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## Treatment approaches for benign tumors of major salivary glands

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### Abstract

**Introduction:** Salivary gland tumours (SGT) are heterogenous group of neoplasms in the maxillofacial area with complex morphologic appearances and different clinical behaviour. They often present as painless enlarging masses, mostly located in parotid glands and mostly benign.

**Epidemiology:** SGT's are more common in women than in men which represents 2%-3% of head and neck neoplasms. Pleomorphic adenomas are most common benign SGT's followed by Warthin tumours.

**Treatment:** Difficulty with salivary gland tumour is they are rare and have long clinical course that requires follow up data for a decade or more. Prospective randomised trails have therefore not been undertaken and hence progress happens slowly. Improved methods of assessment (MRI, CT, Ultrasound, fine needle aspiration biopsy) have had major impact on salivary gland surgery. Most benign tumours are either pleomorphic adenomas (71%) or Warthin's tumours (22%).

**Conclusion:** Treatment for this include both medical and surgical therapy. Medical therapy is indicated for inflammatory infectious masses (eg: reactive or fungal) and lymphoma. When symptomatic, recurrent chronic gland infection (eg: parotitis) proves refractory to conservative medical or endoscopic (i.e. sialoendoscopy) treatments, salivary gland excision is sometimes indicated. Surgical therapy includes parotidectomy and submandibular gland surgery.

**Keywords:** benign tumors, salivary glands, neoplasms

### Introduction

The WHO recategorized salivary gland tumours into 5 major categories in 2017:

1. Benign tumours
2. Malignant tumours
3. Non neoplastic epithelial lesions
4. Benign soft tissue lesions
5. Hematolymphoid tumours

Salivary gland tumours represent 2-4% of head and neck neoplasms and are uncommon.

The major salivary glands include Parotid, Submandibular, Sublingual. Most of the tumours generates in the Parotid glands {approx.80% } and remaining in submandibular, sublingual and minor salivary glands.

Malignancy of SGT is inversely proportional to the size of the gland from which it arises. clinicians may suspect the tumours of salivary glands through physical examination or patient's history. The tumours usually exhibit as growth or enlargement of the affected gland.

Depending on the location of the gland, they can present with nerve compression symptoms when patients are seen later in the course with larger tumours. Clinicians may investigate and exclude a history of weight loss, underlying infectious processes (eg: fever, elevated WBC count, concomitant lymphadenopathy) and clinical indications of lymphoma type-B symptoms (eg: night sweat, fever and chills).

Clinicians should get alert to the possibility of malignant diagnosis with feature such as pain, rapid growth, cranial neuropathies, fixation to soft tissue or bone, associated adenopathy. In addition to that malignant neoplasms originating from salivary tissues or mucosal or cutaneous lining of the head and neck region should be excluded.

Before definitive surgical therapy, Radiographic imaging (eg: ultrasonography, computed tomography [CT] and magnetic resonance imaging [MRI]) often provides useful information.

In some selected cases cytopathologic evaluation such as using fine-needle aspiration (FNA) may help to dictate the extent of surgical management. In most case presenting with salivary masses, the decision to intervene surgically is largely based on clinical assessment and imaging findings.

From 1650-1750, salivary gland surgery was limited to the treatment of ranulas and oral calculi. In 1802, the concept of surgical excision of a parotid tumour has been attributed to Bertrandi. An extensive approach, which causing serious disfiguration and disability are included as initial applications of this surgery.

The focus shifted towards dissection and intimate relation between the facial nerve and parotid glands in 1850. John C Warren, MD was the first to use ether inhalation anesthesia during his resection of parotid tumour in Boston in 1846. Grafting of facial nerve after resection was attempted in early 1950's.

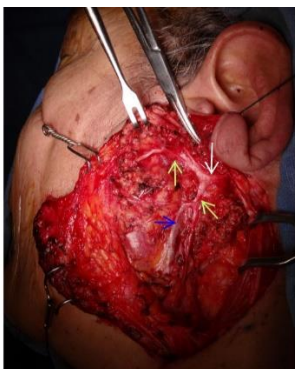
### Anatomy

The parotid gland is situated in the musculo skeletal recess formed by portions of temporal bone, atlas, mandible along with their related muscles. On the basis of the plane in which extra temporal portion of facial nerve runs, the gland is divided into superficial and deep lobes. The deep lobe can extend in para pharyngeal via stylomandibular tunnel. The superficial layer of the deep cervical fascia surrounds the parotid glands. The parotid gland is separated from submandibular gland by this fascia which has an antero-inferior portion that becomes stylomandibular ligament.

The facial nerve exists the stylomastoid foramen just posterior to the base of the styloid, gives off small branches to the post auricular and posterior belly of digastric muscles, and then turns antero-laterally. Just superficial to the retromandibular vein, the main trunk embedded in parotid tissue and divides into temporofacial and cervicofacial branches. In general, however, there are five peripheral nerve branches, as follows:

- Temporal or frontal
- Zygomatic
- Buccal
- Marginal mandibular
- Cervical

Multiple landmarks are used to identify the main trunk of the facial nerve during surgery. (See the image below)



Facial nerve (white arrow) and its divisions (green arrows) are shown. Retromandibular vein is visible (blue arrow).

Facial nerve (white arrow) and its divisions (green arrow) are shown. Retromandibular vein is visible (blue arrow).

Most of the submandibular or digastric triangle are encompassed by the submandibular gland. Like the parotid gland, the submandibular gland can be divided into superficial and deep lobes on the basis of the relationship with the mylohyoid muscle. The marginal mandibular branch of the facial nerve courses between the deep surface of the platysma and the investing fascia that lies over the submandibular gland. Just deep to this nerve, the facial artery and veins are located, and ligation and superior traction of these vascular structures can prevent the nerve injury during surgery.

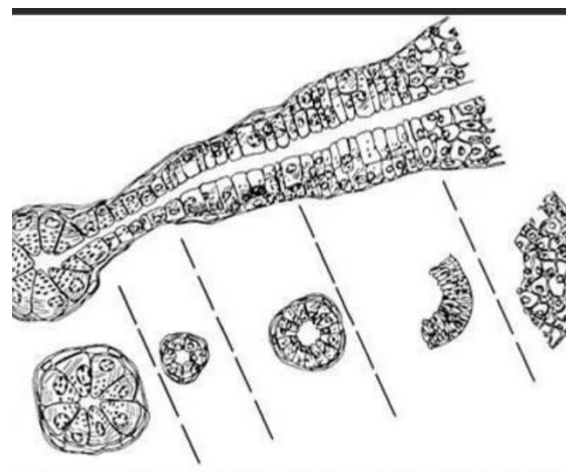
Located along the posterior border of the mylohyoid are the lingual nerve, submandibular ganglion, and submandibular duct (Wharton duct). The hypoglossal nerve courses deep to the tendon of the digastric and thus lies medial to the superficial layer of the deep cervical fascia.

The sublingual gland is located between mylohyoid and hyoglossus muscles. This gland is rather superficial and is covered by thin layer of oral mucosa thus, it can be palpated in the floor of mouth.

The minor salivary glands are widely dispersed through out the upper respiratory tract, including palate, lip, pharynx, nasopharynx, larynx and parapharyngeal space. The greatest densities of the glands are located in hard (250 glands) and soft (150 glands) palates.

### Pathophysiology

The histogenesis of SGT's is based on the salivary gland unit (see the image below). According to the multi cellular theory of SGT's, pleomorphic adenomas originate from intercalated duct cells and myoepithelial cells; oncocytic tumours originate from the striated duct cells; acinic cell tumours originate from the acinar cells; and mucoepidermoid and squamous cell tumours originate from the excretory duct cells.



### Etiology

Although the etiology of SGT's is unknown, associations with environmental or genetic factors have been suggested. Smoking has been closely associated with Warthin tumours. Radiation exposure has been linked to the development of benign warthin tumours and to the malignant mucoepidermoid carcinoma. Epstein bar virus may be a factor in the development of lymphoepithelial tumours of the salivary glands. Genetic alterations (eg: allelic loss, monosomy, and polysomy and structural rearrangement) have been studied as factors in the development of SGT'S.

### Epidemiology

SGT's are more common in women than in men which

represents 2%-3% of head and neck neoplasms. The peak incidence is in 3<sup>rd</sup> and 4<sup>th</sup> decades of life. Pleomorphic adenomas are most common benign SGT's followed by Warthin tumours (papillary cystadenoma lymphomatosum).

### Prognosis

Pleomorphic adenomas, in particular, have a very low rate of recurrence, which is presumed to be the result of incomplete surgical excision due to pseudopod extension of the tumour. If untreated, benign pleomorphic adenoma may, in rare cases, undergo transition to a malignant variant called carcinoma ex pleomorphic adenoma; the rate of such transformation is estimated at 10% over 10- 15 years.

### Clinical Presentation

#### Based on history and physical examination

The classic presentation of benign SGT's is pain less, slow growing mass on the face, angle of mandible, neck or floor of the mouth. One may also appreciate medialisation of palatine tonsil in cases of tumour originating in the deep lobe of parotid and extending into parapharyngeal space. A sudden increase in size may be indicative of infection, cystic degeneration, haemorrhage inside the mass or malignant degeneration. In contrast to malignant SGT's, benign neoplasms are slow growing, are almost always freely mobile and not fixed to the skin, generally do not cause neural palsies such as facial nerve dysfunction, pain, hoarseness etc.

#### Based on classification of tumours

They are classified on the basis of their cytologic, architectural, biologic characteristics. In 2017 WHO classifies head and neck tumours of SGT's into following five categories:

1. Malignant tumours (including various carcinomas, adenocarcinomas and sarcomas).
2. Benign tumours.
3. Nonneoplastic epithelial lesions (sclerosing polycystic adenosis, oncocytic hyperplasia, lymphoepithelial sialadenitis, intercalated duct hyperplasia).
4. Benign soft-tissue lesions (hemangioma, lipoma, nodular, fasciitis).
5. Hematolymphoid tumours (mucosa-associated lymphoid tissue {MALT} lymphoma).

#### Table. 1 WHO classification of benign SGT's

- Pleomorphic adenoma
- Warthin tumour
- Oncocytoma
- Basal cell adenoma
- Myoepithelioma
- Lymphadenoma
- Cystadenoma
- Sialadenoma papilliferum
- Ductal papilloma
- Sebaceous adenoma
- Canalicular adenoma and other ductal adenomas.

### Pleomorphic adenoma

These are the most common tumours of salivary glands which are located in the tail of the parotid gland. When they are found in the minor salivary glands the most frequently involved site is hard palate followed by the upper lip. Because of the epithelial and connective tissue components which composed in varying degrees, these tumours were termed as pleomorphic.

Pleomorphic adenomas that arise in the minor salivary glands usually lack a capsule. Their gross appearance is a round, smooth mass with a thin, delicate incomplete capsule.

This thin, delicate capsule may have pseudopod projections into the surrounding parotid tissue. They may become larger than other SGT's but usually grow slowly. This is considered as particular clinical significance because it contains clean margins as well as avoiding spillage, so they are mandatory to minimize recurrence.

Microscopically, benign mixed tumours are characterized by variable and diverse structural histologic patterns. Frequently, they have growth patterns of sheets, strands or islands of spindle and stellate cells, with a myxoid configuration which is occasionally predominating. Complete surgical excision of the affected gland is indicated as a treatment of benign neoplasms. If the parotid gland is involved, then superficial parotidectomy with standard facial nerve dissection and preservation is the procedure of choice. Due to the tendency towards tumour spillage and recurrence, Enucleation is contraindicated.

### Warthin tumour

Warthin tumour (papillary cystadenoma lymphomatosum or adenolymphoma) was first recognised by Albrecht in 1910 and later described by Warthin in 1929. It is well encapsulated when located in parotid gland and contains multiple cysts.

Histologically the tumour has heavy lymphoid stroma and aciniform epithelial cells that lines the cystic areas with papillary projections. These tumour tends to be bilateral in 10% of cases and usually found in major glands. Malignant transformation is exceedingly rare, and surgical excision is typically curative with excellent prognosis.

### Oxyphilic Adenoma (Oncocytoma)

It was first described by Duplay in 1875. They are very uncommon, occurs more often in women than in men with ratio of 2:1. Superficial lobe of the parotid gland is the most commonly reported location in patients older than 50 years. Oncocytoma rarely occurs in minor salivary glands which manifest as small firm slow growing spherical masses.

Histologically they are large, spherical and have distinct capsule. Uniform cells are arranged in solid sheets. If the excision is incomplete tumour may re occur.

### Myoepithelioma

They are originated as monomorphic cell type which may display a spindle pattern of growth, plasma cytoid pattern or with combination of two. These are less common benign tumours. Any recurrence after surgical excision is due to the result of incomplete resection.

### Ductal Papilloma (DP)

DP is a small tan, fairly smooth lesions found in sub mucosal layer. DP of minor salivary glands is a rare lesion that has been described in various case reports. Microscopically, DP consists of cystically dilated duct partially lined with cuboidal epithelium with complex anastomosing papillary fronds of variable size filling the cystic area.

Histologically the differential diagnosis of DP includes papillary cystadenoma in which intraductal hyperplasia occurs and dilated duct contains some papillary folds and projections.

### Basal cell adenoma

Basal cell adenomas are composed of basaloid cells with scant cytoplasm mostly arise in the major salivary glands. When

compared with other benign monomorphic tumours, recurrence of these tumours is uncommon after surgical excision.

### Other benign SGT's

It includes

- Lymphadenoma
- Cystadenoma
- Sialadenoma papilliferum
- Sebaceous adenoma
- Canalicular adenoma

### Diagnosis

It includes laboratory studies, imaging studies biopsy.

**Laboratory studies:** performing a WBC count to investigate for any evidence of leucocytosis and shift that might indicate a possible infectious process or lymphoproliferative disease.

**Imaging studies:** They are most helpful in diagnosis of SGTs. It includes ultrasonography (US), Magnetic resonance imaging (MRI), Computed tomography (CT),

Ultrasonography is often the first line modality for diagnosing the neoplasm in parotid or submandibular glands. In many cases, high resolution US can assess the size, morphology and type of borders.

Magnetic resonance imaging (MRI) and Computed tomography (CT) may be used to diagnose the larger tumours, those extend beyond the depth that US can assess. MRI is most sensitive test for establishing the borders of soft tissue tumour extension and perineural invasion or spread. In most cases, differentiation between the benign and malignant disease is not reliably used by MRI and CT.

**Biopsy:** in selected cases, fine needle aspiration (FNA) biopsy (FNAB) may facilitate the management of a mass in the salivary gland by helping to distinguish a tumour from certain nonneoplastic or inflammatory processes that may respond better to medical management.

Most benign tumours and low-grade malignancies without lymphadenopathy are treated by surgical extirpation of the primary tumours alone. In most patients who present with a salivary mass, the decision to offer surgical management is likely to be determined by clinical and imaging diagnosis, and FNA may be considered as special consideration based on the cases. Patients with high grade salivary malignancies may require removal of the primary tumour and lymphadenectomy at the same time.

Additionally, the utility of FNA in distinguishing high-grade malignancies from low grade malignancies and benign tumours may be limited by the local availability of expertise. The reliability of FNA in making the diagnosis and determining the grade of malignancies remains a controversial issue. In the absence of the ability to differentiate the grade of malignancy, FNA may play a limited role in the decision to offer an operation; however, if the diagnosis of a high-grade salivary gland malignancy is made preoperatively, FNA may influence the extent of the operation.

### Treatment and Management

Treatment indicates both medical therapy and surgical therapy. When a patient develops salivary gland mass generally surgical excision is indicated by many experienced clinicians. Surgical treatment of salivary gland tumours is also indicated for the following:

- Mass of the face, neck and floor of the mouth
- Presence of clinical signs of malignancy (a rapid growth on a slow growing tumour, bleeding, airway compromise due to larger tumours, and nerve dysfunction such as paraesthesia).

### Medical therapy

Medical therapy is indicated for inflammatory infectious masses (eg: reactive or fungal) and lymphoma. When symptomatic, recurrent chronic gland infection (eg: parotitis) proves refractory to conservative medical or endoscopic (i.e. sialoendoscopy) treatments, salivary gland excision is sometimes indicated.

### Surgical therapy

Complete removal of the neoplasm with an adequate margin of the tissue to avoid recurrence is included as management of benign SGT's. This usually involves extra capsular dissection of the tumour within the affected gland or complete removal of the gland in which the tumour is developed. Excision is performed with general anaesthesia and without paralysis. The endotracheal tube is usually positioned in the corner of the mouth opposite to the surgical field.

### Parotidectomy

The safe localisation of the facial nerve at the main trunk proximal to the gland is the main key to parotidectomy. The possibility of total parotidectomy should be included in the preoperative plan. When a malignant diagnosis has not been ruled out, there should be preoperative discussion of potential need to sacrifice the facial nerve, with immediate grafting, cervical lymphadenectomy and mandibulectomy.

The initial procedure of choice for benign parotid gland tumour is superficial parotidectomy. A modified Blair incision is often used. The incision usually starts just anterior to the ear helix, extends inferiorly below the ear lobe, and then continues on to the neck, paralleling – but staying at least 2 cm below – the body of the mandible. Other approaches including a facelift incision, have been described.

The surgical field is exposed broadly in order to avoid the injury to facial nerve, with the sternocleidomastoid muscles and posterior belly of the digastric muscles serving as anatomic landmarks. Additionally, the cartilage of the external auditory canal is exposed, and the tragal pointer and the tympanomastoid suture line used to direct careful dissection so that the main extratemporal trunk of the facial nerve can be visualised.

Once the main trunk is exposed, dissection is performed to expose, while avoiding injury to, the individual branches of the nerve and ultimately to excise the tumour.

During dissection for confirmation of integrity, the stimulation of the nerve is used by monitoring the facial nerve with an optional electromyographic (EMG). Although this is an exceedingly rare scenario with dissection for benign tumours. If the tumour necessitates resection of a portion of the facial nerve, the nerve should be immediately repaired or reconstructed to afford the best chance of maintaining tone in the muscles or muscles being innervated.

Another potential complication is sacrifice of the greater auricular nerve causing loss of sensation to the ear lobule and surrounding skin. To avoid this, careful dissection through the subcutaneous plane is performed to permit identification and preservation of the nerve as the anatomy allows.

Other approaches using avascular fat graft have also been described. The facial hollowing and loss of facial symmetry that may result from tumour and gland removal can sometimes be

addressed at the time of surgery by placing cadaveric human dermal matrix or even by rotating a portion of the nearby sternocleidomastoid muscle into the deficit.

Postoperative gustatory sweating is rare but may occur with aberrant reinnervation of the parasympathetic after parotid surgery. Use of thick skin flaps, placements of human dermal matrix or both may mitigate this complication.

Enucleation should be avoided so as to minimise the chance of tumour spillage and seeding recurrence. Recurrence of a benign tumour can be avoided with complete excision of the lesion.

### **Submandibular gland surgery**

It is performed with the patient under general anaesthesia with endotracheal intubation. Head rotation is to the opposite side of the tumour.

An incision is made at least 2cm below the body of mandible through the platysma for the identification of superficial layer of deep cervical fascia. A technique of dividing the facial vein and raising a facial flap/plane may be employed to ensure that dissection is deep to the nerve, in order to avoid injury to the marginal mandibular branch of the facial nerve. Other approaches include direct identification of the nerve to avoid injury during dissection.

Careful dissection with appropriate identification and preservation of these structures is recommended. Another potential complication during submandibular gland or tumour excision is injury to the hypoglossal nerve or the lingual nerve.

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