Salivary Gland Neoplasms

Neoplasms that arise in the salivary glands are relatively rare, yet they represent a wide variety of both benign and malignant histologic subtypes. Although researchers have learned much from the study of this diverse group of tumors over the years, the diagnosis and treatment of salivary gland neoplasms remain complex and challenging problems for the head and neck surgeon. Salivary gland neoplasms make up 6% of all head and neck tumors.[1] The incidence of salivary gland neoplasms as a whole is approximately 1.5 cases per 100,000 individuals in the United States. An estimated 700 deaths (0.4 per 100,000 for males and 0.2 per 100,000 for females) related to salivary gland tumors occur annually.

Salivary gland neoplasms most commonly appear in the sixth decade of life. Patients with malignant lesions typically present after age 60 years, whereas those with benign lesions usually present when older than 40 years. Benign neoplasms occur more frequently in women than in men, but malignant tumors are distributed equally between the sexes.

The salivary glands are divided into 2 groups: the major salivary glands and the minor salivary glands. The major salivary glands consist of the following 3 pairs of glands: the parotid glands, the submandibular glands, and the sublingual glands. The minor salivary glands comprise 600-1000 small glands distributed throughout the upper aerodigestive tract.

Among salivary gland neoplasms, 80% arise in the parotid glands, 10-15% arise in the submandibul ar glands, and the remainder arise in the sublingual and minor salivary glands.

Most series report that about 80% of parotid neoplasms are benign, with the relative proportion of malignancy increasing in the smaller glands. A useful rule of thumb is the 25/50/75 rule. That is, as the size of the gland decreases, the incidence of malignancy of a tumor in the gland increases in approximately these proportions. The most common tumor of the parotid gland is the pleomorphic adenoma, which represents about 60% of all parotid neoplasms, as seen in the image below.

Salivary gland neoplasms are rare in children. Most tumors (65%) are benign, with hemangiomas being the most common, followed by pleomorphic adenomas. In children, 35% of salivary gland neoplasms are malignant. Mucoepidermoid carcinoma is the most common salivary gland malignancy in children.

Successful diagnosis and treatment of patients with salivary gland tumors require a thorough understanding of tumor etiology, biologic behavior of each tumor type, and salivary gland anatomy.

Etiology. The etiology of salivary gland neoplasms is not fully understood. Two theories predominate: the bicellular stem cell theory and the multicellular theory.

*Bicellular stem cell theory***.** This 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.

Multicellular theory. In the multicellular theory, each tumor type is associated with a specific differentiated cell of origin within the salivary gland unit. Squamous cell carcinomas arise from excretory duct cells, pleomorphic adenomas arise from the intercalated duct cells, oncocytomas arise from the striated duct cells, and acinic cell carcinomas arise from acinar cells.

Recent evidence suggests that the bicellular stem cell theory is the more probable etiology of salivary gland neoplasms. This theory more logically explains neoplasms that contain multiple discrete cell types, such as pleomorphic adenomas and Warthin tumors.

Associated factors. Radiation therapy in low doses has been associated with the development of parotid neoplasms 15-20 years after treatment. After therapy, the incidence of pleomorphic adenomas, mucoepidermoid carcinomas, and squamous cell carcinomas is increased.

Tobacco and alcohol, which are highly associated with head and neck squamous cell carcinoma, have not been shown to play a role in the development of malignancies of the salivary glands. However, tobacco smoking has been associated with the development of Warthin tumors (papillary cystadenoma lymphomatosum). Although smoking is highly associated with head and neck squamous cell carcinoma, it does not appear to be associated with salivary gland malignancies. However some studies have indicated a relationship between salivary gland malignancies and occupational exposure to silica dust and nitrosamines.

Pathophysiology. As with most cancers, the exact molecular mechanism by which tumorigenesis occurs in salivary gland neoplasms is incompletely understood. Multiple pathways and oncogenes have been implicated, including oncogenes that are known to be associated with a wide variety of human cancers. These include *p53, Bcl-2, PI3K/Akt*, *MDM2*, and *ras*.

Mutation in *p53* have been found in both benign and malignant salivary gland neoplasms and some evidence suggests that the presence of *p53* mutations correlates with a higher rate of tumor recurrence. RAS is a G protein involved in growth signal transduction, and derangements in ras signalling are implicated in a wide variety of solid tumors. *H-Ras* mutations have been shown in a significant proportion of pleomorphic adenomas, adenocarcinomas, and mucoepidermoid carcinomas.[4]

Studies that look at the neovascularization in salivary gland neoplasms have revealed factors that increase angiogenesis and are important in the progression of salivary gland neoplasms. Vascular endothelial growth factor (VEGF) is expressed by over half of salivary gland carcinomas tested and is correlated with clinical stage, recurrence, metastasis, and survival.

Seventy percent of pleomorphic adenomas have associated chromosomal rearrangements. The most common is a rearrangement of 8q12, occurring in 39% of pleomorphic adenomas. The target gene at this locus is *PLAG1*, which encodes a zinc finger transcription factor. The other target gene is *HMGA2*, which encodes a nonhistone chromosomal high mobility group protein that is involved in structural regulation of the chromosome and transcription. This gene is located at 12q13-15. Because these rearrangements are unique to pleomorphic adenomas amongst salivary gland neoplasms, interrogation of these rearrangements by RT-PCR or FISH may aid in diagnosis.

In mucoepidermoid carcinoma, the t(11;19)(q21;p13) chromosomal translocation has be identified in up to 70% of cases. This translocation creates a MECT1-MAML2 fusion protein that disrupts the Notch signaling pathway. This fusion protein is expressed by all cell types of mucoepidermoid when the translocation is present. Interestingly, fusion-positive tumors appear to be much less aggressive than fusion-negative tumors. Fusion-positive patients have significantly longer median survival and lower rates of local recurrence and distant metastasis.

CD117 or c-kit is a tyrosine kinase receptor that is found in adenoid cystic carcinoma, myoepithelial carcinoma, and lymphoepitheliomalike carcinoma. CD117 expression is able to reliably differentiate ACC from polymorphous low-grade adenocarcinoma, and small molecule inhibitors of this receptor are currently being studied as a potential therapeutic agent.

Other salivary gland neoplasms have been associated with overexpressed beta-catenin through abnormal *Wnt* signaling. Adenoid cystic carcinoma with mutations in *CTNNB1* (b-catenin gene), *AXIN1* (axis inhibition protein 1), and *APC* (adenomatosis polyposis coli tumor suppressor) show tumorigenesis via this process. Promoter methylation is known to develop tumors by inactivating tumor suppressor genes. Mutations that cause hypermethylation and downregulation of *14-3-3ó,* a target gene for *p53* in the Gap2/mitosis (G2/M) cell cycle checkpoint, was found to be extensive in adenoid cystic carcinoma (ACC). The methylation of genes that control apoptosis and DNA repair were also found in ACC, especially in high-grade tumors.

Chromosomal loss has been found to be an important cause of mutations and tumorigenesis in salivary gland tumors. Allelic loss of chromosomal arm 19q has been reported to occur commonly in adenoid cystic carcinoma. Mucoepidermoid carcinomas also show the loss of chromosomal arms 2q, 5p, 12p, and 16q more than 50% of the time.

Multiple other genes are being investigated in the tumorigenesis of salivary gland neoplasms. Hepatocyte growth factor (HGF), a protein that causes morphogenesis and dispersion of epithelial cells, has been found to increase adenoid cystic carcinoma scattering and perhaps invasiveness. Expression of proliferating cell nuclear antigen (PCNA) was found in the 2 most common malignant salivary tumors, mucoepidermoid carcinomas and adenoid cystic carcinomas, with higher expression in submandibular gland—derived malignancies. Overexpression of fibroblast growth factor 8b has been shown to lead to salivary gland tumors in transgenic mice.

Newer research in salivary gland neoplasms is focusing on factors that increase tumor invasion and spread. Matrix metalloproteinase-1, tenascin-C, and beta-6 integrin have been found to be associated with benign tumor expansion and tissue invasion by malignant tumors. In adenoid cystic carcinoma, increased immunoreactivity for nerve growth factor and tyrosine kinase A has been correlated with perineural invasion.

History. Taking a thorough history is important in treating patients with suspected salivary gland neoplasms. A diverse variety of pathologic processes, including infectious, autoimmune, and inflammatory diseases, can affect the salivary glands and may masquerade as neoplasms. Although most masses of the parotid gland are ultimately diagnosed as true neoplasms, submandibular gland enlargement is most commonly secondary to chronic inflammation and calculi.

Initial history taking should focus on the presentation of the mass, growth rate, changes in size or symptoms with meals, facial weakness or asymmetry, and associated pain. A thorough general history provides insight into possible inflammatory, infectious, or autoimmune etiologies.

Most patients with salivary gland neoplasms present with a slowly enlarging painless mass. A discrete mass in an otherwise normal-appearing gland is the norm for parotid gland neoplasms. Parotid neoplasms most commonly occur in the tail of the gland. Submandibular neoplasms often appear with diffuse enlargement of the gland, whereas sublingual tumors produce a palpable fullness in the floor of the mouth.

Minor salivary gland tumors have a varied presentation, depending on the site of origin. Painless masses on the palate or floor of mouth are the most common presentation of minor salivary neoplasm. Laryngeal salivary gland neoplasms may produce airway obstruction, dysphagia, or hoarseness. Minor salivary tumors of the nasal cavity or paranasal sinus can manifest with nasal obstruction or sinusitis. Lateral pharyngeal wall protrusions with resultant dysphagia and muffled voice should raise suspicion of a parapharyngeal space neoplasm.

Facial paralysis or other neurologic deficit associated with a salivary gland mass indicates malignancy. The significance of painful salivary gland masses is not entirely clear. Pain may be a feature associated with both benign and malignant tumors. Pain may arise from suppuration or hemorrhage into a

mass or from infiltration of a malignancy into adjacent tissue.

Physical examination. Physical examination of salivary gland masses should occur in the context of a thorough general head and neck examination. Note the size, mobility, and extent of the mass, as well as its fixation to surrounding structures and any tenderness. Perform bimanual palpation of the lateral pharyngeal wall for deep lobe parotid tumors to assess for parapharyngeal space extension. Bimanual palpation for submandibular and sublingual masses also reveals the extent of the mass and its fixation to surrounding structures.

Pay attention to surrounding skin and mucosal sites, which drain to the parotid and submandibular lymphatics. Regional metastases from skin or mucosal malignancies may manifest as salivary gland masses. Also, the cervical lymph node basin should be palpated to assess for metastatic disease from a primary lesion of the salivary glands.

CN VII should be assessed carefully to identify any weakness or paralysis. Facial nerve palsy usually indicates a malignant lesion with infiltration into the nerve.

Embryogenesis. The salivary glands begin to form at 6-9 weeks' gestation. The major salivary glands arise from ectodermal tissue. The minor salivary glands arise from either ectodermal or endodermal tissue, depending on their location. Development of each salivary gland begins with ingrowth of tissue from oral epithelium, initially forming solid nests. Later differentiation leads to tubule formation with 2 layers of epithelial cells, which differentiate to form ducts, acini, and myoepithelial cells. Embryologically, the submandibular gland forms earlier than does the parotid gland. The resulting associated lymph nodes are outside the gland.

The parotid gland becomes encapsulated later in its embryology. This leads to lymph nodes, which are trapped within the gland. Most of the nodes, 11 on average, are located in the superficial portion of the gland, and the rest, 2 on average, are in the deep portion. This embryologic difference explains why lymphatic metastases may manifest within the substance of the parotid gland and not the submandibular gland.

Salivary gland secretory unit. Salivary glands are made up of acini and ducts. The acini contain cells that secrete mucus, serum, or both. These cells drain first into the intercalated duct, followed by the striated duct, and finally into the excretory duct. Myoepithelial cells surround the acini and intercalated duct and serve to expel secretory products into the ductal system. Basal cells along the salivary gland unit replace damaged or turned-over elements.

The parotid gland acini contain predominately serous cells, while the submandibular gland acini are mixed, containing both mucous and serous cells, and the sublingual and minor salivary glands have predominately mucous acini

Parotid gland. The parotid gland is the largest of the salivary glands. It is located in a compartment anterior to the ear and is invested by fascia that suspends the gland from the zygomatic arch. The parotid compartment contains

the parotid gland, nerves, blood vessels, and lymphatic vessels, along with the gland itself.

The compartment may be divided into superficial, middle, and deep portions for describing the contents, but the space has no discrete anatomic divisions. The superficial portion contains the facial nerve, great auricular nerve, and auriculotemporal nerve. The middle portion contains the superficial temporal vein, which unites with the internal maxillary vein to form the posterior facial vein. The deep portion contains the external carotid artery, the internal maxillary artery, and the superficial temporal artery.

The parotid compartment is a wedge-shaped 3-dimensional area with superior, anterior diagonal, posterior diagonal, and deep borders. It is bounded superiorly by the zygomatic arch; anteriorly by the masseter muscle, lateral pterygoid muscle, and mandibular ramus; and inferiorly by the sternocleidomastoid muscle and the posterior belly of the digastric muscle. The deep portion lies lateral to the parapharyngeal space, styloid process, stylomandibular ligament, and carotid sheath.

The deep anatomic relationship is important because tumors may arise in the deep portion and grow into the parapharyngeal space and may manifest as intraoral masses. These tumors are termed dumbbell tumors when they grow between the posterior aspect of the mandibular ramus and the stylomandibular ligament. This position causes a narrow constricted portion with larger unrestricted portions on either side, forming a dumbbell shape. Tumors that pass posterior to the stylomandibular ligament into the parapharyngeal space, forming unrestricted round masses, are called round tumors.

The parotid is a unilobular gland through which the facial nerve passes. No true superficial and deep lobes exist. The term superficial parotidectomy or parotid lobectomy refers only to the surgically created boundary from facial nerve dissection.

The Stensen duct drains the parotid gland. Initially, it is located approximately 1 cm below the zygoma and runs horizontally. It passes anteriorly to the masseter muscle and then penetrates the buccinator muscle to open intraorally opposite the second maxillary molar.

The facial nerve exits the skull via the stylomastoid foramen located immediately posterior to the base of the styloid process and anterior to the attachment of the digastric muscle to the mastoid tip at the digastric ridge. The nerve travels anteriorly and laterally to enter the parotid gland. Branches of the facial nerve that innervate the posterior auricular muscle, posterior digastric muscle, and stylohyoid muscle arise before the nerve enters the parotid gland. Just after entering the parotid gland, it divides into 2 major divisions: the upper and lower divisions. This branch point is referred to as the pes anserinus. Subsequent branching is variable, but the nerve generally forms 5 branches. The buccal, marginal mandibular, and cervical branches arise from the lower division. The zygomatic and temporal branches arise from the upper division

Branches of the external carotid artery provide arterial supply to the parotid gland. The posterior facial vein provides venous drainage, and lymphatic drainage is from lymph nodes within and external to the gland that leads to the deep jugular lymphatic chain.

The gland receives parasympathetic secretomotor innervation from preganglionic fibers that arise in the inferior salivatory nucleus. These fibers travel with the glossopharyngeal nerve to exit the skull via the jugular foramen. They then leave the glossopharyngeal nerve as the Jacobson nerve and reenter the skull via the inferior tympanic canaliculus. The fibers traverse the middle ear space broadly over the promontory of the cochlea (tympanic plexus) and exit the temporal bone superiorly as the lesser petrosal nerve. The lesser petrosal nerve exits the middle cranial fossa through the foramen ovale, where the preganglionic fibers synapse in the otic ganglion. The postganglionic fibers travel with the auriculotemporal nerve to supply the parotid gland.

Submandibular gland The submandibular glands are the second largest salivary glands, after the parotid. They are encapsulated glands located anterior and inferior to the angle of the mandible in the submandibular triangle formed from the anterior and posterior bellies of the digastric muscle and the inferior border of the mandible.

The submandibular gland has a superficial portion located lateral to the mylohyoid and a deep portion located between the mylohyoid and the hyoglossus. The marginal mandibular branch of the facial nerve and the anterior facial vein pass superficially to the gland. Posteriorly, the gland is separated from the parotid gland by the stylomandibular ligament. The facial artery crosses the deep portion of the gland.

The Wharton duct drains the gland. It passes between the mylohyoid and hyoglossus muscles and along the genioglossus muscle to enter the oral cavity lateral to the lingual frenulum.

The lingual nerve and submandibular ganglion are located superior to the submandibular gland and deep to the mylohyoid muscle. The hypoglossal nerve lies deep to the gland and inferior to the Wharton duct.

Arterial blood supply is from the lingual and facial arteries. The anterior facial vein provides venous drainage. The lymphatic drainage is to the submandibular nodes and then to the deep jugular chain.

The submandibular and sublingual glands receive parasympathetic secretomotor innervation from preganglionic fibers, which originate in the superior salivatory nucleus. These fibers leave the brainstem as the nervus intermedius to join with the facial nerve. They then leave the facial nerve with the chorda tympani to synapse in the submandibular ganglion. Postganglionic fibers innervate the submandibular and sublingual glands.

Sublingual glands. The sublingual glands are the smallest of the major salivary glands. Unlike the parotid and submandibular gland, the sublingual gland is unencapsulated. Each gland lies medial to the mandibular body, just

above the mylohyoid muscle and deep to the mucosa of the mouth floor.

Rather than 1 major duct, the sublingual glands have 8-20 small ducts, which penetrate the floor of mouth mucosa to enter the oral cavity laterally and posteriorly to the Wharton duct. Arterial supply is from the lingual artery. Lymphatic drainage is to the submental and submandibular lymph nodes, then to the deep cervical lymph nodes. Innervation is via the same pathway as the submandibular gland.

Minor salivary glands. Approximately 600-1000 minor salivary glands are located throughout the paranasal sinuses, nasal cavity, oral mucosa, hard palate, soft palate, pharynx, and larynx. Each gland is a discrete unit with its own duct opening into the oral cavity.

Together, the salivary glands produce 1-1.5 L of saliva per day. About 45% is produced by the parotid gland, 45% by the submandibular glands, and 5% each by the sublingual and minor salivary glands. Saliva is produced at a low basal rate throughout the day, with a 10-fold increase in flow during meals. Saliva functions to maintain lubrication of the mucous membranes and to clear food, cellular debris, and bacteria from the oral cavity. Saliva contains salivary amylase, which assists in initial digestion of food. Saliva forms a protective film for the teeth and prevents dental caries and enamel breakdown, which occur in the absence of saliva. Also, by virtue of production of lysozyme and immunoglobulin A in the salivary glands, saliva plays an antimicrobial role against bacteriaCT scanning and MRI

- Imaging studies of the salivary glands are usually unnecessary for the assessment of small tumors within the parotid or submandibular gland. CT scanning or MRI is useful for determining the extent of large tumors, for evaluating extraglandular extension, for determining the actual depth of parotid tumors, and for discovering other tumors in one gland or in the contralateral gland. Additionally, CT scanning and MRI are helpful in distinguishing an intraparotid deep-lobe tumor from a parapharyngeal space tumor and for evaluation of cervical lymph nodes for metastasis.
- CT scanning and MRI can be used to predict possible malignancy based on observation of poorly defined tumor margins; MRI is the better of the 2 for this purpose. However, no difference exists between the specificities and sensitivities of CT scanning and MRI for the location or amount of infiltration of tumors in the parotid gland.
- Minor salivary gland neoplasms are often difficult to assess on examination, and the use of preoperative CT scanning or MRI is important for determining the extent of tumor, which is otherwise not clinically appreciable. This imaging is particularly valuable for salivary gland neoplasms in the paranasal sinus, where skull-base or intracranial extension may alter the resectability of the tumors.
- CT-guided needle biopsy can be used to evaluate difficult-to-reach tumors, such as neoplasms in the parapharyngeal space.
- For most small parotid neoplasms without clinical evidence of facial nerve involvement, no pretreatment imaging studies are required.
- Gadolinium-enhanced dynamic MRI can be used to possibly differentiate pleomorphic adenomas from malignant salivary gland tumors using peak time of enhancement at 120 seconds and to differentiate between malignancies and Warthin tumors using washout ratios of 30% with a sensitivity of 100% and specificity of 80%. However, MRI can only suggest a diagnosis; definitive diagnosis requires pathologic examination.

- Ultrasonography
  - New technologies, including high-resolution probes and harmonic imaging, can delineate location, homogeneity or heterogeneity, shape, vascularity, and margins of salivary tumors in the periauricular, buccal, and submandibular area.
  - Ultrasonography may be able to reveal the type of tumor.[6]
  - New ultrasonographic contrast mediums can now reveal the vascularity of the tumor before surgery.
  - Ultrasonography can guide fine-needle aspiration to increase the likelihood of getting a good sample, and it can precisely guide core needle biopsies 97% of the time in an outpatient setting, lessening the need for intraoperative biopsies.
  - Ultrasonography can also guide automated core biopsy systems with a sensitivity of 75%, specificity of 96.6%, and accuracy of 91.9%.
- Nuclear imaging
  - F-18 fluorodeoxyglucose (FDG)-PET can be used to plan treatment of salivary gland malignancies by detecting lymph node metastases that require a neck dissection or by finding distant metastases

that may not have caused abnormalities in routine blood work. This is most useful when combined with CT scanning.

- Technetium-99m (Tc-99m) pertechnetate scintigraphy with lemon juice stimulation can be used to diagnose Warthin tumors with correlation between tumor size and Tc-99m uptake.

Diagnostic Procedures. Fine-needle aspiration biopsy (FNAB)

FNAB is a valuable diagnostic adjunct in evaluation of head and neck masses. Its role in evaluation of salivary gland tumors is controversial.

- Overall sensitivity of FNAB in distinguishing between benign and malignant salivary gland tumors is approximately 95%. Its specificity is approximately 98%.
- FNAB has a positive predictive value of approximately 84% and a negative predictive value of approximately 77%.
- Results that include a predominating lymphocyte indicate the need for further workup for lymphoma, but salivary neoplasms should still be considered. Even if an FNAB result is negative, the test does not replace the clinical judgment in the management of a suspected salivary gland neoplasm.
- Most experts generally agree that FNAB is useful in the evaluation of submandibular masses. Relatively few submandibular triangle masses represent primary submandibular gland neoplasms. Most of these masses are due to either inflammatory diseases or neoplasms that involve the lymph nodes in this region. FNAB is helpful for differentiating between these possibilities and for directing therapy.
- The value of routine FNAB for parotid masses is less clear. Opponents state that FNAB results rarely alter the management of parotid masses, which is carefully planned and executed surgical excision. Proponents believe that obtaining a preoperative histologic diagnosis is valuable for the following reasons:
  - Knowledge of the histologic type may be helpful in preparing patients and surgeons for the more extensive surgery required for high-grade malignancies.
  - Some nonneoplastic causes of parotid masses may be ruled out without surgical intervention.
  - Recent studies have found parotid gland FNAB to have an accuracy of 94-97%, a sensitivity of 83-84%, and specificity of 96-100%. Positive and negative predictive values for malignancy were 84.6% and 96.4%, respectively.
- FNAB for Warthin tumors can have false-positive results, leading to misdiagnosing more dangerous tumors such as pleomorphic adenomas and acinic cell carcinomas. Also, FNAB results have revealed a higher rate of parotitis in patients with Warthin tumors because of susceptibility to infarction and inflammation.
- Complications of FNAB are nondiagnostic biopsies and tissue changes found after excision that may interfere with histological evaluation, including needle tracts and infarction.

- Flow cytometry
  - The value of flow cytometry in salivary gland neoplasms is supporting histopathology by detecting possibly malignant tumors.
  - Flow cytometry has also been shown to help in prognosis in adenoid cystic carcinoma by determining the DNA ploidy of tumor cells. This information has been shown to correlate with overall prognosis and long-term disease-free survival periods.

- Determining aneuploidy versus diploidy by flow cytometry has been found to help grade mucoepidermoid carcinomas by one study, which found that high grade cancers are aneuploidy 89% of the time and diploid cancers are low or intermittent grade 88% of the time.

Histologic Findings A variety of benign and malignant neoplasms can arise in the salivary glands. An accurate histopathologic diagnosis is essential for the rational treatment of patients with salivary gland neoplasms. Batsakis et al have reported the classification system most commonly used in epithelial salivary gland tumors.

Benign salivary gland neoplasms. *Pleomorphic adenoma*, or benign mixed tumor. Pleomorphic adenomas are the most common salivary gland tumor. They represent 60% of parotid tumors and 36% of submandibular tumors. They affect men and women equally and usually appear in the fifth decade of life. The children are effected in adult period. Seldom is happened new-born children (7 and 11 mounths). The tumors are typically slow growing and produce no symptoms. On gross evaluation, the tumors are smooth, multilobular, and encapsulated. The capsule, however, is incomplete

microscopically, and tumor pseudopodia may extend beyond the margin of the apparent capsule. The contents of the tumor appear varied depending on the cellularity and the myxoid content. Microscopically, the characteristic feature is the morphologic diversity of the tumor, with presence of both epithelial and mesenchymal-like elements. Two cells are responsible for the varied appearance: the epithelial cell and the myoepithelial cells. The epithelial cells make up most the cellular regions, and the myoepithelial cells make up the stromal areas. The ratio of cellular elements to stromal elements can vary widely. The stromal component may have a myxoid, fibroid, or chondroid appearance. The presence of pseudopodia that extend beyond the apparent margin of the tumor is responsible for the significant rate of recurrence with simple enucleation of pleomorphic adenomas. The management of choice for pleomorphic adenomas of the parotid gland is superficial lobectomy, taking a cuff of normal glandular tissue with the tumors. Submandibular and minor salivary gland pleomorphic adenomas should likewise be removed with a cuff of normal tissue. Abiding by this principle has led to low rates of recurrence, typically lower than 5%. A premium is placed on initial excision of pleomorphic adenomas because management of recurrent disease is difficult and often frustrating. Recurrent pleomorphic adenomas often occur in a multifocal fashion and can manifest 10-15 years after initial resection. Repeat operation puts the facial nerve at increased risk for permanent injury, and facial nerve monitoring is helpful to diminish this risk. Cure rates are reported to be 25% or lower when a repeat operation for recurrent pleomorphic adenomas is performed. Radiation therapy may be helpful in treating multiple recurrent disease and is decided on a case-by-case basis. The facial nerve should not be sacrificed in the removal of pleomorphic adenomas. Tumor grossly adherent to the nerve should be removed by using microdissection techniques.

Monomorphic adenoma. This tumors are happened only in adult children (12 -18 age). Monomorphic adenomas are often grouped with pleomorphic adenomas. These are distinct tumors histologically, however, and lack pleomorphic features. Basal cell adenomas and clear cell adenomas are included in this group of tumors. Monomorphic adenomas are benign, slow growing, and are the least aggressive of the salivary gland tumors. They probably represent fewer than 2% of salivary gland neoplasms. The most common variety of monomorphic adenomas is the basal cell adenoma. Basal cell adenomas occur most commonly in the minor salivary glands, usually the upper lip. Of the major salivary glands, the parotid gland is the usual location of occurrence. Grossly, the tumors are encapsulated and are smooth. Microscopically, the tumors contain epithelial parenchyma, which is sharply demarcated from the scant stroma by a thick, prominent basement membrane. The epithelial cells have a palisading appearance at the periphery of the tumor parenchyma. The appearance can be confused with adenoid cystic carcinoma, but the distinction is clearly important, as the biologic behavior of the 2 tumors is vastly different.

Treatment consists of surgical excision with a margin of normal tissue for these benign and nonaggressive tumors.

Ranula is a retention cyst arising from the sublingual gland on the floor of the mouth as a result of ductal obstruction and fluid retention. Ranulas can be divided into three types; sublingual, plunging, and sublingual-plunging. A sublingual ranula develops in the floor of the mouth, while a plunging ranula is recognized as a soft cystic swelling in the submandibular or upper cervical region. When a sublingual ranula has a cervical extension through the mylohyoid muscle, the term "sublingual-plunging ranula" is used1. Ranula may be seen at birth or in later life2. It is commonly seen in young adult. Ranula commonly occurs unilaterally, and bilateral ranulas are extremely rare. Othen ranula is discovered occasionally.

Physical examination revealed tense, fluctuant, bluish, cystic lesions .dome-shaped round, covered by a thin smooth, shiny mucosa The tongue was painful and displaced on the upper side of the mouth. Most of the patients with oral ranula presented with a gradually enlarging swelling of the floor the mouth. The lesion is painless, fluctuant and round or oval. When is superfecialy ocated ranula is quite bluish; a deep ranula isappear pinker, reflecting the thicker mucosal covering. It is cannot be emptied by digital pressure. It may drain spontaneously at intervals.

The etiology of ranula is unknown; however, obstruction, trauma, and congenital anomalies have been implicated6-9. The diagnosis of ranula is generally based on the clinical examination and sometimes on computerized tomography or magnetic resonance imaging findings for theThe differential diagnosis of ranula should include masses and swellings in the floor of the mouth and submandibular space region. These are dermoid and epidermoid cysts, branchial cleft cysts, thyroglossal duct cysts, cystic hygroma, lipomas, abscess, and malignant neoplasia6,7,10. Histologically, ranula consists of a central cystic space containing mucin and a pseudocyst wall composed of loose, vascularized connective tissues. Histiocytes predominate in the pseudocyst wall, but over time, these become less prominent. An important feature in the histologic diagnosis is the absence of epithelial plunging lesion. A fine-needle aspiration biopsy determine a sticky clear fluide, like "white of egg" and may be helpful in demonstrating the mucus with inflammatory cells. Chemical analysis of aspiration fluid can reveal high amylase and protein contents.

Mucocele (mucoid cyst). The superfecial mucocele is one of the most frequent bluish lesion to occur on the lower lip, but it can occurnanywhere on the oral mucosa. The mucocele is thought to occur when a duct of a minor salivary land is severed by trauma and the secretion is spilled and pooled in the sperfecial tissues. It seldom posses an epithelial lining and thus is classified as a false cyst.

Clinical features: most commonly occurs on a child's lower lip, a mucocele is usually a fluctuant, blush, soft, nodular or dome-shaped elevation

that is freely movable on the underlaying tissue but cannot be movable independently of the mucosal layer. It cannot be emptied by digital pressure, and aspiration it yields a sticky, viscous, clear liquid. This result hhelps to rule ou the vascușar lesions. Most mucoceles are less than 1 centimeter in diameter.

The patients may report that the swelling is somewhat paroxysmal – suddenly recurring rupturing, and draining periodically.

Treatment and prognosis: any mucocele should be completely removed; a good practice is to remove all the glandular units that protrude into the incision because their ducts will likely have been severed. This practice wil help avoid the embarrassing occurrence of numerous iatrogenic satellite mucoceles. **Malignant salivary gland neoplasms.** *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. It represents approximately 8% of all parotid tumors. Mucoepidermoid carcinomas are divided into low, intermediate, and high grades. These tumors contain 2 types of cells, as the name implies, mucous and epidermoid cells. The grade of tumor is determined by the relative proportion of these 2 cells. Low-grade tumors have a higher preponderance of mucous cells than epidermoid cells do. The ratio of epidermoid cells rises in higher grades, and high-grade mucoepidermoid carcinomas may even resemble squamous cell carcinomas. Low-grade tumors are usually small and appear partially encapsulated upon gross examination. They may have some cystic components. High-grade tumors are usually larger and are more infiltrative. A capsule is usually not recognizable, and the tumors are more solid with a grayish-white appearance. Upon microscopic examination, low-grade tumors contain sheets of mucoid cells separated by bands of epidermoid cells. Mucous cells are clear and plump with small nuclei. Epidermoid components resemble squamous cell carcinoma. High-grade mucoepidermoid carcinomas are nearly entirely composed of nests of malignant epidermoid cells. Few mucous cells or none at all are present, although when specially stained, cells that contain mucus are apparent. This differentiates high-grade mucoepidermoid carcinoma from squamous cell carcinoma. The biologic behavior of mucoepidermoid carcinoma is dependent on the grade of tumor. Low-grade lesions are fairly nonaggressive, and appropriate treatment imparts a good prognosis. High-grade neoplasms are much more aggressive, with high rates of regional lymph node metastases.

Adenoid cystic carcinoma. Adenoid cystic carcinoma is the second most common malignant salivary gland tumor, representing approximately 6% of all salivary gland neoplasms. It is the most common malignancy in the submandibular gland and usually appears as a slow-growing painless mass. Metastasis to regional lymph nodes is uncommon, but distant metastasis (usually to the lung) is more common. Adenoid cystic carcinoma is unique in that survival at 5 years is approximately 65%, but 15-year survival is only 12%.

Because of the slow growth of this tumor, patients may remain free of disease after initial treatment for 10 years or longer, only to develop metastases. Local recurrence is also common. The tendency for this tumor to grow along perineural and perivascular planes, often with skip lesions, helps explain the generally poor success of treatment. Grossly, adenoid cystic carcinomas are usually monolobular and nonencapsulated. They have a gray-pink color and infiltrate the surrounding normal tissue. Microscopically, the tumors consist of basaloid epithelial elements that form cylindrical structures. Tumors are classified by the general architecture into the following 3 types: cribriform, tubular, and solid. The cribriform pattern has the classic Swiss cheese appearance with basophilic mucinous substance filling the cystic spaces. In the tubular pattern, the cells are arranged in smaller ducts and tubules with less prominent cystic spaces. The solid type is characterized by sheets of neoplastic cells with few cystic spaces. Any given tumor may contain all 3 patterns, but common to all types is the propensity for perineural invasion. Perineural extension accounts for the difficulty in eradicating adenoid cystic carcinoma despite extent of excision.

Treatment. *Chemotherapy.* In general, salivary gland neoplasms respond poorly to chemotherapy, and adjuvant chemotherapy is currently indicated only for palliation. Doxorubicin- and platinum-based agents are most commonly used with the platinum-based agents that induce apoptosis versus the doxorubicin-based drugs that promote cell arrest. Platinum-based agents, in combination with mitoxantrone or vinorelbine, are also effective in controlling recurrent salivary gland malignancy. A new form of 5-fluorouracil called fluoropyrimidine that has increased activity against malignant cells and while having fewer gastrointestinal side effects has shown to be efficacious against malignant salivary cancers and to potentiate the effects of radiotherapy by increasing apoptosis. Newer trials with antimicrotubule agents with and without concomitant radiotherapy have shown efficacy. Using a platinum-based agent, cisplatin, and an antimicrotubule drug, docetaxel, with radiation shows some promise in advanced carcinomas of the salivary gland. Using paclitaxel (Taxol), another antimicrotubule drug, alone has had moderate activity against mucoepidermoid tumors and adenocarcinomas but no effect adenoid cystic carcinoma. Various targeted biologic agents such as trastuzumab, imatinib, and cetuximab are currently being investigated.

Radiotherapy. Radiotherapy is still not considered to be the criterion standard after surgical resection of salivary gland neoplasms; however, it is used alone for tumors that are considered nonresectable.

*Surgical Therapy***.** Carefully planned and executed surgical excision is the primary treatment for all primary salivary gland tumors. The principles of surgery vary with the site of origin and are discussed as such.

Superficial parotidectomy with identification and dissection of the facial nerve is the minimum operation for diagnosis and treatment of parotid masses.

Neither incisional biopsy nor enucleation should be performed for parotid masses.

Surgery is the primary treatment of malignant tumors of the salivary glands. This is often combined with postoperative radiation therapy, depending on the specific tumor characteristics and stage. The extent of surgery is based on the size of the tumor, local extension, and neck metastases. The facial nerve is spared unless it is directly involved. Radiation therapy is recommended for all but small low-grade tumors.

Parotid gland. The histopathologic diagnosis of parotid masses is often unknown prior to surgery. Thus, the minimum procedure that should be performed for masses in the parotid gland is a superficial parotidectomy with identification and preservation of the facial nerve. The shift from enucleation, which was popular prior to 1950, to superficial parotidectomy as the minimal procedure for parotid tumors has substantially reduced recurrence rates for both benign and malignant disease. For benign pathology, this procedure is curative. By today's standards, enucleation with incisional biopsies should never be performed.

The specimen removed by superficial parotidectomy should be sent to the pathology department for frozen section analysis to intraoperatively determine whether a lesion is benign or malignant. Malignant diagnoses deserve special consideration.

Submandibular gland. Routine fine needle aspiration biopsy (FNAB) for submandibular masses is helpful to rule out inflammatory disease of the submandibular gland, which is treated nonoperatively, and to rule out metastatic disease to the submandibular region, which is treated on the basis of the primary neoplasm. Benign neoplasms of the submandibular gland require complete excision of the gland. Malignant neoplasms at a minimum require complete excision of the gland plus extended surgery, depending on the specific tumor factors.

Intraoperative Details. Superficial parotidectomy Perform surgery with the patient under general anesthesia without paralysis. The face and neck are exposed and should be draped to allow visualization of facial motion throughout the case. A properly designed incision allows adequate exposure and yields a good cosmetic result. An incision is made in the preauricular crease. The incision may be extended posterior to the tragus. The incision is extended to the attachment of the lobule and carried over the mastoid tip, then extended into the neck in a skin crease. Alternatively, a facelift incision may be used for hidden scar placement in the hairline.

Elevate a skin flap from the underlying parotid fascia, which has a silvery sheen. Carry the flap as anteriorly as necessary to completely resect the lesion. It is important to realize that the branches of the facial nerve approach the flap as elevation proceeds anteriorly and care must be taken not to disrupt the peripheral branches of the facial nerve during flap elevation.

Next, identify the main trunk of the facial nerve. Successful and rapid identification is achieved by using known anatomic landmarks and wide exposure. The important landmarks are the sternocleidomastoid muscle, the cartilaginous external auditory canal and tragal cartilage, the posterior belly of the digastric, the tympanomastoid suture line and associated stylomastoid foramen, and the styloid process. These landmarks are identified sequentially and aid in locating and identifying the main trunk of the facial nerve.

Dissect the tail of the parotid gland anteriorly off the sternocleidomastoid muscle. Take care to preserve the greater auricular nerve if possible. Dissect the tail medially until the posterior belly of the digastric muscle is identified. The posterior belly of the digastric muscle is an important landmark for identifying the facial nerve because the nerve can be identified just superior to the muscle at approximately the same depth.

Next, perform dissection along the anterior aspect of the tragus along the perichondrium. Maintain a wide plane and medially retract the parotid gland . The cartilage forms a point medially, termed the tragal pointer. The facial

nerve lies approximately 1 cm deep to this landmark, slightly anterior and inferior. A more reliable landmark is palpation of the tympanomastoid suture line in this region, which separates the mastoid tip from the tympanic portion of the temporal bone. The main trunk of the facial nerve lies at approximately this level or slightly medial. The styloid process may be palpated, and the facial nerve lies between the styloid process and the posterior belly of the digastric muscle as it inserts on the mastoid tip.

The bridge of tissue created between the preauricular dissection and the dissection to the digastric muscle is divided superficially, and then blunt separation of soft tissues is performed in the direction of the facial nerve to identify the main trunk. A nerve stimulator may be helpful in locating the main trunk and branches, but use it sparingly.

In tissue beds previously operated on or in situations in which bulk tumor causes obstruction, this classic method of identifying the facial nerve may be impractical. In these situations, a peripheral branch of the facial nerve may be identified and traced posteriorly to the main trunk. Alternatively, the mastoid tip may be removed with a drill and the facial nerve identified intratemporally as it exits the stylomastoid foramen.

Once the main trunk of the facial nerve is located, use a fine-tipped hemostat to create a tunnel along the nerve and divide the parotid tissue superficially. This method of dissection involves 4 steps using the dissecting hemostat: push, lift, spread, and cut. If the facial nerve is constantly maintained in view, this method eliminates inadvertent injury.

Identify the pes anserinus (the point of main division of the facial nerve) and dissect each branch of the facial nerve out to the periphery. Depending on tumor location, the surgeon may start with either the inferior or the superior division. Once one division is dissected, a tunnel over the next division is superiorly or inferiorly created and connected to the previous dissection. This is repeated for each branch of the facial nerve, reflecting the parotid gland and tumor away from the facial nerve then dissecting the final soft tissue attachments after each branch of the nerve has been identified. Low-level stimulation of the facial nerve at the conclusion of the operation is performed to confirm that all branches are intact.

Other less commonly used methods of identifying the facial nerve include drilling the mastoid bone to identify the facial nerve in its descending segment, as well as finding a distal branch of the facial nerve and performing retrograde dissection.

This technique yields an intact superficial portion of the parotid gland that contains the tumor. Careful hemostasis is achieved with bipolar cautery. Do not use monopolar cautery near the facial nerve. Insert a closed suction drain through a separate stab incision in the hairline and close the wound in layers. Antibiotic ointment and a gauze dressing may be applied.

Limited parotidectomy Limited parotidectomy, also called extracapsular dissection, has recently been espoused as a method to surgically manage benign tumors of the parotid gland. The impetus for this approach came from a study that demonstrated that, in superficial parotidectomy specimens, no margin of normal parenchyma on the deep aspect existed, as the margin was the facial nerve. This information negated the notion that a cuff of normal tissue was needed to prevent recurrence of benign lesions.

A few studies have demonstrated that even with greater than 10-year follow-up, recurrence rates between limited and superficial parotidectomy for pleomorphic adenomas are the same. The advantages of limited parotidectomy are improved cosmesis and decreased rate of Frey syndrome. A potential disadvantage is the seemingly increased risk of unintentional damage to the facial nerve. However, studies have not shown any increased risk of facial nerve injury with limited parotidectomy.

In this technique, the incision and flap elevation are the same as for superficial parotidectomy; however, instead of identifying the main trunk of the facial nerve, the parotid is incised over the tumor. The tumor capsule is then dissected taking care to have adequate visualization and to use a nerve stimulator as needed to avoid injury to branches of the facial nerve. Being as certain as possible that the neoplasm is benign before using limited parotidectomy is important. Preoperative imaging, physical examination, history, and FNA should be consistent with a benign process.

Total parotidectomy. Strictly speaking, total parotidectomy is a misnomer. The procedure, by definition, involves removal of as much parotid tissue medial and lateral to the facial nerve as possible, along with the accompanying tumor. The exact approach varies depending on tumor location, but it usually involves a superficial parotidectomy to identify and preserve the facial nerve, followed by removal of parotid tissue and tumor deep to the facial nerve.

Attempt to preserve the facial nerve at all times. The nerve is never sacrificed for benign disease and only sacrificed if malignancy is found to be directly infiltrating the nerve. In these situations, remove the involved branch with the specimen and obtain frozen sections to ensure clearance of tumor.

Removal of dumbbell-shaped tumors and parapharyngeal space tumors requires additional exposure. This may be accomplished either transcervically after removal of the submandibular gland or via an extended approach with mandibulotomy and/or lip-splitting incision.

For cases of recurrent tumor and in cases in which difficult dissection is anticipated, intraoperative facial nerve monitoring may be helpful in identifying and preserving the facial nerve.

Submandibular gland excision. Submandibular excision is generally performed with the patient under general anesthesia without paralysis. Make a 5-cm incision in a skin crease of the neck approximately 2-3 cm below the inferior border of the mandible. Carry the incision through the platysma and create small subplatysmal flaps inferiorly and superiorly. The surgeon must avoid injuring the marginal mandibular branch of the facial nerve. The procedure may be accomplished by direct identification and dissection superiorly or by incision of the fascia overlying

the gland and ligation of the posterior facial vein. The vein and fascia are reflected superiorly, protecting the marginal mandibular nerve.

In managing bulky tumors or malignancy, positive identification and dissection of the marginal mandibular branch not only provides wider exposure but also allows complete excision of the level 1 perifacial lymph nodes with the surgical specimen.

The gland and surrounding tissues are then freed from the undersurface of the mandible. The facial artery is usually divided as it approaches the mandible. Dissect the inferior portion of the gland from the digastric muscle. The facial artery is encountered again inferiorly near its origin from the external carotid artery and ligated. Retract the specimen laterally to expose the mylohyoid muscle. The mylohyoid muscle is dissected free and retracted medially. This maneuver exposes the hypoglossal nerve inferiorly, the lingual nerve superiorly, and the submandibular duct (Wharton duct). Retract the specimen inferiorly and identify the submandibular ganglion along the lingual nerve. The hypoglossal nerve is identified inferiorly. Once the lingual nerve, hypoglossal nerve, and submandibular duct are positively confirmed, ligate and transect the submandibular duct and ganglion. Final soft tissue attachments are divided, and the specimen is removed.

If a neck dissection is indicated, this dissection is performed in continuity. Again, nerves are preserved unless directly involved with tumor. With neurotrophic tumors (adenoid cystic carcinoma), frozen sections may be taken from the epineurium with excision of involved nerves.

Achieve careful hemostasis, insert a closed suction drain or Penrose drain, and close the wound in layers. Antibiotic ointment and a gauze dressing may be applied.

Postoperative Details. Examination of the facial nerve should be performed in the recovery room as soon as possible. If any uncertainty exists regarding the surgical integrity of the nerve and paralysis of 1 or more branches is discovered, a repeat exploration with cable grafting of injured segments should be performed.

Patients are usually admitted for one night. Closed drains are placed to bulb or wall suction and removed once output diminishes to approximately 30 mL per day (usually on postoperative day 1).

Patients should be monitored for the development of hematomas in the wound, which should be drained if they are discovered.

Complcation. *Facial nerve injury***.** This is an immediate postoperative complication that can be partial or complete. The surgeon must be confident at termination of the procedure that no branch has been inadvertently divided. If any doubt exists, a repeat exploration is indicated to explore the nerve and repair divided branches. If the nerve is intact, monitor the patient for recovery. The use of steroids in this circumstance is controversial but may have some marginal benefit. This may be because tumor contact or close proximity to the nerve and local inflammatory conditions have been found to be associated with nerve dysfunction after surgery.

Use of ovarian steroids has been effective in rat models in decreasing the amount of apoptosis from trophic insufficiency in peripheral nerves after axotomy. This has led to the use of biodegradable chitosan (ie, chitin-related polymer) prostheses laden with progesterone to bridge gaps in facial nerves after axotomies in rabbits. Preliminary reports have shown increased myelinated fibers in both sides of the incision compared to prostheses with progesterone

For incomplete eye closure, initiate an eye care program that consists of the use of lubricating drops and ointment to prevent exposure keratopathy. Taping the eyelid closed at night may be useful. Consultation with an ophthalmologist is helpful for monitoring the eye, and reanimation procedures are considered at a later date. If facial nerve resection is required, simultaneous insertion of a gold weight into the upper eyelid may be helpful to prevent postoperative exposure keratopathy.

Hematoma Careful hemostasis prevents this complication, but repeat exploration is occasionally required in cases that involve hematoma formation.

*Sialocele or salivary fistula***.** This is a relatively common complication

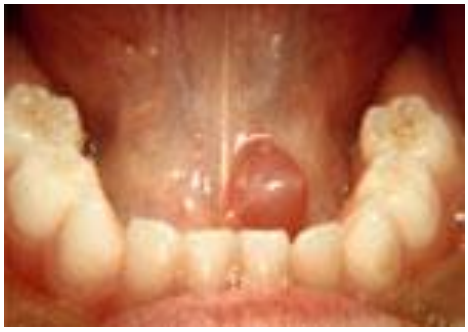
following parotid surgery. It may be treated with aspiration and compressive dressings. Fluid should be sent for amylase testing to confirm the diagnosis of sialocele. Anticholinergic medications, such as glycopyrrolate, may be helpful to reduce salivary flow, and botulinum toxin type A has had preliminary success in resolving sialoceles without causing complications such as facial nerve weakness.

Currently, botulinum toxin type A is being investigated as a treatment option for sialoceles. Preliminary results following a single administration of the toxin into the residual parotid gland have yielded a complete resolution of the fistula. Complications such as facial nerve weakness have not been reported.

*Frey syndrome or gustatory sweating***.** This is the most common long-term complication of parotid surgery. It occurs as a result of inappropriate autonomic reinnervation of sweat glands in the skin from parotid parasympathetics. The patient experiences facial sweating and flushing with meals. This complication is not commonly problematic. For significant symptoms, treatment with glycopyrrolate or topical scopolamine may be considered. Various measures to prevent this complication have been suggested, including dermal grafting, fat grafting, AlloDerm placement, subsuperficial musculoaponeurotic system (SMAS) dissection including temporoparietal fascia flaps, maintenance of a thick skin flap, and sternocleidomastoid flaps. Recently, botulinum toxin type A has been used successfully to treat Frey syndrome, and in patients who become immunoresistant to type A, botulinum toxin type F may have an effect.

Sensorineural hearing loss. This has been recently recognized as a possible long-term complication of radiotherapy for neoplasms in the parotid gland. Studies on the effects of ear radiation found that patients with ear structures included in the irradiated field had a 30-40% chance of a 10 dB hearing loss in that ear at 4 kHz or above. A follow-up study revealed that patients who received higher doses of radiation had an increased chance of hearing loss (up to 15 dB at 4 and 8 kHZ) and recommended avoiding a mean dose of greater than 50 Gy to the cochlea.

Mucocele



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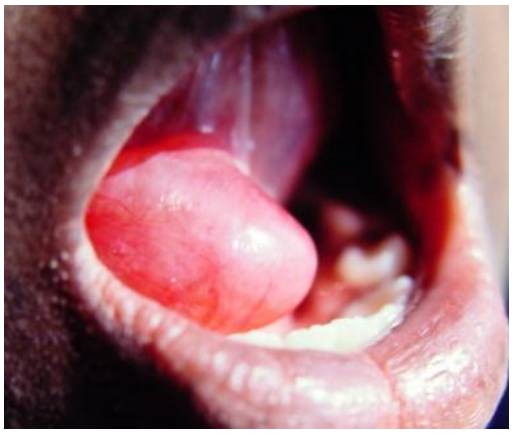

Ranula bilateral