinomas are a slow growing, low grade tumor. It was earlier classified as an "acinic cell tumor" or benign adenoma but later literatures noted of the tumour's high potential for recurrence, metastases and even death, which resulted in WHO's reclassification as a "malignant carcinoma", though with more common low-grade behavior. 95% of the tumours arise in the parotid gland however, some may also occur in the submandibular gland and other major and minor salivary glands. About 3% of acinic cell carcinoma showed bilateral occurrence.

A. ***etiology and Epidemiology***

Acinic cell carcinoma can appear in all age groups. Compared with other salivary gland tumors, it presents at a younger median age, which is 52 years old. Occurrence in children is quite common which is about less than 12%. This type of cancer has a 2:3 male to female ratio of occurrence. About 58.8% of the cancer happens to females than males. There were no studies that show acinic cell tumor has a racial predilection. Acinic cell carcinoma comprises approximately 6%-10% of all salivary gland cancers and accounts for approximately 3-13% of all malignancies of the parotid gland. They make up approximately 4% of all minor, and 2-4% of all major salivary gland tumors.

B. Clinical Manifestations

Patients with acinar cell tumor may present with a swelling or mass in the face, neck, mouth that slowly enlarges over a long period of time usually years. It may or may not cause pain, thus usually asymptomatic. Less than one third of patients with acinic cell carcinoma reported the presence of pain with the mass or swelling. ACC does not normally invade the facial nerve; but when it does, numbness or weakness in the affected part of the face may be present.

C. Prognosis

For parotid tumors, acinic cell carcinomas had the best prognosis with a 10-year relative survival of 88%. Poor prognosis is associated with the following factors:

- **Short duration of symptoms.**
- **Frequent mitoses.**
- **Neural invasion.**
- **Infiltration.**
- **Large size.**
- **Involvement of the deep lobe of the parotid gland.**
- **Incomplete excision.**
- **Focal necrosis.**
- **Pleomorphism.**
- **Stromal hyalinization.**

Mucoepidermoid carcinoma:

Mucoepidermoid carcinoma is the most commonly occurring malignant neoplasm of the parotid gland and is the second-most common malignant neoplasm of the submandibular gland after adenoid cystic carcinoma. Mucoepidermoid tumour represent about 5 to 10% of all salivary gland tumors and occurs predominantly in the parotids. It represents about 8% of all parotid tumours. These neoplasms are composed of variable mixtures of squamous cells, mucus-secreting cells and intermediate hybrids. Mucoepidermoid carcinomas were first described by Masson and Berger in 1924. Since then, they have become well recognized as a common salivary gland neoplasm, accounting for approximately 35% of all malignancies of the major and minor salivary glands in general. Mucoepidermoid carcinomas have been reported at distant and atypical sites, including the breast, Eustachian tube of the ear, bronchi of the lungs, and thyroid. Women are more commonly affected than men (3:2), and the mean age at onset is in the 5th decade of life. MEC is also the most common salivary gland malignancy in children.

A. ***Etiology and Epidemiology***

The etiology of mucoepidermoid carcinoma is not fully understood. The *bicellular stem cell theory* holds that tumors arise from 1 of 2 undifferentiated stem cells, the excretory duct reserve cell or the intercalated duct reserve cell. Excretory stem cells give rise to squamous cell and mucoepidermoid carcinomas, while intercalated stem cells give rise to pleomorphic adenomas, oncocytomas, adenoid cystic carcinomas, adenocarcinomas, and acinic cell carcinomas.

B. Clinical Manifestations

The tumor usually forms as a painless, fixed, slowly growing swelling of widely varying duration that sometimes goes through a phase of accelerated growth immediately before clinical presentation. Symptoms include tenderness, otorrhea, dysphagia, and trismus.

Carcinoma ex-pleomorphic adenoma (CXPA):

It occurs when a carcinoma develops from the epithelial component of a pre-existing pleomorphic adenoma. This complication takes place in about 5% to 10% of these neoplasms. Carcinoma ex-pleomorphic adenoma presents in the 6th to 8th decades of life with patients averaging 10 years older than those with pleomorphic adenomas. It occurs most often in the parotid, followed by the submandibular gland and palate. Clinical features that suggest this event is usually long-standing painless masses that rapidly enlarge over a 3 to 6 month period. They often become painful and fixed to the skin. Facial paralysis is also variably present. A history of previous surgery and/or radiation therapy is often obtained. Documentation that a malignant salivary gland tumor arose from a pre-existent benign mixed tumor may be difficult to obtain. The above history although suggestive of the process, is not by itself diagnostic. It is necessary to

have microscopic evidence of a previously existing benign tumor or to have benign and malignant tumor in the same neoplasm. This may require a thorough sampling of the tumor. Sometimes the preexisting benign lesion is represented only by a totally hyalinized round nodule surrounded by carcinoma. The malignancy is limited to the epithelial component.

The risk of malignant degeneration in a pleomorphic adenoma increases from about 1.5% in the first five years to 9.5% for adenomas present longer than 15 years. Gross pathology of carcinoma ex-pleomorphic adenoma often shows a poorly circumscribed, infiltrative, hard mass. Gross tumors appear firm, unencapsulated, and nodular with areas of central necrosis and hemorrhage. Microscopically, the diagnosis is based on a malignant process that infiltrates a neoplasm, which has the histological features of a pleomorphic adenoma. The malignant portion of the tumor can take the form of any epithelial malignancy except acinic cell. Most commonly this will be in the form of an undifferentiated carcinoma (30%) or adenocarcinoma (25%). This tumor tends to be more aggressive than other salivary malignancies and about 25% of patients will have lymph node metastasis on presentation. Regrettably, these cancers when they appear, are among the most aggressive of all salivary gland malignant neoplasms, accounting for 30% to 50% mortality in 5 years.

The treatment of choice for carcinoma in pleomorphic adenoma has consisted of en-bloc excision with wide margin, often in conjunction with neck dissection, and postoperative radiation therapy but recurrence is common. Prognosis appears to be related to local extent of disease and the histological type of the carcinoma component.

Lymphoma

Is a type of cancer involving lymphocytes, the cells of the immune system. It is a group of cancers that affect the cells that play a role in the immune system, and primarily represents cells involved in the lymphatic system of the body. It is a malignant transformation of either lymphocytes B or T cells or their subtypes. Lymphomas fall into 1 of 2 major categories. Hodgkin lymphoma (HL, previously called Hodgkin's disease) and all other lymphomas (non-Hodgkin lymphomas or NHLs). Hodgkin lymphoma develops from a specific abnormal B lymphocyte lineage. NHL may derive from either abnormal B or T cells and are distinguished by unique genetic markers.

A. Risk Factors

Age: **Generally the risk of NHL increases with advancing age. HL in the elderly is associated with a poorer prognosis than that observed in younger patients.**
Infections: **HIV, human T-lymphocytic virus type 1 (HTLV-1), Epstein-Barr virus (EBV), one of the etiologic factors in mononucleosis, *Helicobacter pylori,* a bacterium that lives in the digestive tract, hepatitis B or hepatitis C virus**
Medical conditions that compromise the immune system: **HIV, Autoimmune disease, Diseases requiring immune suppressive therapy, often used following organ transplant, Inherited immunodeficiency diseases (severe combined**

immunodeficiency, ataxia telangeiectasia) *Genetics:* Family history of lymphoma.

B. Epidemiology

Lymphoma is the most common type of blood cancer in the United States. It is the sixth most common cancer in adults and the third most common in children. Non-Hodgkin lymphoma is far more common than Hodgkin disease. It can occur at any age, including childhood. Hodgkin disease is most common in 2 age groups: young adults aged 16-34 years and in older people aged 55 years and older. Non-Hodgkin lymphoma is more likely to occur in older people. There is no sex predilection (M:F ratio of 1:1)

C. Clinical Manifestations

Often, the first sign of lymphoma is a painless swelling in the neck, under an arm, or in the groin. Lymph nodes or tissues elsewhere in the body may also swell. The enlarged lymph node sometimes causes other symptoms by pressing against a vein or lymphatic vessel (swelling of an arm or leg), a nerve (pain, numbness, or tingling), or the stomach (early feeling of fullness). The following are non-specific signs and symptoms: fevers, chills, unexplained weight loss, night sweats, lack of energy, and itching.

D. Treatment

Standard first-line therapy (primary therapy) for lymphoma includes radiation therapy for most early-stage lymphomas, or a combination of chemotherapy and radiation. For later stage lymphomas, chemotherapy is primarily used, with radiation therapy added for control of bulky disease. Biological therapy, or immunotherapy, is increasingly being used in addition to or as an alternative to these standard therapies.

E. Prognosis

The outlook for HL is very good. It is one of the most curable cancers. The 5-year survival rate after treatment is greater than 80% for adults and greater than 90% for children. As a result of refinements in and more aggressive approaches to therapy, the outlook for NHL has improved significantly in the last few decades. The 5-year survival rate after treatment is 55% for adults and about 80% for children. The addition of immunotherapy to standard treatment for NHLs may further improve survival rates.