

**TITLE: Salivary Gland Neoplasms**

**SOURCE: Grand Rounds Presentation, UTMB, Dept. of Otolaryngology**

**DATE: June 26, 2002**

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## **Introduction**

The salivary glands are the site of origin of a wide variety of neoplasms. The histopathology of these tumors is said to be the most complex and diverse of any organ in the body. Salivary gland neoplasms are also relatively uncommon with an estimated annual incidence in the United States of 2.2 to 2.5 cases per 100,000 people; they constitute only about 2% of all head and neck neoplasms (1). Nearly 80% of these tumors occur in the parotid glands, 15% in the submandibular glands and the remaining 5% in the sublingual and minor salivary glands. Benign neoplasms make up about 80% of parotid tumors, 50% of submandibular tumors and less than 40% of sublingual and minor salivary gland tumors. The following is a discussion on this diverse population of neoplasms (2).

## **Benign Neoplasms**

### **Pleomorphic Adenoma**

The pleomorphic adenoma or benign mixed tumor is the most common of all salivary gland neoplasms. It comprises about 70% of all parotid tumors, 50% of all submandibular tumors, 45% of minor salivary gland tumors but only 6% of sublingual tumors. The most common location of occurrence is the parotid (85%) followed by the minor salivary glands (10%), in which the palate, upper lip and buccal mucosa are most commonly affected. These tumors are most often diagnosed in the 4<sup>th</sup> to 6<sup>th</sup> decades of life and are uncommon in children although they are second only to hemangiomas in this population. They are seen more frequently in women with a female-to-male ratio of 3-4:1.

The typical clinical presentation of a pleomorphic adenoma is a slow-growing, painless and firm mass. In the parotid, 90% occur in the superficial lobe and most commonly are seen in the tail of the gland. Minor salivary gland pleomorphic adenomas most commonly occur on the lateral palate and are covered with normal appearing mucosa. In all locations, they are typically nontender to palpation and tend to be mobile when small but may become fixed with advanced growth. These tumors are nearly always solitary although rare cases of synchronous or

metachronous salivary neoplasms have been reported- either involving a second mixed tumor or a distinct lesion, most commonly Warthin's tumor. Facial nerve paralysis in association with pleomorphic adenomas almost never occurs, even with extremely large tumors.

The gross pathologic appearance of a pleomorphic adenoma is a smooth or lobulated, well-encapsulated tumor that is clearly demarcated from the surrounding normal salivary gland. They are typically solid tumors and may have areas of gelatinous myxoid stroma. Cystic degeneration or tumor infarction and necrosis are rarely seen except in large, long-standing lesions. Microscopically, these tumors are composed of varying proportions of gland-like epithelium and mesenchymal stroma. The epithelial cells may display several different patterns of growth—small nests, solid sheets, ductal structures or anastomosing trabeculae. The stroma is just as variable and may be myxoid, chondroid, fibroid or osteoid. Also on microscopic examination, the incomplete encapsulation and transcapsular growth of tumor pseudopods characteristic of pleomorphic adenoma are demonstrated.

Treatment of pleomorphic adenomas is complete surgical excision with a surrounding margin of normal tissue, i.e., superficial parotidectomy with facial nerve preservation, submandibular gland excision or wide local excision for a minor salivary gland. Simple enucleation of these tumors is what is believed to have led to high local recurrence rates in the past and should be avoided. Rupture of the capsule and tumor spillage in the wound is also believed to increase the risk of recurrence, so meticulous dissection is paramount (1,2,3,4).

### **Warthin's Tumor**

The second most common benign parotid neoplasm is Warthin's tumor, also known as papillary cystadenoma lymphomatosum. It makes up 6-10% of cases of parotid tumors and has only rarely been described as occurring outside the parotid gland. It is primarily a disease of older white males, often being diagnosed in the 4<sup>th</sup> to 7<sup>th</sup> decades of life and occurring with a male-to-female ratio of approximately 5:1. Bilateral or multicentric Warthin's tumors are seen in 10% of cases. Three percent are associated with other benign or malignant tumors.

Like the pleomorphic adenoma, Warthin's tumors typically present as a slowly enlarging, painless mass. They tend to be firm or rubbery in texture and may be nodular. A minority of patients may report rapid enlargement of the tumor with associated pain or pressure.

Grossly, a Warthin's tumor possesses a smooth lobulated surface and a thin but tough capsule. The diagnosis is often obvious just by the appearance of the cut surface of the tumor. Multiple cysts of varying diameter and containing variably viscous fluid are seen. The lining of the cysts appears shaggy and irregular. The lymphoid component makes up the solid areas of the tumor and lymphoid follicles can occasionally be seen. The pathognomonic microscopic features are epithelial cells forming papillary projections into cystic spaces in a background of a lymphoid stroma. The epithelium is a double cell layer with tall columnar cells lining the cystic spaces and cuboidal cells along the basement membrane. The nuclei of the columnar cells is oriented toward the cystic space while the cuboidal cell nuclei is oriented toward the basement membrane.

Treatment of Warthin's tumors is surgical resection. Enucleation of the tumor may be adequate therapy but superficial parotidectomy with facial nerve preservation is the standard

management (1,2,3,4).

## **Oncocytoma**

Oncocytomas are rare tumors that constitute only 2.3% of benign epithelial salivary gland neoplasms. They are most often encountered after the sixth decade of life with a nearly equal male-to-female ratio of occurrence. The majority of these tumors affect the parotid gland (78%), few affect the submandibular gland (9%), none are reported in the sublingual gland and minor salivary gland involvement is most often in the palate, buccal mucosa or tongue.

The clinical presentation of oncocytomas is essentially identical to other benign salivary tumors—a slowly growing, nontender mass, typically in the superficial lobe of the parotid. They are firm, may be multilobulated and mobile on exam. Oncocytomas, along with Warthin's tumors, have been noted to demonstrate increased uptake of pertechnetate anion and therefore can be distinguished from some other neoplasms by using technetium-99m pertechnetate scintigraphy.

Gross pathology findings include a homogenous tumor with a smooth surface that may be divided into lobules by fibrous tissue septae. Microscopically, there are sheets, nests or cords of uniform oncocytes. These cells are large with distinct borders and filled with an acidophilic granular cytoplasm. The granularity of the cytoplasm is due to the presence of large numbers of mitochondria that may constitute up to 60% of the cell volume. Special staining procedures such as the phosphotungstic acid hematoxylin stain, Bensley's aniline-acid fuchsin or Luxol-fast-blue reaction take advantage of this unique characteristic and can help to make the diagnosis of oncocytoma, as can electron microscopy.

Standard treatment of oncocytomas is surgical excision with a margin of normal tissue. There is an exceedingly low rate of recurrence of these tumors if removal is complete. Enucleation or curettage is not appropriate (1,2,3,4).

## **Monomorphic Adenoma**

The term "monomorphic adenoma" refers to a group of rare salivary tumors that includes the basal cell, canalicular, sebaceous, glycogen-rich and clear cell adenoma. Of these, the basal cell adenoma is the most common. It constitutes 1.8% of benign epithelial salivary gland tumors and typically occurs in the 6<sup>th</sup> decade of life. There are conflicting reports of gender predilection for this tumor but it does seem to occur more frequently among Caucasians than African Americans. The majority of basal cell adenomas occur in the parotid gland where they present as a slowly enlarging firm mass. They are well-encapsulated, smooth tumors on gross inspection and are divided into four subtypes based on their microscopic appearance—solid, trabecular, tubular and membranous.

The presentation of canalicular adenoma peaks in the 7<sup>th</sup> decade of life and, like the basal cell adenoma, is more common in whites than blacks. There is a female predominance with a female-to-male ratio of occurrence of 1.8-1. This tumor most commonly involves the minor salivary glands of the upper lip (74%) or buccal mucosal (12%). Clinically it presents as a nonpainful submucosal nodule. On gross pathologic examination, canalicular adenomas may or may not possess a capsule and it is not unusual for there to be multifocal growth. Microscopically

there are cords of single-layer columnar or cuboidal cells forming duct-like structures in a background of fibrous stroma (1,2,3,4).

The majority of monomorphic adenomas display nonaggressive behavior and are adequately treated with surgical excision.

## **Myoepithelioma**

The rare myoepithelioma accounts for less than one percent of all salivary gland neoplasms. They are seen in the minor salivary glands, primarily palate, parotid glands, and occasionally in the submandibular glands. Like pleomorphic adenomas, these present in the 5<sup>th</sup> decade of life and are more common in women. Clinical presentation is similar to other benign salivary neoplasms—an asymptomatic, slow-growing mass. They are well-circumscribed tumors with a gross appearance similar to a pleomorphic adenoma but without the myxoid stroma. Three patterns of microscopic appearance have been described. The spindle cell pattern is the most common overall and is typical for parotid myoepitheliomas. The plasmacytoid pattern is less common but the most frequently encountered pattern in palate tumors. The third pattern demonstrates a combination of the spindle and plasmacytoid cells and is uncommon. Myoepitheliomas tend to exhibit benign behavior and complete surgical excision is appropriate therapy (1).

## **Malignant Neoplasms**

### **Mucoepidermoid Carcinoma**

Mucoepidermoid carcinoma is the most common salivary gland malignancy and makes up between 5 and 9% of all salivary gland neoplasms. It develops most commonly in the major salivary glands, most often the parotid (45-70%). The second most common site of occurrence is the palate (18%). This tumor displays a uniform age distribution between the ages of 20 and 70 years, with a slight peak in occurrence in the 5<sup>th</sup> decade. Although it is rare before age 20, it is the most common salivary gland malignancy in the pediatric and adolescent populations. Mucoepidermoid carcinoma occurs more frequently in women than in men and in Caucasians than in African Americans.

The clinical presentation of a salivary gland malignancy can be very similar to that of a benign lesion. Often the only complaint is the presence of an enlarging but asymptomatic mass. Occasionally patients will report a rapid enlargement of a previously stable mass. Symptoms such as pain, fixation to the surrounding tissues or skin or facial paralysis are uncommon and should increase suspicion for a high-grade tumor. A mucoepidermoid carcinoma occurring in an intraoral minor salivary gland will often be mistaken for a benign or inflammatory process. It is not unusual for them to appear as a bluish or red-purple, soft and smooth growth. Others may present with a papillomatous appearance or as a hard submucosal mass, identical to a torus.

On gross inspection, some mucoepidermoid carcinomas appear well-circumscribed and may be partially encapsulated. Others are poorly defined and infiltrative. The cut surface of the tumor may contain solid areas, cystic areas or both. The cystic spaces contain viscous or mucoid material. Microscopically, these tumors are characterized by the presence of two populations of

cells—the mucus cells and the epidermoid cells, the proportion of which helps to define the grade of the tumor. Low-grade mucoepidermoid carcinoma is characterized by prominent cystic structures and mature cellular elements. This tumor contains proportionally more mucus cells, which may form gland-like structures, and fewer epidermoid cells. Intermediate-grade tumors display fewer and smaller cysts and occasional solid islands of epidermoid tumor cells. Although mucus cells are still present, there is an increasing proportion of epidermoid cells and occasional keratin pearl formation. The high-grade carcinomas are hypercellular, solid tumors with noticeable cellular atypia and frequent mitotic figures. These tumors will often be mistaken for a squamous cell carcinoma and the differentiation between the two can be quite difficult. Positive immunohistochemical staining for mucin indicates a high-grade mucoepidermoid carcinoma rather than a squamous cell carcinoma.

Appropriate therapy for mucoepidermoid carcinoma depends primarily upon the stage of disease, but is also influenced by tumor grade and location. Stage I and II disease can often be treated by surgical excision alone—parotidectomy with facial nerve preservation, submandibular gland excision or wide local excision of an involved minor salivary gland. Stage III and IV disease often require more radical excision and may warrant additional intervention such as a neck dissection or postoperative radiation therapy (1,2,3,5).

### **Adenoid Cystic Carcinoma**

Adenoid cystic carcinoma is the second most common salivary gland malignancy overall, but is the most common in the submandibular, sublingual and minor salivary glands. It occurs equally in men and women, peaks in the 5<sup>th</sup> decade of life and is more common in Caucasians.

Clinical presentation is often an asymptomatic mass, however, this tumor is more likely than others to present with pain or paresthesias. Facial paralysis remains rare, but again, may be seen more frequently with adenoid cystic than with other tumors. Minor salivary gland involvement is characterized by a submucosal mass with or without pain and ulceration.

Gross appearance is typically a well defined but not encapsulated mass that can be seen infiltrating surrounding normal tissue. Despite their name, these are solid tumors that rarely display obvious cystic spaces on the cut surface. Microscopic appearance is described as cribriform, tubular or solid. The cribriform pattern is the most common and most easily recognizable. It is often referred to as the “swiss cheese” pattern. Tumor cells are arranged in nests around cylindrical spaces that may contain a mucinous or hyalinized material. Cells that are arranged in layers and form ductal structures characterize the tubular pattern. The solid pattern contains sheets of tumor cells with no intervening spaces.

Current treatment recommendations for adenoid cystic carcinoma include complete surgical resection and postoperative radiation therapy. Because of the propensity for this tumor to demonstrate perineural invasion, sacrifice of the facial nerve may be necessary for tumor eradication. Elective neck dissection is usually not indicated because this tumor rarely involves the cervical lymph nodes. Even with seemingly adequate treatment, local recurrence of adenoid cystic carcinoma is unfortunately not uncommon. Tumor recurrence rates vary in the literature but reportedly can be as high as 42%. Another problem with this tumor is its propensity for distant metastasis, the most common site being the lung. Both local recurrence and distant metastasis can

develop many years after initial treatment and multiple recurrences in the same patient have been reported. Although the prognosis for complete cure is poor, the course of disease is often indolent and patients with adenoid cystic carcinoma may survive for many years before eventually succumbing to the disease (1,2,3,5).

### **Acinic Cell Carcinoma**

Acinic cell carcinoma is the second most common parotid malignancy and the second most common pediatric salivary gland malignancy. It is a rare tumor that accounts for about 1% of all salivary neoplasms. This malignancy will typically present in the 5<sup>th</sup> decade of life and is more common in women and Caucasians. Bilateral parotid disease occurs in approximately 3% of cases.

Clinical presentation is similar to other neoplasms—often an asymptomatic enlarging mass.

Gross appearance demonstrates a mass that is well circumscribed but lacks a true capsule. The cut surface is grayish, friable, and displays solid and cystic areas. Microscopic appearance has been categorized as solid, microcystic, papillary cystic and follicular. Tumor cells are dark staining and have granular or honeycomb cytoplasm. The surrounding stroma often demonstrates a lymphoid infiltrate.

Treatment of acinic cell carcinoma includes surgical excision. Elective neck dissection is not warranted. Postoperative radiation therapy may be helpful in cases of questionable residual disease after surgery. This tumor is generally regarded as a low-grade malignancy. Early survival rates are quite good—82% at 5 years, 68% at 10 years—but this drops off to about 50% by 25 years after treatment. This is due to the fact that this tumor, like adenoid cystic, can recur locally or develop distant metastasis many years after initial treatment (1,2,3,5).

### **Adenocarcinoma**

Adenocarcinomas of the salivary glands are rare but aggressive tumors. They tend to present in patients over 40 years of age and occur with nearly equal frequency in men and women. About half of these tumors present in the parotid glands, the minor salivary glands, particularly the palate, lip and tongue are the next most commonly affected sites.

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

Gross pathology reveals a firm mass with irregular borders and infiltration into surrounding tissue. It is generally a solid tumor without any cystic spaces. These malignancies can demonstrate a wide range of growth patterns and, for this reason, can be somewhat difficult to classify. However, all adenocarcinomas have in common the formation of glandular structures and they are described as grades I, II or III based upon the degree of cellular differentiation. Grade I lesions have well- formed ductal structures while Grade III lesions have a more solid growth pattern with few glandular characteristics.

Because these are more aggressive tumors, treatment for adenocarcinoma is more aggressive. Complete local excision is the mainstay of therapy. In the parotid this may include facial nerve sacrifice. In the minor salivary glands, a portion of the maxilla or mandible may have to be resected with the tumor. Although the efficacy hasn't been definitely proven, postoperative radiation therapy does seem to be of some benefit. Lymph node metastasis is not uncommon and in patients with palpable neck disease neck dissection is warranted. Elective neck dissection should probably be reserved for patients with extensive local disease or high-grade lesions. Local recurrence rates vary in the literature but have been cited as high as 51%. Regional metastasis has been reported in 27% and distant metastasis in 26%--most often to the lung and bone. Survival is dependent on the disease stage, which takes into account the extent and location of disease as well as the histologic tumor grade. The overall cure rate at 15 years is 67% for stage I, 35% for stage II and 8% for stage III (1,2,3,5).

### **Malignant Mixed Tumors**

Carcinoma ex-pleomorphic adenoma is the most common of three salivary neoplasms that are broadly referred to as malignant mixed tumors. It occurs when a carcinoma develops from the epithelial component of a preexisting pleomorphic adenoma. The other two tumors in this category, carcinosarcoma and metastasizing mixed tumor, are much less common. In a carcinosarcoma, the metastatic lesions contain both the stromal and epithelial elements. This is different from the carcinoma ex-pleomorphic adenoma in which only the epithelial elements are present in metastasis. The metastasizing mixed tumor refers to an otherwise benign acting pleomorphic adenoma that develops metastatic deposits of tumor.

Carcinoma ex-pleomorphic adenoma accounts for about 3.6% of all salivary neoplasms. It presents in the 6<sup>th</sup> to 8<sup>th</sup> decade of life with patients averaging 10 years older than those with pleomorphic adenomas. It occurs most often in the parotid, followed by the submandibular gland and palate. Presentation is usually a painless mass but some patients will report recent rapid enlargement of a long-standing nodule. Pain, fixation to the skin and facial weakness are variably present. The risk of malignant degeneration in a pleomorphic adenoma increases from about 1.5% in the first five years to 9.5% for adenomas present longer than 15 years. Gross pathology of carcinoma ex-pleomorphic adenoma often shows a poorly circumscribed, infiltrative, hard mass. Microscopically malignant appearing cells are present adjacent to a typical appearing pleomorphic adenoma. The malignant portion of the tumor can take the form of any epithelial malignancy except acinic cell. Most commonly this will be in the form of an undifferentiated carcinoma (30%) or adenocarcinoma (25%). This tumor tends to be more aggressive than other salivary malignancies and about 25% of patients will have lymph node metastasis on presentation. Treatment includes radical surgical resection, often in conjunction with neck dissection, and postoperative radiation therapy. Prognosis appears to be related to local extent of disease and the histologic type of the carcinoma component.

Carcinosarcomas, or true malignant mixed tumors, are very rare tumors accounting for only .05% of salivary gland neoplasms. Average age at presentation is about 60 years and men and women appear to be equally affected. The parotid is the most frequent site of occurrence. Microscopically, these tumors have both sarcomatous and carcinomatous elements. In the majority, the sarcoma is the dominating component and chondrosarcoma is the most common cell type. The carcinoma element is usually an undifferentiated or high-grade ductal adenocarcinoma.

This is also an aggressive tumor and it is not uncommon for patients to have distant metastasis on presentation. Currently recommended treatment includes radical surgery, neck dissection for palpable nodes and postoperative XRT. Although efficacy has yet to be proven, chemotherapy is likely to have a role in the treatment of this disease given the high rate of distant metastasis (1,2,3,5).

### **Squamous Cell Carcinoma**

Primary squamous cell carcinoma of the salivary glands is quite rare, accounting for about 1.6% of salivary gland neoplasms. In order to make this diagnosis, high-grade mucoepidermoid carcinoma, metastatic squamous cell to the gland or intraglandular nodes and direct extension of a squamous cell carcinoma must first be excluded. There is a 2:1 male-to-female ratio of occurrence and patients are usually over age 60. These tumors present as firm enlarging masses that are not uncommonly fixed to surrounding tissue and associated with pain or facial weakness. The gross and microscopic appearance is similar to squamous cell carcinoma of other primary sites and varies from well-differentiated with keratinization to poorly-differentiated without keratinization. Salivary gland squamous cell carcinoma displays aggressive behavior with rapid growth and early spread to regional lymph nodes. Treatment consists of surgical resection, neck dissection and postoperative radiation (1,2,3,5).

### **Polymorphous Low-grade Adenocarcinoma**

Polymorphous low-grade adenocarcinoma (PLGA) is the second most common malignancy in the minor salivary glands and occurs most frequently in the palate, lip and buccal mucosa. This tumor typically presents in the 7<sup>th</sup> decade of life and is more common in women (67%). It presents as a painless submucosal swelling that gradually enlarges and may ulcerate and bleed. The microscopic appearance of these tumors is what gives them their name. Any of a variety of growth patterns (solid, tubular, trabecular, glandular, cribriform, cystic) can be seen within the same lesion or among different lesions. PLGA displays a tendency for perineural and perivascular invasion, however it typically follows an indolent course. Treatment consists of conservative yet complete local excision. Postoperative radiation and neck dissection are probably not necessary. Distant metastasis has not been reported (1,2).

### **Clear Cell Carcinoma**

Clear cell carcinoma has also been called glycogen-rich carcinoma. These are rare tumors that occur most frequently in the minor salivary glands of the palate and the parotid. They occur equally in men and women and typically present in the 6<sup>th</sup> to 8<sup>th</sup> decades of life. Microscopically, these tumors display a uniform pattern of round or polygonal cells with peripherally displaced dark nuclei and clear cytoplasm. Tumor cells may grow in nests or cords separated by fibrous stroma or solid sheets of cells. Locally infiltrative growth is characteristic. Clear cell carcinomas are classified as low-grade tumors and are treated with complete local excision (1,5).

### **Epithelial-myoepithelial Carcinoma**

Epithelial-myoepithelial carcinoma constitutes less than 1% of salivary gland neoplasms. It occurs in the 6<sup>th</sup> and 7<sup>th</sup> decades of life, in women more often than men, and typically in the

parotid gland. Some studies have suggested that patients with these tumors are at increased risk for a second primary malignancy—either in the salivary glands or in a separate site (breast and thyroid have been reported). Grossly, these are well-circumscribed, multinodular firm masses with irregular cystic spaces. The microscopic appearance can be highly variable but displays a very typical biphasic character. “Subunits” of tumor growth include a surrounding thickened basement membrane, outer clear myoepithelial cells, and inner cuboidal epithelial cells lining small duct-like structures. Treatment consists of complete surgical resection. Because this tumor is so rare, little is known about whether adjuvant radiotherapy or chemotherapy is beneficial (1).

## **Undifferentiated Carcinoma**

The undifferentiated carcinomas are uncommon but behave aggressively and have a poor prognosis compared to other salivary gland tumors. Lymphoepithelial carcinoma of the salivary glands occurs most commonly in North American and Greenland Eskimos and Asians. Among Eskimos, the parotid gland is most often affected, there is a female predominance and a familial pattern of the disease. Among Asians, the submandibular gland is the most common site and men are affected more often than women. Undifferentiated large-cell carcinoma has a bimodal age distribution with the first peak in the 6<sup>th</sup> and 7<sup>th</sup> decades of life and a second peak in the 9<sup>th</sup> decade. Men are affected more frequently than women and the parotid is the most common site. Undifferentiated small-cell carcinoma occurs most often in the parotid, in patients 50-70 years old, and with a 1.6:1 male-to-female ratio. All of these malignancies have a tendency for local recurrence, regional and distant metastasis. Treatment centers around complete surgical excision, with neck dissection for palpable disease and consideration given to postoperative radiation therapy and possibly chemotherapy (1).

## **Controversial Issues**

### **Management of the N0 Neck**

There is no doubt that treatment of the clinically positive neck, most often with neck dissection and postoperative XRT, is indicated in patients with salivary gland malignancies. However, there still remains no consensus on how the clinically N0 neck should be managed. Clearly, though, this issue should be carefully contemplated because we do know that patients who experience a recurrence of disease in the neck have a low likelihood of salvage. The overall incidence of clinical neck disease in parotid malignancies is 16%. The average 5-year survival for parotid malignancies is 74% when neck nodes are not involved, this drops to 9% when neck metastasis are present. Similarly, for the submandibular gland, the incidence of clinically positive nodes is 8%, 5-year survival in patients with a negative neck is 41%, and this drops to 9% when the neck is positive.

Many studies have been done over the years attempting to identify patient or tumor factors that increase the risk for occult neck disease. The outcomes of these studies are somewhat variable but most seem to agree that high-grade lesions and advanced primary tumor stage have an increased incidence of neck metastasis. Other factors that have been found to be significant in some studies are “high-risk” histology (undifferentiated carcinoma, squamous cell carcinoma, adenocarcinoma, high-grade mucoepidermoid carcinoma and salivary duct carcinoma), larger tumor size (>3cm), facial paralysis, patient age over 54 years, extraparotid extension of tumor and

perilymphatic invasion.

In addition to deciding when to treat the N0 neck, one must also decide how to treat the N0 neck—with neck dissection or with radiation. The benefit of a neck dissection is that it provides a pathologic stage of neck disease, which helps for predicting prognosis and counseling patients. The disadvantages of a neck dissection include a longer operating time, increased potential complications, and potential functional problems or aesthetic concerns for the patient. If elective neck dissection is chosen, the type of neck dissection should be tailored to address those levels of the neck most at risk for occult disease. Parotid malignancies that develop occult neck metastasis have been shown to most commonly involve the jugular nodes in levels II, III and IV. Submandibular tumors typically involve nodes in level I, II and III. Therefore, selective neck dissection addressing these levels and sparing all normal structures would be the method of choice to surgically manage the N0 neck.

The advantage of primary irradiation of the neck is that it avoids all of the sequelae of surgery. The main disadvantage is the radiation effect upon surrounding normal tissue, which can, like surgery, cause functional problems and cosmetic concerns for the patient. Also of concern, particularly in younger patients, would be the occurrence of radiation induced second malignancies. The argument for treating the N0 neck with primary irradiation is that those factors that increase the likelihood of occult neck metastasis are essentially the same factors that are considered indications for the use of postoperative radiation to the primary tumor. Therefore, if the primary tumor already necessitates adjunctive radiation therapy then it seems reasonable to use radiation to treat the neck as well (6,7,8,9).

### **Fine-needle Aspiration Biopsy**

The efficacy of fine-needle aspiration of salivary gland masses is well established. The accuracy, sensitivity and specificity reported in the literature vary from 84-97%, 54-95% and 86-100% respectively. It has also been established as a safe procedure and one that is well tolerated by patients. Additionally, as surgeons and cytopathologists have become more familiar with the technique, the high false-negative results seen in the past have now been reduced to below 10% in most studies. The only remaining controversy over the use of FNA for salivary neoplasms is whether or not it has any impact on clinical management. Opponents of preoperative FNA claim that regardless of the histology of a major salivary gland neoplasm, surgery will be the treatment and knowing the type of neoplasm does not change the surgical approach. Other reported arguments against FNA include the possibility of altering the tumor histopathology to the point of obscuring final pathologic diagnosis and the frequency of “inadequate” sampling. Proponents of FNA claim that it offers important information regarding the benign or malignant nature of the tumor and that this information is vital for optimal preoperative patient counseling. Knowledge of the type of tumor is also said to allow the surgeon to formulate a more thorough operative plan and avoid intraoperative surprises. Additionally, FNA is highly reliable in differentiating between neoplastic and nonneoplastic lesions. Many patients with nonneoplastic salivary gland lesions can be managed, and should be managed, without surgery. This fact alone contradicts the thinking that any salivary gland mass will be managed with surgery and that FNA will not influence patient management (10,11,12,13).

## Tumorigenesis

Two hypotheses have been developed in an attempt to explain and understand the wide variety of histopathology demonstrated by salivary gland neoplasms. These hypotheses, the bicellular and multicellular theories, propose that certain cells that make up the salivary gland unit are responsible not only for normal gland cell turnover and maintenance, but also for the development of different salivary gland tumors.

The bicellular theory was first proposed by Eversole in 1971 and later supported by Regezi and Batsakis in 1977. This hypothesis states that neoplastic development within salivary glands originates from the basal cells seen in the excretory and intercalated ducts. The excretory duct stem cells are believed to give rise to squamous cell carcinoma and mucoepidermoid carcinoma. The intercalated duct stem cells are the origin of pleomorphic adenoma, Warthin's tumor, oncocytoma, acinic cell carcinoma and adenoid cystic carcinoma. The second hypothesis, the multicellular theory, states that neoplasm development occurs from differentiated cells within the salivary gland unit. In this theory, the striated duct cells give rise to oncocytic tumors, acinar cells give rise to acinic cell carcinoma, excretory duct cells give rise to squamous cell carcinoma and mucoepidermoid carcinoma, and the intercalated duct cells and myoepithelial cells give rise to pleomorphic tumors.

Despite the prevalence of these theories in the otolaryngologic literature and teaching, little if any scientific evidence exists to support their validity. In fact, many physiologic studies have found evidence directly contrary to these hypotheses. Such evidence includes the finding that duct luminal cells, as well as basal cells, are readily capable of replication. Additionally, acinar cells, which are excluded from the histogenetic theories, have clearly been shown to enter the cell cycle. In studies of gland regeneration, two-thirds of acinar cells will replicate and participate in gland recovery while basal cells do not seem to participate in gland regeneration. Finally, several salivary gland neoplasms have been demonstrated to express the S-100 protein by immunohistochemical staining. In normal salivary gland tissue, this protein is found only in autonomic nerve tissue, not in any secretory or duct cells. This again, argues against the idea that ductal basal cells are the only site of origin of salivary gland tumors (1,14,15).

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