

# Salivary Glands and Its Myriad Forms of Cancers – Diagnosis And Therapy

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**Abstract-** Salivary gland is a complex, compound secretory tissue seen in the oral cavity, which produces saliva and maintains oral homeostasis. Salivary gland diseases can range from swelling of the gland to malignancies. In order to understand the localization and the diagnosis of the salivary gland diseases, it is important to understand the development, structure and function of the gland. This review article summarizes the biology, diseases and the diagnostic tool available to investigate and evaluate the disease.

**Index Terms-** Saliva, parotid gland, submandibular gland, sublingual gland, seromucous acini, diseases, diagnosis.

## I. INTRODUCTION

The oral cavity and upper digestive tract are bathed by 1,000 to 1,500 cc. of saliva per day, providing the lubrication necessary for speech and swallowing (1). Some of these secretions are contributed by three large paired major salivary glands: the parotid glands, the submandibular glands, and the sublingual glands. In addition, there are hundreds of submucosal minor salivary glands, primarily in the oral/ nasal cavities, paranasal sinuses, lips, tongue, hard and soft palate, and pharynx and larynx that constitute and supply a substantial portion of the total saliva. Saliva produced contains antibacterial, antiviral, antifungal, digestive and buffering enzymes that are essential for eating, speaking, tasting, and oral hygiene (2). Developmentally and histologically the minor salivary glands resemble the larger paired glands. Therefore, they are subject to the same pathologic processes. Procedure for Paper Submission

## II. DEVELOPMENT OF THE SALIVARY GLANDS

All of major and minor salivary glands share a common embryogenesis in that the development of the glandular structure is the result of highly orchestrated complex interaction between 2 distinct tissues, namely the oral epithelium and the underlying mesenchyme (3). The first sign of glandular development consists of a thickening of the oral epithelium, also called as placode or prebud stage. In humans, between the fourth and sixth embryonic weeks, the parotid anlagen appear first while the placodes for the submandibular glands appear later at the sixth week of embryonic development in the medial paralingual sulcus (4). The sublingual gland anlagen arise from multiple epithelial

placodes during the seventh to eighth week of embryonic development. Finally at the twelfth week, development of the minor salivary glands occurs (Fig 1)(5).

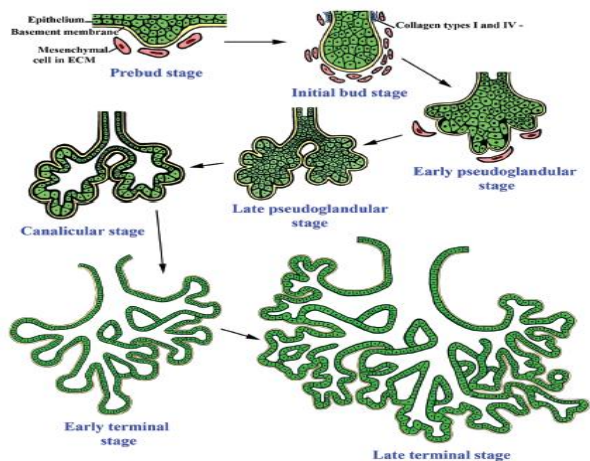
On the oral side of each parotid gland epithelial placode, an opening in the epithelium appears, which marks the opening of the main duct of the parotid gland into the oral cavity. The main duct of the parotid gland is called Stensen's duct. However, for the submandibular gland, the epithelium medial to the initial epithelial placode rolls up resulting in a tube that runs alongside the base of the tongue and opens up in the oral cavity at the submandibular caruncle. Thus, for the submandibular gland, the opening of the main duct in the oral cavity is not at the site of the original epithelial placode. The main duct of the submandibular gland is called as the Wharton's duct. Finally, on both sides of the tongue, the sublingual epithelial placodes will form a gland with a separate excretory duct called as the duct of Rivinus.

Following the prebud stage, the thickened epithelium invaginates into the underlying mesenchyme, leading to the formation of a bud which constitutes the primordium of the intralobular parenchyma. The bud is connected to the oral epithelium through a thick solid epithelial stalk, that later gives rise to the main salivary duct. Mesenchymal cells cover the bud, which subsequently form the protective capsule of the gland. A division formed at the surface of the epithelial bud, divides the bud into 2 to 3 secondary buds as a result of high mitotic activity of the epithelial cells. This leads to the formation of a multilobed gland and hence this stage is called as the pseudoglandular stage (Fig 1). The development of the epithelial glandular tree is formed by the solidification of the chords in the canalicular stage. The chords hollow out to give rise to a lumen, which serves as a passage between the glandular structure and the oral cavity.

The final stage of development known as the terminal differentiation stage starts with morphological and functional differentiation of the epithelial cells lining the ducts, tubules, and acini. The ducts differentiate into excretory, striated, and intercalated ducts. The cells within the acini differentiate into serous or mucous secretory cells and myoepithelial cells. The intercalated ducts lead from the acini to the striated ducts. The primary function of the ducts is primarily the transport of saliva to the oral cavity. However, these ducts play a role in modifying the salivary contents of electrolytes.

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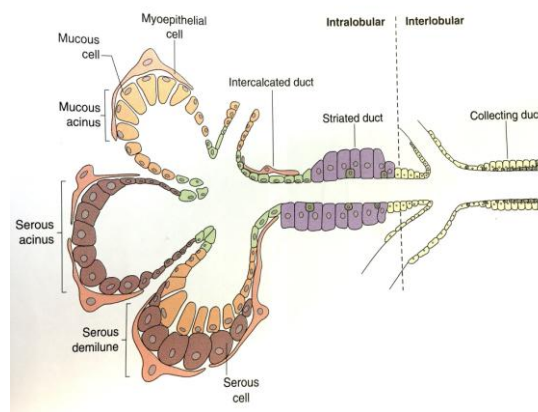


**Figure 1:** Different stages in salivary gland development.

(Adapted from Som P.M., Miletich I. The embryology of the salivary glands: An update. Neurographics. 2015 July/August; 5(4):167-177)

### III. STRUCTURE OF THE SALIVARY GLANDS

Epithelial outgrowths give rise to secretory units called as acini and ducts. These acini and ducts are of ectodermal origin for the major glands while it is of ectodermal and endodermal in origin for minor salivary glands of the oral cavity. The gland is covered by an outside capsule, which is filled with stroma. The stroma is further divided into septae, which divides the gland into lobes and lobules. Each lobule contains acinuses that are serous or mucous cells depending on the gland. The acinar cells are pyramidal, with basally located nuclei surrounded by dense cytoplasm and secretory granules that are most abundant in the apex. Mucous acini store a viscous, slimy glycoprotein (mucin) within secretory granules that become hydrated when released to form mucus. Mucous acini store a viscous, slimy glycoprotein (mucin) within secretory granules that become hydrated when released to form mucus. Mixed or seromucous acini contain components of both types, with one type of secretory unit dominating. The presence of serous demilunes (or half-moons) capping mucous cells is common. Between the epithelial cells and basal lamina of the acinus, flat myoepithelial cells also called as basket cells form a latticework that aids in contraction, and thus resulting in forced secretion of the acinus (Fig 2).

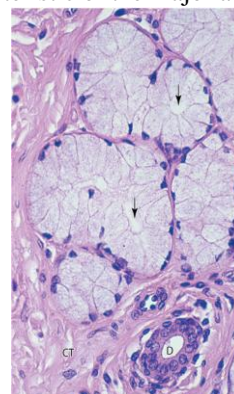


**Figure 2:** Structure of salivary gland showing serous and mucous acinus cells and the ducts. (Adapted from Moxham BJ et al., Oral Anatomy, Histology and Embryology, fourth edition).

### IV. HISTOLOGY OF SALIVARY GLANDS

The nature of salivary secretion varies from serous to mucous saliva. The parotid gland secretes mucous saliva while the sublingual gland secretes serous saliva and the submaxillary glands yields a mixer of both mucous and serous saliva. Mucous glands secrete mucinogens, largely glycosylated proteins that swells upon hydration to a thick lubricant called mucin (Fig 3). Serous glands secrete an enzyme rich water fluid. This makes it easy for differentiating these two cell types histologically. Mucous cells does not stain darkly and will look almost clear on the tissue section. Due to the presence of proteins in the watery secretion of serous cells, they stain fairly darker.

Apart from the above mentioned major salivary glands of the oral cavity, there are other minor gland that produces a mixed mucous and serous secretion. It is this diverse secretion that accounts for the histological spectrum of tumors characteristic of the major and minor salivary glands.



**Figure 3:** Mucous cells of salivary glands are typically larger than serous cells, with flattened basal nuclei and the cytoplasm is filled with secretory granules containing mucinogen. The lumens (arrows) of mucous tubules are

larger than those of serous acini. Much connective tissue surrounds the mucous tubules and ducts (D). X200. PT.(Adapted from AL Mescher, Junqueira's Basic Histology Text and Atlas, 13th Edition)

## V. SALIVA

Saliva is an exocrine secretion that is made of 99% water and also contains electrolytes and proteins (6). These components are responsible for the wide variety of function that saliva has such as lubricating oral tissues and acting as a buffer by neutralizing acids that cause enamel demineralization. Other saliva functions include the initial digestion of starch by secreting a digestive enzyme called amylase and contains antibacterial properties like secretory immunoglobulin A (IgA) that neutralizes viruses, enzyme, and bacterial toxins (7). A healthy daily range for saliva production is 1 to 1.5L which is critical for the maintenance of oral tissues (1). Saliva contains a high potassium concentration, low osmolarity and high volume compared to the weight of the salivary glands due to a high secretion rate, up to 1 mL per salivary gland gram per minute. The low osmolarity of saliva can increase with an increased secretion rate though saliva is mostly hypotonic compared to plasma (8).

## VI. PHYSIOLOGY OF SALIVARY GLANDS

Saliva, which is isotonic in comparison to plasma, is first secreted by acini through small canaliculi. These canaliculi then transfer the saliva into the intercalated ducts which in turn empty into striated ducts within the glandular lobule. Squamous and cuboidal epithelium line

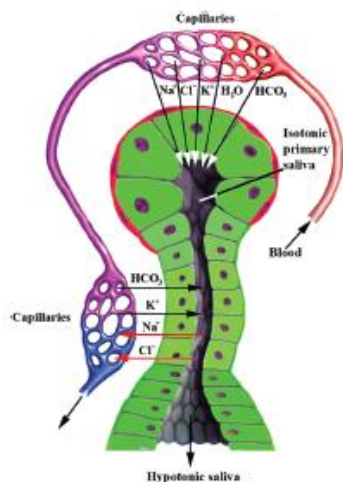


Figure 4: Schematic diagram depicting the flow of electrolyte into and outside of the ductal and acinar system. (Adapted from Som P.M., Miletich I. *The embryology of the salivary glands: An update*. Neurographics. 2015 July/August; 5(4):167-177)

the irregular myoepithelial layer that composes the intercalated discs. The saliva secreted by the acini reabsorbs chloride in the intercalated duct segment and bicarbonate is secreted into this saliva. Membrane invagination and mitochondria provide the distinguishable basal striations seen in the striated ducts. These ducts also have mitochondria that are lined with simple columnar epithelium and are involved in sodium reabsorption from the acini primary secretion as

well as being associated with potassium secretion in the product. The large number of mitochondria present in the striated ducts are mandatory for water and electrolyte transportation. The single secretory unit known as a salivon is composed of a striated duct, intercalated disc, and the acinus. Excretory ducts that lie between lobes and within the connective tissue of salivary gland septae, comprise the next section of the duct system. Goblet cells distributed between pseudostratified columnar cells make up the epithelial lining. The composition of the oral cavity's epithelial lining changes as the diameter of the duct increases, progressing from stratified columnar to nonkeratinized stratified squamous cells.

Salivary glands function to produce and secrete saliva to aid in biological processes like digestion, taste, and protecting tooth enamel integrity. High potassium and low sodium concentrations are found in salivary glands when compared to plasma but increased flow rates cause  $\text{Na}^+$  concentration to increase and  $\text{K}^+$  concentration to decrease slightly and then level off. Chloride is also present in salivary glands and its concentration follows the same trend as  $\text{Na}^+$ , meaning both ions are slowly absorbed and secreted from acinus to duct. At lower secretion rates, a hypertonic concentration of bicarbonate is present when compared to plasma. Saliva generally remains hypotonic to plasma because  $\text{Na}^+$  and  $\text{Cl}^-$  reabsorption is greater than  $\text{K}^+$  and  $\text{HCO}_3^-$  secretion in salivary ducts (Fig .4)(8).

The autonomic nervous system controls the secretion, blood flow, and growth of salivary glands but the parasympathetic branch has more influence on the rate of secretion. Stimulation of the parasympathetic nervous system activates acinar activity and ductal transport mechanisms which lead to vasodilation of glands and the contraction of myoepithelial cells that causes the expulsion of secretions. A neurotransmitter called acetylcholine binds to the muscarinic receptors of the salivary glands and causes an influx in calcium ions that greatly affects the volume of salivary secretions, - the larger the amount of calcium, the larger the volume that is produced (9).

## VII. SALIVARY GLAND SWELLING

### A. Sialolithiasis

Sialolithiasis is a condition also known as salivary duct stones that is characterized by pain in the salivary glands at mealtimes along with occasional swelling. This irregularity is commonly caused by a calculus build up, usually on the floor of the mouth blocking the submandibular duct, which creates pressure to build up and leads to swelling. Treatment for these obstructions range from a non-invasive technique of removing the stone to a more aggressive removal of the entire gland in cases where the stone was closer to the gland making it less accessible.

### B. Infection

A sudden onset of pain and swelling in the salivary glands typically indicates the presence of an infection. Viral



infections in these areas are commonly caused by mumps that present in a bilateral fashion while acute bacterial infections are usually unilateral. Bacterial infections are often seen in elderly people due to dehydration that reduces salivary flow. Antibiotics are used to treat bacterial infections along with recommendations to remain hydrated and increase the consumption of citrus drinks. Supportive care is given for viral infections in the form of anti-inflammatory medications, instructions on good oral hygiene and adequate hydration.

### C. Sialadenosis

The enlargement of the acinar component of salivary glands can cause a generalized swelling of the gland called sialadenosis. Sialadenosis is usually a bilateral, gradual enlargement of the glands and may be a symptom of many systemic diseases. This condition is usually seen in patients that have alcoholism or are bulimic. Management of the underlying cause of this condition usually returns the glands back to their normal state, however, resection of the gland can be done if there is cosmetic concerns.

## VIII. TUMORS OF THE SALIVARY GLANDS

There is a large variety of benign and malignant tumors that occur in the salivary glands, usually appearing in the parotid gland, the largest of the salivary glands. Benign tumors are noncancerous tumors but can be just as harmful to health if not removed or treated and managed.

A mixed tumor is the most common type of benign lesion and make up about 85% of all salivary tumors(10).The term “mixed” came from the original thinking that these lesions were of epithelial and mesenchymal origin although we now know that they are of only epithelial origin. Due to their unusual make-up of histological components such as chondroid, hyalinized mesenchymal, and myxomatous elements, these tumors have beguiled pathologists. Mixed benign tumors are thought to be multicentric because of their high rate of recurrence after excision though there is little evidence to show multicentricity(11).These tumors show tendency to invade the skin or facial nerves surrounding salivary glands and they are typically asymptomatic.

Warthin’s Tumor or papillary cystadenomalympomatousum, is another type of benign tumor that is thought to result from the evolution of heterotopic salivary epithelium in the lymph nodes. This tumor type is usually bilateral, soft and has a multicentric origin that causes a higher rate of recurrence after excision. A predominance of occurrence in men has been shown as a 9:1 ratio (10).

Oxyphilic adenoma, also known as oncocytoma, is a unilateral benign tumor that shows a slow-growing progression along with being solid to the touch. These tumors have a unicentric origin and distinctively large cells with eosinophilic cytoplasm. Recurrence is unusual in oncocytoma tumors.

Malignant tumors are divided into three major classifications including malignant mixed tumors, mucoepidermoid carcinoma, and adenocarcinoma, all of which occur at equal frequencies composing 80 to 90 percent

of salivary gland cancers(10).Malignant mixed tumors are thought to originate from benign mixed tumors and comprise 20 to 30 percent of salivary gland cancers. (10, 12) They have also been found to occur twice as often in women (10).

Mucoepidermoid carcinoma are comprised of mucus-secreting cells, epidermoid cells, and intermediate types of basal or nonmucus-secreting cells. They originate from salivary duct epithelium and more commonly occur in the parotid gland with lessening percentages in smaller glands (10).These tumors can be divided into high and low grade groups characterized by their contents, high grade tumors tend to contain epidermoid and intermediate cells while low grade contain mucus-secreting and intermediate cells.

Adenocarcinomas are further branched into three classifications: adenocystic, acinic cell, and squamous carcinomas based on their histologic appearance and clinical course. Adenocystic carcinomas are the most commonly found cancer in the minor salivary glands. Another name for these tumors is cylindroma, portraying the pattern that is seen from the mucin or hyaline cylinders within areas of epithelial tissue. Adenocystic tumors have been speculated to evolve from peripheral duct system canaliculi and intercalated ducts while presenting clinical similarities to mixed tumors (13).Infiltration of lymphatic vessels,perineural spaces are common in these tumors. Metastases of bone, lung, regional, and visceral lymph nodes are seen in late stages.

Acinic cell carcinoma are low grade and tend to also mimic mixed salivary tumors. Classifications of acinic carcinomas are based on their histologic appearance and include anaplastic, trabecular, solid undifferentiated, and mucus-cell carcinomas. These tumors tend to metastasize on lung and bone tissue and are highly aggressive with the propensity to recur.

Like most salivary gland tumors, squamous carcinomas appear regularly in the parotid gland but are also frequently found in the submaxillary gland. There has been much debate on the origin of this tumor line but it is speculated that they begin as ductal squamous carcinomas or mucoepidermoid carcinomas where the epidermoid element has become predominant(10).This disease is progressing rapidly as shown by a study in which 50 percent of diagnosed patients died within one year(14).

## IX. OTHER DISEASES IN SALIVARY GLAND

Sjogren’s syndrome is an autoimmune disorder commonly seen in menopausal women. This syndrome causes the body to produce autoantibodies that attack gland cells, such as salivary glands, causing suppression of normal gland secretion. This suppressive action leads to this syndrome’s two most common symptoms, dry mouth and dry eyes. Though the cause for Sjogren’s syndrome is unknown, scientists speculate that viral or bacterial infection act as a trigger that is then propagated by a certain gene that alters the immune response(15).

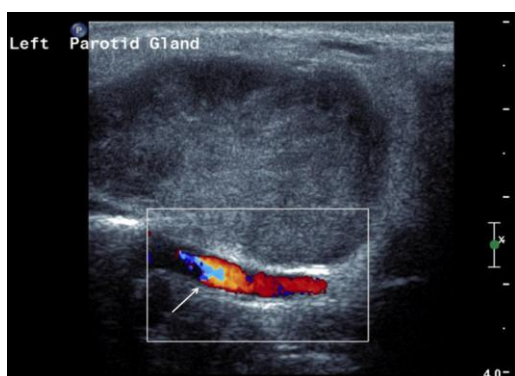
## X. DIAGNOSIS OF THE SALIVARY GLAND TUMORS

Tissue diagnosis of salivary gland tumors is achieved by fine needle aspiration cytology (FNAC) and is very simple to perform. This method is often chosen over open biopsy because it offers a clean operative field and eliminates the

need for surgery in patients with conditions such as sialadenitis, tuberculosis, and lymphoma. Studies show a 95% confidence interval of FNAC when determining non-neoplastic conditions versus neoplastic conditions(16).Ultrasound guidance is used to help optimize diagnostic information gained through FNAC and the incorporation of a cytologist to determine specimen adequacy or immediate diagnosis promotes the efficacy of this method. A study that consisted of 292 samples that were aspirated using ultrasound guidance and 600 samples that were collected by free hand, were compared showing a 23% accuracy improvement in the ultrasound guided specimens (17). Another, more recent, method of salivary tissue biopsy is a core needle biopsy that claims to be minimally invasive. Studies done on this new method showed that the core needle biopsy was more accurate than the FNAC, however, it is limited by the risk of damage it poses to other local structures, patient discomfort, and the need for local anesthesia(18).

#### A. High-Resolution Ultrasonography

A quick and safe method of tumor imaging is a high-resolution ultrasonography. These images are able to provide a detailed look at the margins and internal characteristics of salivary lesions while also providing the ability to detect features of malignancy. Ultrasonography is not just useful for identifying benign and malignant tumors (Fig 5), but also gives detailed insight in non-neoplastic diseases of the salivary glands, such as, identifying and guiding drainage from infections and tracing dilated ducts to assess salivary duct stones(19).A comparative analysis showing the efficacy in identification of salivary duct stones using ultrasonography vs. standard sialography, radiographic examination, was performed in a study of 24 patients and showed an 80% specificity and sensitivity with the ultrasonography (20).



**Figure 5:** A high resolution ultrasonography image of a pleomorphic adenoma in the left parotid gland. (Hisham Mehanna. Salivary Gland Swellings. BMJ. 2012.)

#### B. Magnetic Resonance Imaging

When evaluating masses in the parapharyngeal space, magnetic resonance imaging (MRI) is the preferred examination method because it can discriminate between deep lobe parotid tumors and other pathology (19) (Fig 6).This imaging system allows for detailed images to be taken

on different planes, has better resolution when compared to computed tomography (CT), and less harmful radiation that the patient is exposed to. The resolution that MRI's provide enables for a more detailed look at tumor margins and improves the accuracy of local staging. Useful anatomical information can be seen on these images to aid in surgical removal and is very helpful in tumors that involve the deep parotid lobe.



**Figure 6:** Magnetic resonance image of a pleomorphic adenoma of the parotid gland. (Hisham Mehanna. Salivary Gland Swellings. BMJ. 2012.)

#### C. CT And Positron Emission Tomography

Computed tomography (CT) provides a two-dimensional view of salivary glands which make relationships between glands and other neighboring vital structures more clear, particularly in the assessment of parotid and submandibular glands. These scans can also detect distant metastasis from the primary malignancy, which is imperative for patients with salivary gland malignancies, by using a contrast enhanced version of CT. PET, positron emission tomography, is a method of detecting distant metastasis and recurrence in which it has proven to be highly sensitive and specific. PET scans use F-fluorodeoxyglucose, a radiopharmaceutical, that both benign and malignant tumors take up and causes these tissues to fluoresce in PET images. A study done on 55 salivary gland cancer patients showed that PET-CT scans have 74.4% sensitivity and 100% specificity for recurrence and distant metastasis recognition (21) (Fig 7).



Figure 7: CT image with contrast enhancement of a right parotid mass. Solid arrow shows the parotid mass infiltrating subcutaneous fat while the dotted arrow shows the spread of the mass to the right upper lymph node. (Hisham Mehanna. Salivary Gland Swellings. BMJ. 2012)

### D. Salivary Ductal Imaging

Intricate ductal systems of the parotid and submandibular glands can be exposed by salivary ductal imaging which injects an iodinated contrast media that allows detailed radiographs to be taken and assessed. Magnetic resonance imaging can also be implemented as a non-invasive technique and can be combined with procedures for therapeutic salivary intervention. Contrast sialography and magnetic resonance imaging were compared in a study of 80 patients which found an 80% sensitivity and 98% specificity in favor of magnetic resonance sialography (22).

### E. Radiologic And Endoscopic Examination

Visualization of the pathology for glands and ducts is an invaluable resource when diagnosing salivary gland tumors. The endoscopic evaluation of salivary glands is called sialendoscopy, which minimally invasive and involves a narrow-diameter fiber optic endoscope. Probes gently dilate ducts and then an endoscope is used for evaluation. This method allows for the diagnosis, treatment, and therapy for benign tumors to be completed.

## XI. TREATMENT OPTIONS

After securing a definitive diagnosis and classification for a salivary gland tumor, which can be considerably difficult, the most common treatment for salivary neoplasms is surgical excision. Special precautions must be taken when removing the tumor as to not spill any of the contents which may cause regrowth. Malignant tumors require larger excision margins to ensure that all cancerous matter is removed and an elective or therapeutic neck dissection may be indicated to manage nodal metastasis. After surgical removal, postoperative radiotherapy is often given with respect to surgical resection margins, size, and histological grade of the tumor.

## XII. CONCLUSION

Salivary gland malignancies are rare but the key determinants of the disease, includes staging (early/advanced), histologic grading (low/high) and margin status (clear/positive). However, successful treatment begins with surgical management coupled with the appropriate use of radiation therapy and chemotherapy. Although an optimal management approach has not been established, aggressive salvage surgery is favored due to the morbidity associated with tumor progression towards the skull base. Apart from that, the anatomic complexity of the region with relation to the facial nerve, requires sound surgical planning and decision

making based on pre ad intra operative findings. Early diagnosis of this disease is still under investigation. With the discovery of valuable saliva based prognostic biomarkers, the detection of salivary gland cancers in its infancy could be identified.

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