The clinical evaluation of salivary gland tumors requires the physician to rely heavily on previous experience, a thorough knowledge of head and neck anatomy, and an understanding of the biologic behavior of the numerous histologically varied tumors that can occur in this system of glands. Historically, the salivary gland neoplasms were vaguely classified until Foote and Frazell presented their correlation of histopathologic and biologic behavior in 1953. The early ambiguity in histologic classification and biologic characteristics for salivary gland tumors meant that therapy was poorly directed prior to the 1950s. McFarland in 1933 stated that surgical treatment of these neoplasms was unnecessary. The integration of pathologic and clinical knowledge along with more sophisticated surgical and anesthetic methods during the last three decades has led to more appropriate and effective treatment.

The majority of masses in the major salivary glands represent neoplasms. It is the physician's responsibility to determine the benign or malignant nature of these tumors and to counsel the patient appropriately. A thorough history and physical examination along with selected radiographic and pathologic tests allow for these therapeutic decisions. It is the selection of tests and the decisions that are made on the basis of these tests that are becoming more and more crucial as the cost-effectiveness of therapy is examined more closely and the physician is scrutinized more closely by a consumer-conscious public. The physician has been confronted with numerous new tests and pressure to supply the patient with more and more information concerning disease processes and possible complications and outcomes from therapeutic measures. Often when evaluating a patient for the first time it is difficult to immediately recommend an operative procedure that may be extensive and involve major complications of head and neck deformity. This is the dilemma of the salivary gland surgeon and specifically the parotid gland surgeon who deals with the facial nerve. It is at this point that the physician may feel pressured to order ancillary tests even though they may be superfluous to the actual decision-making process.

This chapter examines the process of clinical evaluation of salivary gland neoplasms. We will utilize the history and physical examination as the foundation for this evaluation and selectively recommend supplemental examinations with computed tomography (CT), sialography, nuclear imaging, and aspiration needle biopsy.

**Etiology**

The etiology of salivary gland neoplasms, like that of most neoplasms, has been elusive. Other than a few reports of radiation-induced neoplasms, the mechanisms of induction of abnormal growth in these complex glands is unknown. The greatest insight into the understanding of these neoplasms and their cellular origins is gained by looking at the histogenesis of salivary gland neoplasms.
Embryologically the salivary glands originate from the aerodigestive tract as small buds off the oral cavity. This occurs at the end of the second week of gestation. Full differentiation is probably not completed until 6 weeks after birth.

In the fully developed salivary gland, the differentiated tissues have formed mucous and serous acini. The acini lead into the intercalated duct, which leads to the striated duct and then into the extralobular excretory duct. Around the acini and intercalated duct are the myoepithelial cells. The myoepithelial cell is a contractile cell that actively forces secretions from the acini and the intercalated ducts. Multiple myofilaments are found in the myoepithelial cells on electron microscopy.

The ductal component of the salivary gland unit consists first of a relatively undifferentiated intercalated duct and a well-differentiated striated duct. The striated duct cells show deep basal membrane invaginations and many intracellular mitochondria. The function of these cells is thought to be water and electrolyte transport.

The basal cell is found in the area of the intercalated duct and the excretory duct. These cells are thought to represent progenitor cells. Their capacity to differentiate into other salivary gland cells and tumor cells is an important aspect of the salivary gland histogenesis.

Theoretically, there are two possible explanations for the histogenesis of salivary gland neoplasms. The first would require differentiated cells to dedifferentiate into the multiple cell types. The second theory utilizes the progenitor cell (basal cell) present in the intercalated duct and excretory duct to explain differentiation into the various histologically varied neoplasms. Regezi and Batsakis organized the latter theory into the cell differentiation scheme.

### Histogenic Scheme for Salivary Gland Neoplasms

<table>
<thead>
<tr>
<th>Normal structure</th>
<th>Cell of Origin</th>
<th>Neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excretory duct</td>
<td>Excretory duct reserve cell</td>
<td>Squamous cell ca</td>
</tr>
<tr>
<td>Acinus</td>
<td>Intercalated duct reserve cell</td>
<td>Mucoepidermoid ca</td>
</tr>
<tr>
<td>Intercalated duct</td>
<td></td>
<td>Acinic cell ca</td>
</tr>
<tr>
<td>Myoepithelium</td>
<td></td>
<td>Mixed tumor</td>
</tr>
<tr>
<td>Striated duct</td>
<td></td>
<td>Monomorphic adenoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Myoepithelioma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adenoid cystic ca</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oncocytic tumors</td>
</tr>
</tbody>
</table>

The benign mixed cell tumor contains two types of cells - epithelial and myoepithelial. Each tumor is represented by a certain concentration of each cell type. The majority of neoplasms of this type contain an epithelial preponderance, although on rare occasion the monomorphic type appears which has mainly epithelial or myoepithelial elements.
The adenoid cystic carcinoma contains cells that resemble the intercalated duct cells. The major controversy has centered around the reports of two types of cell types in this neoplasm.

The squamous cell carcinoma or mucoepidermoid carcinoma theoretically can originate from any of the salivary gland cell types because of their epithelial anlage.

The oncocytic neoplasms contain the oncocyte, which is generally found along the entire salivary gland unit as an individual ages. The oncocyes contain hyperplastic and pleomorphic mitochondria. They are thought to represent a form of cellular degeneration.

Acinous cell carcinoma contains cells that have secretory granules. It is thought that the cell of origin is the intercalated duct reserve cell. It is also thought that the adenocarcinomas arise from the intercalated duct reserve cells.

Incidence

The physician must keep in mind that palpable lesions in the major salivary glands are almost always neoplasms. Statistics show that 95 per cent of palpable parotid lesions will demonstrate neoplastic growth. Parotid neoplasms are the most numerous and will account for approximately 80 per cent of salivary neoplasms. The submandibular gland makes up 10 per cent, and other glands make up the other 10 per cent. The palate is the most common location for involvement of the minor salivary glands.

The most common parotid tumor is in the lower pole of the gland and is in the superficial lobe. Eighty per cent of tumors in the parotid are in this location. The remainder of tumors in the parotid are in the pole and in the deep lobe, and only about 1 per cent or less account for the so-called "dumbbell" tumor.

Tumors of the salivary glands are indeed rare. They account for less than 3 per cent of all neoplasms in the head and neck region. The overall incidence of salivary gland neoplasms as reported by Biorklund from the Karolinska Institut in Stockholm is 40 cases per million persons. The incidence of malignancy among these neoplasms is nine cases per million population. Benign neoplasms far outweigh the malignant ones. In general, 80 per cent of parotid tumors will be benign, whereas two thirds of submandibular and one half of palatal salivary gland neoplasms will be benign.

Childhood salivary gland neoplasms are commonly separated into benign and malignant. The benign tumors contain the vascular lesions such as the lymphangioma and hemangioma. Schuller and McCabe reported the lymphangioma as the most common vascular neoplasm and the benign mixed tumor as the most common nonvascular benign neoplasms of the salivary glands. The figure shows a lymphangioma of the left parotid gland and neck. The history revealed that the mass had been present since the child's birth, and physical examination revealed easy transillumination of the mass. The mucoepidermoid carcinoma is the most common malignant neoplasm in children. Their report made special note of a high incidence of malignant neoplasms in the salivary glands of this childhood group. When only the nonvascular neoplasms were considered, they found a 57.5 per cent incidence of malignancy in childhood salivary gland masses.
Parotid Tumors in Children

Benign
- Mixed: 22
- Hemangioma: 16
- Lymphangioma: 5
- Cystic Hygroma: 1
- Plexiform Neurofibroma: 1
- Lipomatosis: 1
- Schwannoma: 1

Malignant
- Mucoepidermoid: 13
- Acinic Cell: 4
- Metastatic: 4

Total: 66

There is no demonstrable sex difference among the salivary gland neoplasms in Caucasians, but in the nonwhite population in the USA and Africa the salivary gland neoplasms are most commonly found in females. The African Negro presents most often with mixed tumors of the minor or lesser salivary gland rather than the parotid or submandibular gland.

Breast cancer and salivary gland cancer correlations have been reported in the literature. Even though this remains a controversial subject, the statistics presented appear to make strong evidence for this association.

Classification

The salivary glands are said to give raise to more types of histologically varied neoplasms than any other system of the body. The fact is exemplified by the great difficulty which pathologists and clinicians have had in classifying these tumors. Batsakis has proposed the most extensive classification of salivary gland tumors based on histopathologic data.
Classification of Epithelial Salivary Gland Tumors (Batsakis)

Benign

1. Mixed tumor (pleomorphic adenoma)
2. Papillary cystadenoma lymphomatosum (Warthin's tumor)
3. Oncocytoma (oncocytosis)
4. Monomorphic tumors
   a) Basal cell adenoma
   b) Glycogen rich adenoma (?)
   c) Clear cell adenoma
   d) Membranous adenoma
   e) Myoepithelioma
5. Sebaceous tumors
   a) Adenoma
   b) Lymphadenoma
6. Papillary ductal adenoma (papilloma)
7. Benign lymphoepithelial lesion
8. Unclassified

Malignant

1. Carcinoma ex pleomorphic adenoma
2. Malignant mixed tumor (biphasic malignancy)
3. Mucoepidermoid carcinoma
   a) Low-grade
   b) Intermediate grade
   c) High-grade
4. Adenoid cystic carcinoma
5. Acinous cell (acinic) carcinoma
6. Adenocarcinoma
   a) Mucus-producing adenopapillary and non-papillary carcinoma
   b) Salivary duct carcinoma (ductal carcinoma)
   c) Other adenocarcinomas
7. Oncocytic carcinoma (malignant oncocytoma)
8. Clear cell carcinoma (nonmucinous and glycogen-containing or nonglycogen-containing)
9. Primary squamous cell carcinoma
10. Hybrid basal cell adenoma/adenoid cystic carcinoma
11. Undifferentiated carcinoma
12. Epithelial-myoepithelial carcinoma of intercalated ducts
13. Miscellaneous (include sebaceous, Stensen's duct, melanoma and carcinoma ex lymphoepithelial lesion)
14. Metastatic
15. Unclassified
The difficulty and controversy in this area are related to the rarity of these neoplasms and the lack of large experience in any one medical center. Only the added experience of the future will help to solidify these concepts.

The TNM tumor *staging scheme* was first proposed by Denoix in 1946. It was an effort to correlate the state of a tumor prior to treatment with the biologic severity of the disease. Spiro first proposed a staging system for cancer of the parotid gland in 1975.

**Clinical Staging, Parotid Gland (Spiro)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Region</th>
<th>Nodal</th>
<th>Metastatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>0-3 cm in diameter</td>
<td>Solitary</td>
<td>前三颗淋巴结</td>
</tr>
<tr>
<td>T2</td>
<td>3.1-6 cm</td>
<td>Freely mobile or skin fixation</td>
<td>Ulceration</td>
</tr>
<tr>
<td>T3</td>
<td>6 cm or more</td>
<td>Cranial nerve VII intact</td>
<td>Cranial nerve VII dysfunction</td>
</tr>
</tbody>
</table>

Levitt has more recently in 1981 presented a more involved system of staging. Unfortunately, the experience with these classification systems is limited, and it appears that use of the methods is slow to gain popularity.

**Patient Evaluation**

The patient presenting with a salivary gland mass may have a variety of signs and symptoms because of the vast number of possible locations between the major and minor salivary glands. Certainly, for practical purposes the parotid and submandibular glands can be stressed in this discussion. The minor salivary gland tumors may cause signs and symptoms from the oral pharynx into the laryngopharyngeal region and tend to have less consistency in presentation.

The most common presentation of the parotid or submandibular gland neoplasms is a lump noted incidentally while washing the face or shaving. The history of duration is usually indefinite and not too meaningful. The location of the glands in relatively inconspicuous areas of the head and neck leads to this inaccuracy in time of onset and duration. The most common site for parotid neoplasms is the lower pole, or tail, of parotid area. The figure shows a moderate-sized tail of parotid neoplasm presenting in the tail of the parotid gland. The mass in this figure is more subtle than the mass in the previous figure and represents a mixed cell tumor. The following figure illustrates a left parotid mass that was metastatic carcinoma from a nasopharyngeal primary. This location frequently remains unobserved by patients and may even be missed by physicians. Also, changes in the deep portions of the gland may go unnoticed for long periods of time. If the patient or family gives a history of definite rapid enlargement or change in growth pattern, the physician must pay particular attention to the possibility of malignancy or infection. It must always be remembered that the major salivary glands may be the location for metastases from other areas of the body. The majority of metastases are from squamous cell carcinoma of the skin.
or melanoma. This figure demonstrates a parotid mass that is a lymph node involved with squamous cell carcinoma metastatic from the ear.

The benign neoplasm located in the superficial lobe of the parotid will have no other signs or symptoms. The physical examination will demonstrate a mobile nontender mass. The mass will usually be firm and solitary. The presence of multiple masses would be indicative of primary malignancy or metastatic disease. An exception would be the recurrent benign mixed tumor, which may have many foci of seeding.

A parotid region mass may indeed represent other anatomic structures in the area. The diagram demonstrates the location of possible areas of confusion. The mandibular coronoid process and condyle may be prominent in the cheek and preauricular area, respectively. The masseter may be markedly hypertrophied and may cause confusion. The angle of the mandible may be prominent, and the transverse process of the second cervical bone will frequently present in the retromandibular region as a mass.

The lesion that involves the deep lobe of the parotid gland may be extending into the parapharyngeal space. These lesions can be examined intraorally by performing a thorough head and neck examination. The parapharyngeal space is bounded cephalad and laterally by the base of skull and mandible, respectively. These boundaries make medial and caudal growth the path of least resistance. In general, the patient notes minimal changes in voice or deglutition until the mass is large. As a mass in the parapharyngeal space enlarges, the nasopharynx, eustachian tube, and lateral oropharynx may be affected, as is demonstrated in the computerized tomographic (CT) scan, in which a parapharyngeal paraganglioma is displacing the pharynx and parotid. The most common history is probably the incidental finding of the lesion on medical or dental examination.

On occasion, the history may include that of previous biopsy. The examiner may notice scarring and fibrosis of the palate. This practice means by definition that the constrictor and palatal musculature has been violated if the neoplasm has been entered and a successful biopsy has been obtained. Such a method of preoperative clinical evaluation is to be discouraged. It not only makes surgical removal more difficult in the palatal and pharyngeal area but also is commonly unsuccessful because of the depth of the neoplasm.

If the tumor is isolated to the parapharyngeal space, no palpable mass in the lateral face or neck will be observable or palpable. If the lesion is the true "dumb-bell" tumor described by Thackray, it will pass through the stylomandibular tunnel into the retromandibular area. The great vessels of the neck and the ninth, tenth, eleventh, and twelfth cranial nerves are located in this space. It is extremely rare to have nerve involvement by a tumor unless it is of neurogenous origin or is malignant. These tumors are now most clearly defined by using CT studies of the base of skull and neck. Computerized radiographic imaging of the body tissues has helped the salivary gland surgeon mainly with the deep lobe tumors in preoperative planning and patient counseling. The CT scan shows the combined use of sialography and CT to demonstrate a deep lobe mass.

Facial nerve paralysis or weakness associated with a salivary gland neoplasm is accepted as an extremely ominous sign. Conley and Haymaker report an incidence of facial paralysis in malignant neoplasms of the salivary gland as 12 per cent. Eneroth reported an
incidence of 14 per cent and a mortality rare of 100 per cent. Adenoid cystic carcinoma is commonly associated with perineural invasion of the nerves. This is thought to be the major route of spread and to lead to its poor long-term prognosis.

Metastatic lymph node involvement in primary salivary gland neoplasms in general occurs late in the course of the disease. Conley records an incidence of 60 per cent for metastasis in patients having facial paralysis. A recent development of examining the neck with CT scanning for occult nodes may supplement the physical examination of the neck. The figure shows a CT examination of the neck showing nodes that were not palpable on physical examination.

Eneroth examined pain as a possible indicator of malignancy and found 5.1 per cent of benign neoplasms presented with pain and 6.5 per cent of malignant neoplasms presented with pain. Spiro and associates found that those malignant neoplasms presenting with pain carry a poorer prognosis. He reported that the group presenting with pain had a 35 per cent 5-year survival rate compared with the nonpain group survival rate of 68 per cent.

The physical examination of the patient with a salivary gland mass requires that the physician note specifically several areas of the head and neck examination. It is particularly helpful to discern whether the primary mass is extraglandular or intraglandular. If an extraglandular mass is identified, a thorough examination of the head and neck for possible skin neoplasms should be performed. Squamous cell carcinoma and malignant melanoma are the most common malignancies metastatic to the parotid region. These malignancies may arise from relatively hidden areas of the hair-bearing scalp and eye. A complete examination of these areas along with the mucous membrane surfaces of the aerodigestive tract may uncover a primary lesion. The figure demonstrates the large number and distribution of extraglandular lymph nodes in the parotid and submandibular region. In general, superficial or extraglandular nodes are mobile, and in the instance of the submandibular region the nodes may be rolled over the edge of the mandible. This is not possible if the mass is intraglandular because of the fascial attachments from the gland to the mandible. Careful scalp and eye examinations may reveal inconspicuous primary lesions metastatic to the salivary gland regions. The area of the retromandibular parotid gland extension is a difficult area to evaluate and should be noted specifically in these patients. The pharyngeal examination should note the presence of a parapharyngeal mass. Cranial nerve examination should be systematically performed and recorded in the record. Finally, the cervical lymph node chain should be palpated and suspicious nodes noted.

Radiology

The advances in radiographic imaging of body tissues have been phenomenal in the last decade. The sophisticated techniques of computed tomography have added much to the evaluation of many head and neck problems. Even though the salivary gland surgeon has seen these significant additions made to his armamentarium of diagnostic tests, there are only a few occasions when any procedures beyond the complete head and neck history and physical examination are warranted in evaluating salivary gland neoplasms.

It is imperative that the physician put the various diagnostic tests in perspective and be selective in ordering them. This is important from a cost-effective standpoint and also from
that of the patient, who needs to understand that in the majority of salivary gland masses only an adequate microscopic examination of tissue will allow the physician the important information for decision-making regarding therapy. The ordering of multiple tests must not be done to delay the decision of salivary gland surgery. The decision to perform surgery can usually be made after the first examination of a salivary gland mass. It may be prudent to have an initial interview with the patient and schedule a follow-up appointment to further discuss surgery and allow the patient to adjust to the surgical recommendation.

In general, supplemental diagnostic tests should be reserved for the 10 per cent or fewer salivary gland masses that are located in the retromandibular and parapharyngeal region of the parotid or are in debilitated patients unable to tolerate surgery.

Plain Radiography

The plain radiograph is used in salivary gland evaluation when calculi are suspected. The majority of calculi are radiopaque concretions that can be seen on plain radiographs. The radiopaque submandibular calculi are easily visualized on plain radiographs. There is no indication for a plain radiograph in routine evaluation of salivary gland masses. If base of skull involvement or mandibular erosion is suspected, much more information can be obtained from a computed tomography study.

Sialography

Contrast sialography is indicated in inflammatory diseases of the salivary glands in an effort to delineate their etiology. Salivary gland sialectasis, calculi, or strictures are the main problems to be identified by this method. It is seldom indicated and can be contraindicated in salivary gland neoplasms. The potential problem with performing contrast sialography in an obstructive situation is the possibility of inciting an inflammatory or infectious episodes by injecting foreign material under pressure in the duct system. The exception may be the combined use of contrast sialography and computed tomography in studying deep lobe and parapharyngeal space masses.

The technique utilizes a catheter placed in the parotid or submandibular gland duct for contrast introduction into the gland. The contrast is injected until the patient feels considerable pressure or slight pain. Many radiologist will allow the patient to perform the injection. A set of films are taken when filling is complete. These are followed by giving the patient a sialogogue to empty the ductal system. A normal gland will empty in less than 5 minutes. Follow-up films in 30 minutes may be helpful to observe delayed function of the gland.

Normally the ductal system will fill to the intercalated ducts. In strictures usually multiple areas of ductal narrowing can be identified. Calculi, if radiolucent, will be seen as a bubble in the duct. Radiopaque calculi will be seen on a plain film taken prior to contrast injection. Sialectasis is diagnosed by observing areas of the duct. Salivary gland neoplasms will distort the ductal architecture and leave areas of the gland devoid of contrast material.
**Radiosialography**

Radiosialography is based on the concentrating ability of the salivary gland striated ductal epithelium. The cells of this portion of the salivary gland unit have the ability to extract $^{99m}$Tc (pertechnetate) from the capillary network of the salivary glands. Gamma emissions from the radioactive material secreted by the ducts can then be identified during scanning of the gland.

Radiosialography has been most useful in the presence of salivary gland masses in the elderly or debilitated. The scan will identify a mass lesion and delineate the location, size, and activity. The presence of a "hot" mass is usually indicative of a Warthin's tumor or oncocytoma. However, several reports have indicated that "hot" masses can also represent malignancy. A malignant neoplasm usually appears as a "cold" nodule. Neoplasms such as a benign mixed tumor may on occasion appear cold. I have found the $^{99m}$Tc scan to be helpful in counseling the elderly and high-risk surgical patient who presents with a salivary gland mass.

**Computed Tomography**

The advances in the field of computed tomography have revolutionized diagnostic medicine. This is certainly true of the head and neck region. These techniques allow the head and neck physician to investigate in a noninvasive manner the base of the skull and the retromandibular and parapharyngeal spaces. The study of a deep lobe mass extending into the parapharyngeal space is an elegant application of this method of evaluation.

Several reports in the literature have advised the combination of contrast sialography and computed tomography for further delineation of the glandular tissue and neoplastic growth. It is probable that as the sophisticated new generations of equipment for computed tomography and nuclear magnetic resonance become available, this will be unnecessary.

**Angiography**

The use of conventional intra-arterial angiography or digital subtraction venous angiography (DSVA) for the evaluation of salivary gland neoplasms has limited application. Vascular studies of the deep lobe and parapharyngeal space tumors are useful in diagnostic and preoperative planning efforts. If a mass is suspected to be of vascular origin, a screening DSVA study is helpful. This study is performed on an outpatient basis and requires only a venous injection. If a vascular neoplasm or involvement is identified, further study utilizing conventional angiography may be necessary to selectively study the vascular supply to the area.

**Diagnostic Techniques**

Other diagnostic techniques short of excisional biopsy include core-needle biopsy and fine-needle aspiration biopsy. Techniques such as sialometry, scintigraphy, and radiosialometry are function tests that give no useful information in a diagnostic evaluation of salivary gland neoplasms.
Fine-Needle Aspiration Biopsy

The fine-needle aspiration biopsy was developed in the Scandinavian countries during the 1950s. It has been advocated as a direct and inexpensive method of salivary gland neoplasm diagnosis. The method as described by Zajicek involves introducing a 22-gauge needle into the mass in question and obtaining an aspirate of tissue by applying negative pressure. The pressure is then allowed to equalize before removing the needle. The aspirate is then applied to a glass slide and is fixed in 95 per cent ethyl alcohol and Papanicolaou solution. It must be stressed that this is a cytologic examination and requires a pathologist well versed in salivary gland pathologic appearance and cytologic methods. Sismanis and associates report an 82.2 per cent concurrence between cytologic diagnosis and subsequent histologic diagnosis.

Complications from this method are minimal when the operator and pathologist are adept at the procedure. Suggestions that seeding along the tract of the needle may occur have not been substantiated by review of numerous cases.

Core-Needle Biopsy

In contrast to the fine-needle aspiration biopsy, which utilizes cytologic methods of evaluation, the core-needle biopsy actually uses a core of tissue for histologic examination. This should be viewed as an incisional biopsy and utilized when definitive surgery is not possible because of tumor size or patient disability. The large reticulum cell sarcoma is an example of a parotid mass successfully biopsied with a core biopsy.

In contrast to the fine-needle aspiration biopsy, reports of seeding the tract of the needle path have appeared in the literature. These reports have occurred with the Vim-Silverman needle. It is now more common to use the disposable Medi-Cut needle, which brings about a smoother operation.

After all tests and examinations are performed, the excisional biopsy provides the physician and patient the most useful information. In the majority of patients, the biopsy is both diagnostic and therapeutic.