Paparella: Volume III: Head and Neck

Section 2: Disorders of the Head and Neck

Part 3: Salivary Glands

Chapter 20: Salivary Gland Tumors

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Salivary gland neoplasms represent the most complex and diverse group of tumors encountered by the head and neck oncologist. Their diagnosis and management is complicated by their relative infrequency (1 per cent of head and neck tumors), the limited amount of pretreatment information available, and the wide range of biologic behavior seen with the different histopathologic lesions. Proper management of these tumors requires an accurate diagnosis by the pathologist and correct interpretation by the surgeon. Therefore, a working knowledge of salivary gland histopathologic characteristics is mandatory for the head and neck surgeon. Surgical anatomy of the parotid, submandibular, and parapharyngeal spaces is complex and also demands careful study. The salivary gland surgeon must have a clear understanding of these neoplasms, with an awareness of pitfalls in pathologic diagnosis, and a well-formulated plan of treatment.

Incidence

The salivary glands are divided into major salivary glands, consisting of the paired parotid, submandibular, and sublingual glands, and the minor salivary glands, composed of the 600 to 1000 glands distributed throughout the upper aerodigestive tract. Approximately 80 per cent of all salivary gland neoplasms originate in the parotid gland, with 10 to 15 per cent arising from the submandibular glands, and the remainder located in the sublingual and minor salivary glands. The probability of a salivary gland neoplasm being malignant is inversely proportional to the size of the gland. Most large series report benign histologic features in 70 to 80 per cent of parotid neoplasms and in 40 to 60 per cent of submandibular tumors. In the sublingual and minor salivary gland group, less than 40 per cent of tumors are benign, being as low as 12 per cent in one series.

Salivary gland tumors are relatively uncommon in children, accounting for approximately 5 per cent of all salivary gland neoplasms. Although the majority of these neoplasms are benign, 35 per cent of pediatric salivary gland tumors are reported to be malignant (Tables 1 and 2). The spectrum of disease is similar to that seen in adults, with the addition of the hemangioendotheliomas and congenital angiomas seen in childhood. The most common benign tumor in children is the hemangioma; the most common benign epithelial tumor is the benign mixed tumor. If a solid nonvascular mass is found in a child, the probability of malignancy is greater than 50 per cent. Mucoepidermoid carcinoma is the most frequently encountered malignancy, accounting for approximately 50 per cent of malignant salivary gland tumors in the pediatric age group.

Etiologic Factors

The etiologic agents for salivary gland neoplasms are poorly understood. Tobacco and alcohol, important factors in the majority of head and neck neoplasms, do not relate to most salivary gland neoplasms. However, cigarettes may play a causative role in the development of epidermoid carcinomas. Although salivary gland tumors have been produced in mice by inoculation of polyoma virus and carcinogenic hydrocarbons, there is no evidence for a similar causative relationship in humans. Several studies have shown an increased incidence of salivary gland neoplasms in patients with breast cancer; however, others fail to support this relationship.

Table 1. Benign Salivary Gland Tumors in Children

Hemangioma	111
Mixed tumor	94
"Vascular proliferative"	40
Lymphangioma	18
Lymphoepithelial tumor	3
Cystadenoma	3
Warthin's tumor	3
Other	7
Total	279.

Low-dose radiation therapy has been implicated in the development of salivary gland neoplasms. Katz and Preston-Martin noted this relationship in 11.3 per cent of patients, and similar figures were reported by Spitz and Batsakis. The radiation was most often given for treatment of benign disorders, such as acne or obstructing lymphoid tissue in the oral cavity or nasopharynx. Radiation delivered for the treatment of malignant disease has not been implicated, suggesting that high-dose irradiation is less of a risk factor than low-dose irradiation. The parotid gland is the site of radiation-associated neoplasm in most of the reported cases. The radiation-induced salivary gland tumors follow a pattern similar to those found in the thyroid gland. Latent periods range from 15 to 20 years, with the most frequent tumor seen in this group being the benign mixed tumor. In the latter study, there was an increased incidence of mucoepidermoid and epidermoid carcinomas in the patients with radiation exposure when compared with the nonirradiated group.

Table 2. Malignant Salivary Gland Tumors in Children

Mucoepidermoid carcinoma	73
Acinous cell carcinoma	18
Undifferentiated carcinoma	14
Adenocarcinoma	11
Undifferentiated sarcoma	9
Carcinoma ex-mixed tumor	9
Adenoid cystic carcinoma	6
Other	9
Total	149.

Anatomy and Embryology

The anatomy and embryology of the salivary glands is covered in detail in Volume I, Chapter 16. An understanding of cellular origins of the various salivary gland tumors is predicted on a clear understanding of the salivary gland unit. Two major theories of histogenesis have been proposed for salivary gland neoplasms. The multicellular theory matches each neoplasm with a particular cell within the salivary gland unit. In this system, oncocytic tumors arise from the striated ductal cells; acinous cell tumors arise from acinar cells; squamous and mucoepidermoid carcinomas develop from excretory ductal cells; and mixed tumors arise from the intercalated ductal cells and myoepithelial cells.

In the alternative theory, the bicellular theory of development, the basal cells of the excretory duct and intercalated duct act as stem cells for the mature cells in the salivary gland unit. According to this theory, the mixed tumor, Warthin's tumor, oncocytoma, acinic cell carcinoma, adenoid cystic carcinoma, and oncocytic carcinoma all arise from reserve cells of the intercalated duct, whereas the squamous cell carcinoma and mucoepidermoid carcinoma arise from the reserve cells of the excretory duct. In this theory, the state of differentiation of the stem cell will determine whether the tumor is benign or malignant. Recent studies using histochemical, immunochemical, and immunogenetic techniques have attempted to give support to the histogenetic relationships of various tumors. Caselitz and colleagues demonstrated similar histochemical tracers in adenoid cystic carcinoma and benign mixed tumor. The same immunofluorescent markers have been found in both benign mixed tumors and intercalated ducts, suggesting this site as the origin of the benign mixed tumors. As these techniques become more sophisticated and specific, we expect to find increasing evidence to support one or the other of these theories.

Histopathologic Classification

As stated previously, an accurate histopathologic diagnosis is the basis for a rational approach to management of salivary gland neoplasms. Foote and Frazell in 1953 made a major contribution to the understanding of the histopathologic features and biologic behavior of salivary gland neoplasms. This classification system has subsequently been modified by Batsakis and colleagues and forms the basis for classification of epithelial salivary gland tumors (Table 3). The most common benign and malignant tumors will be discussed.

Benign Lesions

Benign Mixed Tumor (Pleomorphic Adenoma)

The benign mixed tumor is the most common of all salivary gland neoplasms. Approximately 65 per cent of all salivary gland tumors are classified as benign mixed tumor or pleomorphic adenoma. The term *benign mixed tumor* was first proposed by Minssen in 1874 to describe the two components of the tumor, mesenchymal and epithelial. Although the derivation of the tumor is still uncertain, it is generally felt to be an epithelial tumor. A more recent term, *pleomorphic adenoma,* has been used to describe this tumor, but both terms are used interchangeably. These lesions are slow growing and asymptomatic. They are most frequently found in the parotid gland, then the submandibular gland, followed by the minor salivary glands. Benign mixed tumor also represents the most common tumor of each gland,

composing 77 per cent of parotid gland tumors, 60 per cent of submandibular gland tumors, and 53 per cent of tumors arising in the palate. These tumors also represent the largest group of epithelial neoplasms in children - again, being most common in the parotid gland.

Table 3. Classification of Epithelial Salivary Gland Tumors According to Batsakis

Benign Lesions

Mixed tumor
Papillary cystadenolymphoma (Warthin's tumor)
Oncocytosis - Oncocytoma
Monomorphic adenoma
    Basal-cell adenoma
    Glycogen-rich adenoma and clear cell adenoma
    Others
Sebaceous adenoma
Sebaceous lymphadenoma
Papillary ductal adenoma
Benign lymphoepithelial lesion.

Malignant Lesions

Carcinoma ex-pleomorphic adenoma
Mucoepidermoid carcinoma
    High grade
    Intermediate grade
    Low grade
Hybrid basal cell adenoma - adenoid cystic carcinoma
Adenoid cystic carcinoma
Acinous cell carcinoma (acinic carcinoma)
Adenocarcinoma
    Mucus-producing adenopapillary and nonpapillary carcinoma
    Salivary duct carcinoma (ductal carcinoma)
Oncocytic carcinoma (malignant oncocytoma)
Clear cell carcinoma
Epithelial-myoepithelial carcinoma of intercalated ducts
Squamous cell carcinoma
Undifferentiated carcinoma
Metastatic lesions
Miscellaneous lesions.

On gross inspection, the tumor is smooth and lobular and demonstrates a well-defined capsule. When the tumor is transected, the appearance of the cut surface will vary depending on the cellularity and myxoid component. On microscopic examination, both epithelial and mesenchymal elements are present. The epithelial component forms a trabecular pattern within a stroma that is myxoid in some areas and fibroid in other areas. The myoepithelial cells, which are felt to be the source of the stromal components, are found most commonly in the myxoid areas. Great variation in the stroma may be seen from tumor to tumor, being scant

in one tumor and abundant in another. The stroma may be myxoid, chondroid, fibroid, or even osteoid in appearance, with any combination within a single tumor. The key to a correct diagnosis is location of a focus of myxoid or chondroid stroma.

Warthin's Tumor (Papillary Cystadenoma Lymphomatosum)

In 1895, Hildebrand first described papillary cystadenoma lymphomatosum, which he felt represented a congenital cyst of the neck. In 1929, Warthin reviewed all parotid gland tumors treated at the University of Michigan and reported two cases of papillary cystadenoma lymphomatosum. These lesions were described as being adenomatous with a lymphoid stroma and were again felt to represent a developmental abnormality and not a neoplasm. In 1944, Martin and Erhlich first used the term *Warthin's tumor* in recognition of the previously mentioned author's work in this area. A number of names have been used to describe this tumor. The terms currently in use include *adenolymphoma,* popular in European literature, and *papillary cystadenoma lymphomatosum,* which is used in the pathology literature in the USA. The term *Warthin's tumor* is frequently used by surgeons for its simplicity.

Warthin's tumor composes 6 to 10 per cent of all parotid tumors, being the second most common benign neoplasm of the parotid gland. This tumor is almost exclusively confined to the parotid gland, although a few cases of submandibular gland Warthin's tumor have been reported. It is generally regarded as a neoplasm of older men, with the preponderance of cases developing between the fourth and seventh decades of life. However, the tumor has been found in the pediatric age group, and at least one series reports an equal sex distribution. This neoplasm usually presents as a slowly growing mass in the tail of the parotid gland. Approximately 12 per cent of Warthin's tumors are bilateral. Malignant transformation is rare.

On gross inspection, these tumors are well encapsulated with a smooth wall. The cut section reveals multiple cystic spaces of varying size filled with a thick mucinous material. Microscopically, multiple papillae filled with a lymphoid stroma are seen to be projecting into the cystic spaces. The lymphoid tissue found within this tumor confronts to that of lymph node. A high-powered photomicrograph demonstrates the double-layered granular epithelium. The apical row of cells is composed of eosinophilic granular cells with their nuclei oriented toward the lumen, whereas in the inner layer of cells, the nuclei are oriented toward the basement membrane.

The origin of this tumor is controversial as with many of the parotid gland neoplasms. Thompson and Bryant suggested that these tumors arise from ectopic ductal epithelium that has developed within intraparotid lymph nodes. This theory is attractive, since it would account for the almost exclusive location in the parotid gland, which is the only salivary gland containing lymph nodes. Incorporation of the lymph nodes within the gland is felt to be a function of late encapsulation, which allows a lymph node to become trapped within the gland. Another theory suggests that these lesions are not true neoplasms but rather represent a hypersensitivity reaction. Recent immunologic investigation of the lymphoid component of these tumors has been inconclusive.

The location of these lesions at the inferiormost portion of the gland may provide confusion for the inexperienced surgeon. If the lesion is confined to the lower portion of the gland, identification of the lower division of the facial nerve may be sufficient for an adequate excision.

Oncocytoma

The oncocytoma accounts for less than 1 per cent of all salivary gland neoplasms and, like Warthin's tumor, occurs almost exclusively within the parotid gland. This tumor is most commonly seen in the older age group, since oncocytes are rarely seen in salivary gland tissue before the fifth decade of life. There is no sex preponderance, and the malignant counterpart of this tumor (oncocytic carcinoma) is rare. Gross examination reveals a smooth, firm, rubbery mass within the parotid tissue. A photomicrograph will demonstrate round, plump, granular eosinophilic cells with small indented nuclei (oncocytes). Familiarity with this cell is important, since the oncocyte also forms the glandular epithelium of Warthin's tumor. Electron microscopy will demonstrate an excessive number of mitochondria, which characterize this cell.

Another feature of the oncocytoma, which is shared with Warthin's tumor, is the ability to image the tumor on the technetium scan. The oncocytes within the tumor concentrate the scanning material and will reveal a hot nodule on the scan.

The majority of these tumors are found in the superficial lobe of the gland, and therefore a superficial parotidectomy with facial nerve preservation is curative. When the lesion is found in a minor salivary gland, a margin of normal tissue will provide sufficient therapy for cure.

Monomorphic Adenomas

The monomorphic adenomas comprise a group of neoplasms that are often grouped with the pleomorphic adenomas. However, they do not possess the pleomorphic features of the mixed tumors. Included in this group are the basal cell adenoma, clear cell adenoma, glycogen-rich adenoma, and other rarer lesions. These tumors are generally regarded as slow growing and are the least aggressive of the salivary gland tumors. The most common monomorphic adenoma is the basal cell adenoma. It is commonly found arising from minor salivary glands, with the most common location being the upper lip. Of the major salivary glands, the parotid gland is most frequently involved. Rows of peripheral pallisading cells with a thick basement membrane are the distinctive features of this tumor. Since basal cell adenoma may be confused with adenoid cystic carcinoma, the surgeon must be aware of this tumor and the possibility of confusing these two cell types. For this reason, we feel that it is important to regard this lesion as a separate and distinct entity rather than including the lesion with the more common pleomorphic adenoma. Basal cell adenoma is considered to be benign, although there have been two cases of transition to adenoid cystic carcinoma, and Batsakis suggests that adenoid cystic carcinoma may represent the malignant counterpart of basal cell adenoma.

As a group, the monomorphic adenomas are considered to be benign and nonaggressive. Resection with a margin of normal tissue is considered sufficient therapy. If difficulty occurs in differentiating this tumor from adenoid cystic carcinoma, the surgeon should await permanent section analysis rather than performing a more extensive excision.

Malignant Neoplasms

Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma is the most common malignant tumor of the parotid gland and the second most common malignant tumor in the submandibular gland, following adenoid cystic carcinoma. This tumor constitutes 6 to 9 per cent of all major salivary gland neoplasms. Sixty to 70 per cent of mucoepidermoid carcinomas are located in the parotid gland, with the palate being the next most frequent site. These tumors have been divided into low-grade and high-grade tumors. The low-grade lesions are characterized by a higher ratio of mucous cells to epidermoid cells, whereas the high-grade lesions may resemble squamous cell carcinoma. Special stains are often required to differentiate high-grade mucoepidermoid carcinoma from squamous cell carcinoma. Although the low-grade lesions may behave in a benign fashion, they do have the capacity for local invasion and metastatic behavior.

Although the low-grade lesion is usually small and partially encapsulated, the high-grade lesion is usually larger with minimal encapsulation. On cut section, the low-grade tumors may demonstrate a mucinous fluid, whereas the high-grade tumors demonstrate a solid gray-white mass. A low-power photomicrograph demonstrates the two cell types with aggregates of mucoid cells separated by strands of epidermoid cells. A high-power photomicrograph reveals the two cell types in close proximity, with the mucous cells demonstrating well-defined boundaries and small peripheral nuclei and the epidermoid cells resembling an area of squamous cell carcinoma. A high-grade mucoepidermoid carcinoma sometimes does not have any visible mucoid elements. A special mucin stain may identify the presence of mucus and yield the proper diagnosis. Management of these tumors depends on the extent of tumor and the grade, as will be discussed later in this chapter in the section on management.

Adenoid Cystic Carcinoma

Adenoid cystic carcinoma accounts for approximately 6 per cent of all salivary gland neoplasms. It is less common than the mucoepidermoid carcinoma in the parotid gland, but it is the most common malignancy in the submandibular gland and in the minor salivary glands. This tumor composes more than 30 per cent of the minor salivary gland tumors and accounts for 2 to 14 per cent of parotid gland tumors and 17 to 30 per cent of submandibular gland tumors. As is the case with most salivary gland tumors, whether benign or malignant, these lesions most often present as asymptomatic masses. Pain and facial paralysis are the presenting symptoms in a relatively small percentage of cases. On gross inspection, the adenoid cystic carcinoma is usually monolobular and is either nonencapsulated or partially encapsulated. On cut section, the mass is gray-pink and demonstrates infiltration of surrounding normal tissue. The microscopic picture demonstrates an eosinophilic hyaline stroma with cylindric formations. The term *cylindroma* has been used to describe this tumor based on this typical microscopic appearance. Different histologic patterns have been

identified and classified into cribriform, solid, cylindromatous, and tubular. An attempt to correlate histologic classification with clinical course has met with conflicting results.

A feature typical for this tumor is perineural invasion. Perineural invasion can be seen in most cases of adenoid cystic carcinoma and explains the difficulty in eradicating this tumor despite the extent of excision. Although a radical surgical excision is generally justified in the management of this lesion, there has been some recent support for a more conservative surgical approach with the addition of adjunctive radiation therapy. Because of the slow, relentless progress of this disease, long-term follow-up is mandatory in assessing the results of therapy.

Acinous Cell Carcinoma

One per cent of all salivary gland neoplasms, and 2.5 to 4 per cent of parotid gland tumors are acinous cell carcinomas. Ninety to 95 per cent of these tumors arise in the parotid gland; the remainder are found in the submandibular gland, with occurrence in the minor salivary glands being rare. This distribution is not surprising, since these tumors are composed of serous cells, which are found predominantly in the parotid gland. In children, this tumor ranks second in incidence behind mucoepidermoid carcinoma. Bilateral involvement occurs in 3 per cent of cases, and these tumors are more commonly seen in females.

Grossly, these lesions are well defined and well circumscribed. A fibrous capsule is often present. Two different types of cells are seen, those resembling serous acinar cells in the salivary gland and those with a clear cytoplasm. These lesions may take on a variety of configurations (cystic, papillary, vacuolated, or follicular). Batsakis and colleagues have attempted to classify high-grade tumors as those demonstrating a predominance of undifferentiated cells in a medullary pattern while describing a low-grade component with an acinar lobular pattern and a cystic or papillary growth. These tumors demonstrate a benign course in the early years, but as reported by Eneroth and Hamberger, long-term survival may approach 50 per cent when followed for 20 to 25 years. A superficial or total parotidectomy is generally sufficient for local control. The facial nerve is preserved unless directly involved.

Adenocarcinoma

The adenocarcinomas were originally grouped with the acinous cell carcinoma and adenoid cystic carcinoma, but their behavior and histologic appearance require a separate classification. A variety of subtypes are seen within the general classification of adenocarcinoma. The adenocarcinomas are most commonly seen in the minor salivary glands, followed by the parotid gland. As a group, adenocarcinomas arising within the salivary glands are highly aggressive with a predilection for local recurrence as well as for distant metastasis. The degree of glandular formation has been used as a histologic criterion for grading these tumors. The mucous types of adenocarcinoma may be confused with the mucoepidermoid tumors, necessitating special keratin staining. A subtype seen only in minor salivary glands, the polymorphous low-grade adenocarcinoma, has a more benign and protracted course. Management of these lesions is similar to other high-grade carcinomas of the salivary glands.

Carcinoma Ex-pleomorphic Adenoma (Ex-mixed Tumor)

Carcinoma ex-pleomorphic adenoma must be differentiated from the primary malignant mixed tumor. The primary malignant tumor involves both epithelial and mesenchymal elements of the mixed tumor, and a metastasis from this lesion also contains both elements. This is a very rare tumor. The more common tumor is one that arises from a pre-existing benign mixed tumor. In this instance, the malignant components of the primary tumor, as well as the metastases, are purely epithelial in origin. This tumor composes 2 to 5 per cent of salivary gland tumors. The typical history of these tumors is that of a slowly growing mass demonstrating a sudden increase in growth. The duration of onset of the tumor mass and the diagnosis of malignancy has been demonstrated to be 10 to 18 years. The risk of malignant transformation of a benign mixed tumor increases with the duration of the tumor. Bjorklund and Eneroth report a 1.6 per cent incidence of malignant transformation in tumors of less than 5 years' duration as compared with 9.4 per cent in tumors noted for greater than 15 years. Grossly the tumors are firm and may be nodular or cystic. Encapsulation is usually minimal. The diagnosis depends upon evidence of infiltration of a malignant neoplasm that is arising in a neoplasm having the characteristics of a mixed tumor. Sometimes a relatively undifferentiated epithelial carcinoma has ductal characteristics found within a mixed tumor. Occasionally, there is a chondroid focus from the mixed tumor component. The malignant portion of the tumor may appear as an adenocarcinoma, squamous cell carcinoma, undifferentiated carcinoma, or some other form of malignancy. The diagnosis may be confusing, since on one hand the benign mixed tumor may be virtually completely replaced by malignant disease, and on the other hand, a very small focus of malignant disease may be found within a benign mixed tumor. The single most helpful histologic findings is that of destructive, infiltrating growth. The one clinical feature that is most suggestive of malignancy is a rapid increase in growth of a tumor that has been slowly growing over a number of years. Although the incidence of this tumor is low, in the series of Eneroth and colleagues this lesion carried the poorest prognosis, with no long-term survivors. Local and distant metastases are common.

Aggressive therapy of combined surgery and post-operative radiation therapy is required for these lesions, and patients with known or suspected benign tumor should be encouraged to undergo surgery early on in their disease to avoid malignant degeneration at a later date.

Other Malignant Neoplasms

Primary squamous cell carcinoma of the salivary glands is rare, accounting for 0.3 to 1.5 per cent of salivary gland tumors. One must always consider a metastatic lesion to the parotid gland or an incorrectly diagnosed mucoepidermoid carcinoma. The possibility of this diagnosis is always more likely than that of a primary squamous cell carcinoma. The incidence is somewhat higher in the submandibular gland than in the parotid gland. The prognosis for squamous cell carcinoma within the parotid gland is poor, with a high incidence of both local and regional metastatic disease.

Undifferentiated carcinoma is also rare, and by definition is so poorly differentiated that it cannot be included in any of the preceding groups. This tumor is extremely aggressive, with marked local invasion and early distant metastases. It has been reported as arising in

benign lymphoepithelial lesions. Aggressive combined therapy with a consideration for chemotherapy must be applied to these highly malignant tumors.

Diagnostic Studies

A variety of imaging techniques have been devised to evaluate salivary gland configuration and function. Although imaging studies are not particularly helpful in solitary, mobile, superficial lesions, valuable information can be gained in evaluating the more extensive and complicated masses.

Masses contained within the deep lobe with parapharyngeal extension may be delineated accurately with the computed tomography (CT) scan. Although a sialogram may be combined with the scan, the 2-mm cuts that are now available create scans with sufficient information for an accurate diagnosis. The intravenous contrast enhancement allows differentiation between masses originating in the deep lobe of the parotid gland and those within the parapharyngeal space. The periparotid fat strip separating the deep lobe of the parotid gland from the parapharyngeal space is an important anatomic landmark and allows the differentiation of deep lobe tumors in the parapharyngeal space from tumors arising within parapharyngeal structures. The relationship of the tumor to the facial nerve may also be surmised from scanning information. Other tests have not been proved to be of real value when evaluating tumors of the salivary glands. Sialography has been used for many years to evaluate the configuration of the ductal system and to delineate the location of masses within the salivary glands as they relate to the ductal system. Refinement of this technique has been devised by including the sialogram with the CT scan as well as a digital subtraction study. With improved resolution by CT scanning, we expect that the application of sialography will be further diminished. Imaging techniques that provide information relating to the histopathologic diagnosis include nuclear scans and magnetic resonance imaging (MRI). Although nuclear scans provide information concerning salivary gland function, they have limited use in diagnosing neoplasms. Technetium pertechnetate scans have been useful in diagnosing Warthin's tumors and oncocytomas, since the oncocytes contained within both of these tumors have the ability to concentrate these substances at greater levels than does normal parotid gland tissue. Although the scan may yield useful information in this respect, it usually does not alter the course of management. MRI, or nuclear magnetic resonance (NMR), is in its early clinical stages, but it may complement CT scanning in characterizing salivary gland neoplasms. At the present stage of development, MRI shows greater contrast between tumor and surrounding tissue, but less tissue detail. The application of this technique to salivary gland neoplasms will, of course, depend upon progress in MRI technology. At the present time, CT scanning remains the single most useful technique for radiologic assessment of salivary gland neoplasms.

The application of the fine needle aspiration technique in salivary gland neoplasms has become increasingly popular in recent years. Although needle biopsy techniques have been discouraged in the past because of the potential for seeding, the thin needle (22-gauge) technique has proved to be very safe and also accurate when managed by an experienced cytopathologist. As the surgeon and the pathologic gain increasing experience, the diagnostic accuracy should continue to improve. For squamous cell carcinoma of the head and neck, the accuracy for fine needle aspiration is more than 90 per cent. In the area of salivary gland neoplasms, the diagnostic accuracy is somewhat less, being 60 to 80 per cent in reported

series. This is certainly understandable considering the great diversity of pathologic characteristics that one encounters in the salivary glands. As with all tests, the results of the aspiration biopsy must be used with caution, particularly if the result does not fit the clinical picture. Repeat aspiration or a direct surgical approach may be required in certain instances.

The CT scan and needle aspiration biopsy techniques have become the most useful and popular techniques for evaluating salivary gland neoplasms. The histologic information obtained from the biopsy and delineation of the lesion provided by the CT scan are sufficient for appropriate medical and surgical management.

Staging

The current staging system for salivary gland malignancies is described in the American Joint Committee on Cancer Manual for Staging Cancer, 1988 (Table 4). This system applies to malignancies of major salivary gland origin (parotid, submandibular, and sublingual glands) but not to those arising from the minor salivary glands. The T classification is based on size only in the T_1 to T_3 groups. T_4 is subdivided into T_{4a} and T_{4b}. T_{4a} tumors are those tumors greater than 6 cm without local extension, whereas T_{4b} tumors are all tumors, regardless of size, that demonstrate significant local extension. This is defined as evidence of tumor involvement of skin, soft tissue, bone, or lingual or facial nerves. When compared with previous staging systems, this classification gives more emphasis to local extension, particularly since all tumors with loss of nerve function, regardless of tumor size, are given the T_{4b} classification. The N classification is more simplified than the system used for metastatic epidermoid carcinoma in most head and neck regions. If nodes are present, the tumor is staged N_1 regardless of size, location, or number of nodes. The M classification denotes the presence of lack of distant metastases.

Factors Influencing Survival

We have compiled a list of factors that are considered important in viewing the aggressiveness of the disease and ultimately the survival of the patient (Table 5). Many of these factors are incorporated into the staging system, but will be discussed separately to demonstrate the contribution each factor has to the development of the staging system. If a staging system is accurate, the progression from stage 1 to stage 4 disease should correlate with diminishing survival.

Tumor Size

Spiro and colleagues matched tumor size with 5-year survival using a T system that classifies tumors in the following manner: tumors up to 3 cm, T_1; 3 to 6 cm, T_2; greater than 6 cm, T_3. The 5-year survival rates were 85 per cent for T_1, 67 per cent for T_2, and 14 per cent for T_3.

Table 4. Staging of Salivary Gland Malignancies

Primary Tumor (T)

T_x Minimum requirements to assess the primary tumor cannot be met.
T_0 No evidence of primary tumor.
T_{is} Carcinoma in situ.
T_1 Tumor 2 cm or less in greatest diameter without significant local extension.
T_2 Tumor greater than 2 cm but not more than 4 cm in greatest diameter without significant local extension.
T_3 Tumor greater than 4 cm but not more than 6 cm in greatest diameter without significant local extension.
T_{4a} Tumor greater than 6 cm in greatest diameter without significant local extension.
T_{4b} Any size tumor with significant local extension.

Significant local extension is defined as evidence of tumor involvement of skin, soft tissue, bone, lingual nerve, or facial nerve.

Nodal Involvement (N)

N_x Minimum requirements to assess the regional nodes cannot be met.
N_0 No evidence of regional lymph node involvement.
N_1 Evidence of regional lymph node involvement.

Distant Metastases (M)

M_x Minimum requirements to assess the presence of distant metastasis cannot be met.
M_0 No known metastasis.
M_1 Distant metastasis present.

Facial Nerve Paralysis

It has long been recognized that the presence of facial nerve paralysis associated with salivary neoplasms is a reliable indicator of malignancy. The incidence of facial nerve paralysis varies according to the histologic characteristics, with undifferentiated and squamous cell tumors having the highest incidence and acinous cell carcinoma having the lowest. Eneroth found no cases of facial nerve paralysis in a series of 1790 benign parotid tumors, but in 378 malignant parotid tumors, he found 46 cases of facial nerve paralysis (12 per cent). The mortality rate was 89 per cent at 5 years and 100 per cent at 10 years in the group with facial nerve paralysis, compared with a 33 per cent 5-year mortality rate in patients without paralysis. The average survival after the onset of paralysis was 2.7 years. In a follow-up multi-institutional study in 1977, Eneroth and colleagues reviewed 1029 cases of malignant parotid gland tumors and found facial nerve paralysis in 14 per cent, associated with a 5-year survival rate of 9 per cent. Conley and Hamaker report 10-year disease-free survival of 15 per cent in patients with facial paralysis secondary to parotid gland malignancy. However, not

patient with adenocarcinoma or squamous cell carcinoma and associated facial nerve paralysis survived 5 years. Katoh and co-workers correlated facial nerve involvement with other prognostic indicators. They found no significant relationship between paralysis and tumor size. A higher incidence of perineural invasion, lymph node metastases, and distant metastases was seen in patients with facial nerve paralysis. They reported a higher incidence of facial nerve involvement (35 per cent) as well as a higher 5-year survival rate (32.5 per cent) when compared with other series.

Table 5. Factors Influencing Survival

Histopathologic diagnosis.
Incidence of lymph node metastases.
Pain.
Facial nerve paralysis.
Skin involvement.
Stage.
Location.
Incidence of recurrence.
Distant metastases.
Radiotherapeutic sensitivity.
Chemotherapeutic sensitivity.

Skin, Soft Tissue, and Bone Involvement

When invasion of surrounding tissue is evident, prognosis is poor, particularly when coupled with an unfavorable histologic picture. If surgical resection is feasible, wide excision of affected structures, including bone and skin, is required for local control.

Lymph Node Metastases

Lymph node metastases are dependent both on the size and location of the salivary gland cancer, as well as on the histopathologic features of the lesion. Spiro and co-workers reported an incidence of lymph node metastases from lesions of the parotid gland of 1 per cent for T_1 lesions, 14 per cent for T_2 lesions, and 67 per cent for T_3 lesions. Similarly, Fu and associates reported figures of 13 per cent, 13 per cent, and 33 per cent, respectively. Pooled data from several series demonstrate that the highest incidence of lymph node metastases occurs in high-grade mucoepidermoid carcinoma, squamous cell carcinoma, adenocarcinoma, undifferentiated carcinoma, and carcinoma ex-mixed tumors (Table 6). The incidence of occult cervical nodes has been reported as 5 per cent for all parotid gland tumors except squamous cell carcinoma, in which the incidence is 40 per cent (Table 7). The submandibular gland has the highest incidence of lymph node metastases, followed by the parotid gland and minor salivary glands.

Table 6. Percentage of Lymph Node Metastases by Histologic Appearance

Type of Lesion	Metastases (%)
Mucoepidermoid carcinoma	44
Squamous cell carcinoma	36
Adenocarcinoma	26
Undifferentiated carcinoma	23
Carcinoma ex-mixed tumor	21
Acinous cell carcinoma	13
Adenoid cystic carcinoma	5.

Distant Metastases

Distant metastatic disease indicates a poor prognosis. The incidence of distant metastases in parotid gland cancer is 20 per cent overall (Table 8). The incidence is highest in adenoid cystic carcinoma and undifferentiated carcinoma. The most frequent sites are the lung, bone, and brain. Distant metastases often occur beyond 5 years, emphasizing once again the importance of long-term follow-up in salivary gland malignancies.

Table 7. Occult Lymph Node Metastases

Type of Lesion	Metastases (%)
Squamous cell carcinoma	40
Mucoepidermoid carcinoma (high grade)	15
Adenocarcinoma	8
Acinous cell carcinoma	6
Malignant mixed tumor	0
Adenoid cystic carcinoma	0.

Pain

The relationship of pain to survival is uncertain. Lambert reported a higher incidence of malignancy in patients with facial pain. However, Eneroth reported pain as an initial symptom in 34 of 665 patients with benign tumors (5.1 per cent) and 9 of 137 patients with malignant tumors (6.5 per cent). When reviewing the significance of pain as a prognostic factor in malignant disease, Mustard and Anderson as well as Spiro and co-workers found that the 5-year survival rate dropped from approximately 66 per cent to 33 per cent when pain is present. Therefore, it appears that pain is not a reliable indicator for malignancy. However, patients with painful malignant tumors carry a worse prognosis than those who are asymptomatic.

Histopathologic Features

Histopathologic diagnosis is an important prognostic factor, since biologic aggressiveness and histologic characteristics are closely related. In 1953, Foote and Frazell developed a classification in which the histologic appearance was correlated with the biologic

behavior of the neoplasms. This classification, with some modifications, allows these tumors to be divided into high-grade and low-grade malignancies.

Table 8. Distant metastasis

Type of Lesion	Metastases (%)
Adenoid cystic carcinoma	42
Undifferentiated carcinoma	36
Adenocarcinoma	27
Carcinoma ex-mixed tumor	21
Squamous cell carcinoma	15
Acinous cell carcinoma	14
Mucoepidermoid carcinoma	9.

The low-grade cancers include acinous cell carcinoma and low-grade mucoepidermoid carcinoma. The high-carcinomas include adenoid cystic carcinoma, high-grade mucoepidermoid carcinoma, carcinoma ex-mixed tumor, squamous cell carcinoma, adenocarcinoma, and undifferentiated carcinoma (Table 9).

Table 9. Local Recurrence by Histologic Appearance

Type of Lesion	Metastases (%)
Squamous cell carcinoma	64
Undifferentiated carcinoma	64
Adenoid cystic carcinoma	61
Carcinoma ex-mixed tumor	60
Adenocarcinoma	48
Acinous cell carcinoma	15
Mucoepidermoid carcinoma	5.

Low-grade malignancies have 5-year survival rates greater than 90 per cent. Conversely, for undifferentiated and high-grade mucoepidermoid malignancies, this figure may decrease to less than 20 per cent. As several series have demonstrated, survival is decreased at 10 years for many malignant tumors, with only the mucoepidermoid and acinous cell carcinomas having 10-year survival rates, comparable to the 5-year survival rates. As survival statistics are carried further, adenoid cystic carcinomas continue to fall, with long-term (greater than 15 years) survival less than 25 per cent.

Within each histopathologic subgroup, attempts have been made to further subdivide these tumors based on particular histologic features. Much attention has been given to the adenoid cystic carcinoma, which can be described as either cribriform or solid. Szanto and colleagues report 15-year survival rates for predominantly cribriform tumors of 39 per cent compared with 5 per cent survival rates in predominantly solid tumors. The difference in survival was even more pronounced in the series of Eneroth and co-workers, in which there was 100 per cent survival of patients with cribriform-pattern adenoid cystic carcinoma with follow-up of 5 to 20 years, compared with a 0 per cent survival of patients with the solid-type

lesions. Other series have reported no correlation between histologic grading and survival. Batsakis and Regezi emphasize that the histologic grading, perineural invasion, margins at time of resection, and the presence of distant metastases are inseparable factors that determine prognosis.

Similar attempts have been made to subclassify other salivary gland malignancies. Batsakis and colleagues divided the acinous cell carcinoma in 35 patients into high-grade and low-grade patterns and reported a strong correlation between these patterns and survival. Fifty-eight per cent of patients with high-grade tumors died of their neoplasm, whereas only 5 per cent of patients with low-grade tumors died of the disease. These findings are supported by Spiro and colleagues, who associated capsular invasion and a papillary-cystic histologic pattern with a poor prognosis.

There is also a high correlation between the differentiation of mucoepidermoid carcinoma and prognosis. At one time, low-grade mucoepidermoid carcinoma was considered by some to be a benign lesion, but a malignant clinical course was demonstrated even in the most well-differentiated of these lesions. In their series of mucoepidermoid carcinomas, Spiro and colleagues reported 5-, 10-, and 15-year survival rates for low-grade lesions to be 92 per cent, 90 per cent, and 82 per cent, respectively, whereas for high-grade malignancies the respective figures were 49 per cent, 42 per cent, and 33 per cent. Histologic grade and clinical stage were the two most important determinants of survival. These findings are supported by other investigators. Low-grade and high-grade varieties of other malignant neoplasms, including malignant mixed tumors and adenocarcinomas, have also been described. Increased local recurrence rates in benign mixed tumors have been correlated with epithelial hypercellularity, increased mitosis, and lack of capsular formation, although inadequate surgery and tumor spillage are well recognized as the predominant factors.

The importance of tumor differentiation relates primarily to postoperative decisions, notably the advisability of adjunctive therapy. Errors inherent in frozen section analysis of salivary gland neoplasms usually preclude its use in intraoperative decision-making.

Location

The location of a salivary gland malignancy can be correlated with survival. Parotid gland malignancies carry a better prognosis than do those arising in other sites. The location of the tumor within the parotid gland, whether in the superficial portion, tail, or deep lobe, does not affect prognosis. Johnson and Spiro found a 69 per cent survival rate for deep lobe lesions. Submandibular gland neoplasms are more aggressive when compared with those in the parotid gland, with a much higher mortality rate seen with mucoepidermoid carcinoma in particular.

Spiro and co-workers determined that the prognosis of adenoid cystic carcinoma was most closely related to the location, with involvement of the maxillary sinus and submandibular gland yielding the worst prognosis. Overall, long-term survival appears to be better in the major salivary glands than in the minor salivary glands, in large part because of the more favorable outcome for parotid gland lesions. Among the minor salivary gland sites, the palate, lip, and cheek have a more favorable prognosis than do the nose and paranasal sinuses.

Recurrence

Recurrent salivary gland malignancy carries a poor prognosis. If a parotid carcinoma recurs, survival varies from 17 to 49 per cent, compared with 67 per cent for nonrecurring cancers. The incidence of recurrence in parotid gland malignancy varies from 27 to 38 per cent. In the series of Hodgkinson and Woods, a 38 per cent recurrence rate was noted, despite the sacrifice of the facial nerve in 64 per cent of patients. These indicate that recurrences are frequent for parotid gland cancer despite aggressive surgery. These figures suggest that less frequent sacrifice of the facial nerve but more aggressive adjunctive therapy may preserve function and improve local control.

Miscellaneous Factors

Sex and race have been correlated with survival in salivary gland malignancies. Spitz and Batsakis found survival was higher for white female patients than for white male patients. Black female patients likewise had a higher survival than did black male patients. Finally, survival rates were higher for black patients than for white patients.

Treatment for Tumors of the Parotid Gland

Surgery

Surgical procedures for the parotid gland have developed over many years. The concept of "shelling out" parotid gland tumors, particularly benign mixed tumors, was practiced prior to 1950. Recurrence rate of 35 to 50 per cent demonstrated the inadequacy of that approach. Most tumors of the parotid gland arise in either the superficial lobe or the tail of the gland. The designation of superficial versus deep lobe is strictly surgical and is not based on developmental growth. The facial nerve defines the two lobes, with the parotid tissue lateral to the nerve described as the superficial lobe and the portion medial to the facial nerve designated as the deep lobe. With the early experience of recurrence following limited and inadequate surgery for benign mixed tumor, the concept of superficial parotidectomy (or total parotidectomy for deep lobe tumors) arose as the procedure of choice, both for biopsy and treatment. Identification of the main trunk of the facial nerve and dissection of the individual branches allows removal of the tumor with a surrounding cuff of normal tissue, with protection of the individual nerve branches. The technique of nerve identification, allowing more accurate and complete tumor excision, has resulted in a decrease in the local recurrence rate and improved survival. In most parotid gland tumors, the entire branching system is dissected. However, in selected cases of small tumors, the entire superficial lobe may not need to be resected. Nevertheless, the branches of the facial nerve must be identified in all cases to allow adequate excision and avoid inadvertent facial nerve injury.

The treatment of the facial nerve in parotid gland malignancies has been controversial. Hodgkinson and Woods reviewed 224 parotid gland malignancies, of which 65 required facial nerve sacrifice. The indications for nerve sacrifice included the presence of high-grade malignancy, preoperative facial nerve paralysis, pain, and rapid growth of tumor. The nerve was sacrificed in 80 per cent of malignant mixed tumors, in 71 per cent of high-grade adenocarcinomas, in 53 per cent of high-grade squamous cell carcinomas, and in 41 per cent of adenoid cystic carcinomas. They concluded that with the histologic features discussed

previously, facial nerve sacrifice should be strongly considered. Eneroth and Hamberger limited facial nerve sacrifice to tumors with clinical involvement of the nerve, as well as to undifferentiated carcinomas and sarcomas. Others feel that the nerve should be sacrificed only when there is gross involvement of the nerve with tumor. Finally, the dismal prognosis associated with clinical facial nerve involvement has led some to suggest that the nerve should never be sacrificed and that those lesions necessitating extirpation of the nerve would then be classified as inoperable.

Our approach to the facial nerve as well as to other issues, such as neck dissection, recurrent tumors, and adjunctive therapy, will be discussed later in this chapter.

Planning the Surgical Procedures

Planning an appropriate surgical procedure upon the parotid gland, as with all operations, begins with a careful history and physical examination. Most parotid gland tumors, whether benign or malignant, are asymptomatic. As we have shown, pain is not an accurate indication of malignancy. Rapid growth may suggest a malignant lesion, particularly in a previously noted, slowly growing mass. However, patients may not always accurately document their tumor growth characteristics. Of much greater importance is a careful head and neck examination. The location, size, mobility, and configuration are assessed. Any alteration in facial nerve function is noted and recorded, since this finding almost always signifies malignancy in a patient without prior surgical intervention. Facial nerve involvement invariably indicates the need for total or partial facial nerve sacrifice. Fixation of the mass to underlying bone or muscle also represents malignancy, as does skin fixation or erosion. If such a situation exists, sacrifice of adjacent structures will be required.

The oral examination is extremely important in all parotid gland tumors to search for deep lobe and parapharyngeal extension. A lateral bulge and medial displacement of the tonsil suggest a large parapharyngeal component. Palpation will allow delineation of the visualized abnormality and will also allow detection of masses that are not of sufficient size to cause visible deformity of pharyngeal contour. The presence of cervical adenopathy suggests metastatic spread from a parotid gland primary tumor or may indicate that the disease process is not of parotid gland origin, such as lymphoma, melanoma, or metastatic carcinoma from another site.

The aspiration needle biopsy technique, as described previously, is a useful tool in experienced hands. Although the histologic diagnosis will not change therapy in most cases, it may significantly alter the approach in certain instances. A diagnosis of lymphoma, melanoma, oat cell carcinoma, or squamous cell carcinoma may change the surgical procedure and direct the diagnostic evaluation and treatment to the appropriate area.

A number of radiologic tests have been devised to evaluate salivary gland function and configuration and have been presented elsewhere in this chapter. For most parotid gland tumors, the information obtained from these tests is superfluous. The CT scan, with the 2-mm cuts now available, is useful to delineate deep lobe and parapharyngeal tumors and those tumors demonstrating aggressive local behavior. However, if a parotid gland mass is mobile, well circumscribed, and contained within the lateral portion or the tail of the gland, imaging techniques are not necessary. The sialogram in particular must be used with caution because

of the risk of overinjecting the ductal system. Extravasation of dye may cause a severe inflammatory reaction, preventing a clear demarcation of tumor margins, and may also delay the planned surgical procedure.

With the evaluation completed, the appropriate surgical procedure will usually be apparent. Most parotid gland tumors are managed with a lateral or superficial parotidectomy, allowing removal of the tumor with a margin of normal parotid tissue with dissection and preservation of the facial nerve. If the tumor presents in the deep lobe with limited medial extension, the superficial lobe is removed, the mass is mobilized and the tumor is removed from beneath the nerve. If the mass demonstrates significant medial extension, additional maneuvers may be required. Often, access is improved by removal of the contents of the submandibular triangle. This allows access to the stylomandibular ligament, which is transected, allowing entry into the parapharyngeal space. Most deep lobe tumors may be dissected from the surrounding muscular, neural, and vascular structures using the fingers, with good success. This pertains to benign mixed tumors in particular. If a needle aspiration has confirmed the diagnosis prior to the procedure, the surgeon may approach the tumor in this manner with a reasonable degree of confidence. However, in certain instances, the mandible must be displaced in some fashion for adequate exposure to ensure successful tumor removal. The mandible may be dislocated anteriorly, or a mandibulotomy may be performed at the angle to allow medial access. For massive parapharyngeal tumors, particularly those with skull base extension, a lip-splitting incision and median mandibulotomy may be required. The incision is carried along the floor of the mouth posteriorly to the pharyngeal wall. Complete and direct exposure to the entire parapharyngeal space from the skull base to the lower neck is accomplished.

Facial nerve paralysis indicates the need for nerve sacrifice in virtually all cases, unless the tumor is judged inoperable and only a biopsy is performed. Only branches of the nerve directly involved with the tumor should be sacrificed. If sufficient distal remnants remain, grafting using microscopic anastomotic technique is accomplished. Temporal bone exploration and facial nerve dissection may be required with excision of the main branch of the facial nerve. Again, immediate grafting is performed when possible after frozen section confirmation of a tumor-free margin. Tumors demonstrating local invasive properties require extensive dissection and excision of surrounding structures, with attendant reconstructive procedures.

Specific Surgical Procedures

Superficial Parotidectomy

In superficial parotidectomy, the patient receives an antiseptic soap facial scrub and a shampoo the night before surgery. Induction of a general anesthetic using a short-acting muscle relaxant is acceptable, but the anesthesiologist is instructed to avoid the use of long-acting muscle relaxants. The face and neck are exposed and may be covered with a transparent adhesive drape for complete visualization of the face during the procedure. The preferred incision begins in the preauricular area and extends to the attachment of the lobule. The incision is placed in a preauricular crease or may be placed behind the tragus. The incision is carried posteriorly in the neck, preferably in a skin crease. A vasoconstrictive agent may be injected for hemostasis. If an anesthetic agent is included in the solution, care must

be taken to avoid deep injection and risk of facial nerve paralysis during the procedure.

The skin flap is sharply dissected from the underlying parotid gland fascia or tumor. As the flap is dissected anteriorly, care must be taken to avoid peripheral branches of the nerve as they emerge from the gland. With the flap elevated, a search for the facial nerve is undertaken. Successful and rapid identification of the main trunk depends upon familiarity with important landmarks and wide exposure. The tail of the parotid gland is dissected free from the sternocleidomastoid muscle, mastoid tip, and auricular cartilage. As the cartilage is followed medially, it usually terminates in a point and is therefore termed the *pointer cartilage.* The main trunk of the facial nerve is approximately 1 cm deep to this cartilage, lying slightly anterior and inferior. The tympanomastoid suture line is a groove easily palpated with the index finger and separates the mastoid tip from the tympanic portion of the temporal bone. The main trunk of the facial nerve exits approximately 6 to 8 mm medial to this suture line. The posterior belly of the digastric muscle may be exposed as it sits medial to the parotid gland; elevating the gland off of the muscle allows better access to the stylomastoid foramen. The trunk may be palpated as the examining finger is passed posterosuperiorly along the digastric muscle toward the stylomastoid foramen. The importance of adequate exposure, especially elevation of the tail from the underlying musculature, cannot be overemphasized. Wide exposure will prevent "working in a hole" and will allow good visualization of all pertinent landmarks required for rapid identification of the main nerve trunk. A nerve stimulator may be used for confirmation of the nerve but should be used sparingly to avoid fatigue. Once the nerve trunk is identified, the individual branches are followed peripherally, and the tumor with parotid gland tissue is removed from the nerve. If the main trunk cannot be located, one of the peripheral branches must be found and followed retrograde to the main trunk. The marginal mandibular branch may be found by locating the posterior facial vein and dissecting superiorly. The marginal mandibular branch passes over the vein in close proximity. The buccal branch is usually within millimeters of Stensen's duct. The duct may be found as it passes over the masseter on the line between the upper lip and the lobule of the ear. The nerve stimulator may be useful in confirming these peripheral branches. When the dissection has been completed, the nerve trunk should be stimulated to be certain that all branches are functioning normally. If any portion of the nerve is not functioning upon stimulation, careful inspection of the branch, using the microscope if necessary, is imperative. A suture may be seen to be encompassing the nerve, or an actual separation of the nerve may be found and will require microsurgical repair. After bleeding has been completely controlled, a drain is inserted. We recommend either a flat silicone drain under gentle suction or a flat rubber drain with a compression dressing.

If a malignant tumor is invading a peripheral branch, that portion of the nerve should be resected and grafted. We currently advise a microscopic epineural suture technique using 7-0 monofilament nylon. The nerve graft may be harvested from the neck using the great auricular nerve or other branches of the cutaneous system in either side of the neck. Important factors for success include a close match of nerve and graft diameter, sharp nerve transection, and a tension-free anastomosis. Surrounding the nerve with a protective sleeve of vein, gel film, or other material may also be beneficial in protecting the graft and discouraging neuroma formation. If the tumor involves the main trunk, the nerve must be followed proximally until frozen section analysis of a tumor-free margin is confirmed. The mastoid tip may be removed with an osteotome, rongeur, or drill to allow a more complete exploration of the foramen. Temporal bone exploration may be required, and both the patient and the

surgeon should be prepared for this eventuality. If the nerve is transected in the temporal bone and all branches are transected, a cable graft should be developed so that the branches to the eye and the mouth are reinnervated. This can be accomplished by locating a branching nerve system in the neck and finding portions of these nerves that are appropriate for grafting. Again, the principles of microscopic nerve grafting are used as described previously. Sutures are not necessarily required in the temporal portion as long as tension is avoided.

Total Parotidectomy

A total parotidectomy, strictly speaking, is a misnomer. Removal of all parotid gland tissue is nearly impossible and is usually not necessary in the majority of parotid gland surgical procedures. The concept of a total parotidectomy is that of removal of parotid gland tissue, both medial and lateral to the facial nerve, with the accompanying tumor. The particular technique employed may differ depending upon the location of the tumor. If the tumor is confined to the deep lobe, the superficial lobe does not, by definition, need to be removed. However, in most cases, identification of the nerve is accomplished most easily by a superficial parotidectomy. After the nerve is satisfactorily exposed, it is freed over the tumor, and the mass is removed from beneath the nerve. This maneuver may result is some postoperative weakness, but if the surgeon avoids undue tension and stretching of the nerve, function will return. Some deep lobe tumors are "dumbbell" in configuration, with the isthmus or waist being found at the stylomandibular ligament. When this situation occurs, further exposure to the portion of the gland medial to the facial nerve is required. The first approach should be through the submandibular triangle with removal of the submandibular gland. This maneuver allows access to the anterior compartment of the parapharyngeal space. If additional exposure is required, anterior mandibular dislocation or a mandibulotomy can be performed at the angle of the mandible, and the space medial to the mandible can then be more completely exposed. Almost all parapharyngeal space tumors can be removed by this technique.

If the tumor is massive within the parapharyngeal space, a lip-splitting incision with median mandibulotomy might be considered. If after attempting exposure through the neck, the surgeon feels that a lateral mandibulotomy will not allow sufficient additional access, the neck incision is carried through the lip in the anterior midline, and the mandible is transected in a stepwise fashion. The incision is carried along the lateral floor of the mouth, avoiding injury to the lingual and hypoglossal nerves and submandibular gland contents. As the tongue is pulled medially and the mandible is pulled laterally, the incision is carried to the tonsil and pharyngeal regions. With this direct approach to the parapharyngeal space, any mass from the skull base to the lower neck can be removed under direct vision. Although additional cosmetic deformity is encountered because of the lip incision, this approach provides direct access to parapharyngeal space tumors.

It is apparent that for difficult parotid gland tumors, the surgeon and patient must be prepared for a variety of approaches to ensure complete removal.

Complications of Parotid Gland Surgery

Complications of parotid gland surgery may be divided into those that occur early and those that are delayed. Common immediate or early complications are partial or complete paralysis of all or some of the branches of the facial nerve. If extensive dissection was performed around particular branches, some loss of function is not unusual. However, complete loss of function of all branches is a potentially serious complication. For this reason, stimulation of the nerve at the termination of the procedure confirms function and nerve integrity, or if some branches are not functional, a careful inspection will confirm anatomic integrity. The surgeon must be confident at the termination of the procedure that he or she has a clear understanding of the status of the dissected nerve. If a suction drain is being used and immediate loss of function is noted, the drain should be converted to gravity drainage and a compression dressing should be applied. If marked loss of function is noted in the immediate postoperative period, the operating surgeon may wish to consider steroid therapy. The use of steroids in facial paralysis remains controversial; however, it is generally agreed that if steroids are used, they should be given immediately. The initial dose is in the range of 60 to 80 mg of prednisone or an equivalent dosage of a comparable steroid preparation. This is maintained for 5 to 7 days and is then tapered over a total course of 10 days. The intent is to reduce nerve edema in both the extra- and infratemporal portions of the nerve. If paralysis continues without improvement, electromyography should be performed to search for evidence of denervation. If the nerve is denervated, presumably from an undetected injury, a variety of possible reanimation procedures may be considered at a later date. The subject of facial reanimation is beyond the scope of this chapter.

A relatively common complication is postoperative salivary fistula or sialocele formation. Since some parotid gland tissue inevitably persists following parotid gland surgery, the potential for a salivary gland fistula is always present. A fistula or sialocele occurs when the flap fails to seal over the remaining parotid gland tissue, and saliva gathers underneath the flap or drains into the neck. Elimination of the fistula requires complete evacuation of salivary contents from beneath the flap and application of continual extrinsic pressure to overcome the secretory pressure of the remaining tissue. This may require repeated aspirations and application of a compression dressing on a daily basis until the complication has cleared. Atropine-like drugs may be of some benefit to counteract salivary stimulation. If compressive dressings are used, one must take care to protect the ear to avoid necrosis of the soft tissue surrounding the ear. Hematoma formation is also a potential complication. If a hematoma does occur, it will require exploration of the wound. Of course, with the facial nerve being exposed, extreme care must be used to avoid injury to the nerve.

The most common long-term complication is that of gustatory sweating or Frey's syndrome, which occurs when inappropriate autonomic reinnervation of the skin develops from the innervation to the remaining transected gland. The postganglionic secretory sympathetic motor parasympathetics of the parotid gland reinnervate the postganglionic fibers in the skin. With Frey's syndrome, the patient has sweating or flushing, or both, of the skin overlying the remaining parotid gland prior to during meals. The incidence of this syndrome is quite high, estimated to be 35 to 60 per cent of postparotidectomy patients. A surgeon must make the patient aware of this potential complication so that if it occurs he or she is not alarmed. Medical therapy has included topical scopolamine and glycopyrrolate. Surgical intervention includes placement of a dermal graft or muscle between the remaining parotid

gland and the skin to prevent reinnervation. Tympanic neurectomy has also been used to interrupt parasympathetic supply to the remaining gland.

Radiation Therapy

In the past 3 decades, there has been an evolution in the role of radiotherapy in managing salivary gland neoplasms. It was appreciated early that radiation therapy did not replace the need for adequate surgical treatment of these cancers. Indeed, these tumors have been reported to be radiation-resistant. It is now apparent that combined surgery and radiation therapy may be the optimal treatment in certain salivary neoplasms.

The use of radical radiation therapy alone has been reported in several series. Elkon and co-workers reported 19 patients with advanced parotid gland disease (base of skull or cervical node involvement). Control was achieved in only two of these patients, one with an adenoid cystic carcinoma and the other with squamous cell carcinoma. King and Fletcher reported local control of 81 per cent in patients with inoperable or recurrence parotid gland cancers, although the follow-up time varied from 2 to 20 years. Recent work with neutron beam therapy shows similar results in patients treated solely by this method compared with those receiving postoperative electron or photon therapy following radical resection.

Most reports demonstrate the advantage of combination surgery and postoperative irradiation for advanced disease. In a retrospective study, Rossman reported a 17 per cent recurrence rate in patients with parotid gland malignancies treated with combined therapy, compared with a 65 per cent recurrence rate in patients treated with surgery alone. Similarly, Elkon and associates report local control in 14 of 17 patients irradiated for microscopic residual disease. Tapley, reviewing the experience at the MD Anderson Hospital, reported a 30 per cent local failure rate in 54 patients treated with surgery alone and a 9 per cent incidence in patients treated with combined therapy. He discusses the need to increase the ports to include the base of the skull in patients demonstrating perineural invasion. Fu and co-workers treated 35 patients with microscopic tumor at or close to the surgical margin with postoperative radiation therapy. They achieved local control in 86 per cent of these cases, compared with 46 per cent in a similar group of patients receiving surgery alone. Treatment failures decreased from 50 to 30 per cent when combination therapy was employed (compared with surgery alone) in the series of Shidnia and co-workers. In one of the few reports offering 10-year follow-up figures, Tu and co-workers report an increase in 10-year survival to 71 per cent in patients treated with surgery and postoperative radiation therapy, compared with 53 per cent in patients treated with surgery alone. Combined therapy was most useful for high-grade malignancies, recurrent tumors, locally advanced disease, and tumor involvement of the facial nerve.

Radiation sensitivity has also been discussed with regard to specific salivary gland histopathologic conditions. Alaniz and Fletcher found similar control rates for various parotid gland malignancies, regardless of the histologic picture, as for squamous cell cancer of the neck. Because of the propensity for perineural invasion and associated tumor-containing surgical margins, radiation therapy for adenoid cystic carcinoma has received much attention. Eby and colleagues noted that radiation therapy was "uniformly useful in promoting tumor regression and pain relief in locally advanced and metastatic tumors". Cowie and Pointon reviewed 82 patients with adenoid cystic carcinoma treated by a radical course of radiation

therapy. Forty-four of these were major salivary gland tumors, whereas the remainder were of minor salivary gland origin. The surgical treatment in both groups had been either excisional biopsy or incomplete surgical excision. Local tumor control overall was achieved in 67 per cent of patients. This number increased to 86 per cent if those patients who had biopsy only were excluded. They concluded that combined therapy was the treatment of choice in adenoid cystic carcinoma. Similar conclusions were reached by Simpson and associates after reviewing 71 cases of adenoid cystic carcinoma in patients treated at Washington University. In a comparison of radical surgical therapy alone versus nonradical surgery plus radiation therapy, Dal Maso and Lippi reported similar survival rates in a group of 37 patients.

Rafla found that adenocarcinoma of the parotid gland had a better radiation response than did salivary gland tumors with other histopathologic features. High-grade mucoepidermoid carcinomas and undifferentiated carcinomas have also been found to be radiation-responsive. Low-grade mucoepidermoid carcinoma and acinic cell carcinoma may not benefit from combined therapy.

It is apparent that the long-held theories that salivary gland cancer is radiation-resistant are incorrect. Indeed, the use of radiation therapy in combination with surgery has improved the local and regional control in aggressive lesions. The current indications for the use of postoperative radiation are derived from Guillamondegui and co-workers as modified by Johns:

1. High-grade cancers.

2. Recurrent cancers.

3. Deep lobe cancers.

4. Gross or microscopic residual disease.

5. Tumor adjacent node metastases.

6. Regional lymph node metastases.

7. Invasion of muscle, bone, skin, nerves, or any extraparotid gland extension.

8. Any T_3 or T_4 parotid gland cancer.

These indicators all signify tumors with a poor prognosis and a high incidence of local and regional recurrence.

Chemotherapy

There have been few clinical trials of chemotherapy for salivary gland malignancies. Suen and Johns performed a questionnaire study designed to collate the experience of many oncologists with these neoplasms. A total of 85 cases were able to be evaluated - 39 from the literature and 46 from their survey. Fifty-three of these cases were adenoid cystic carcinoma.

Four patients achieved complete response. Significant pain relief is achieved in patients with adenoid cystic carcinoma who respond to chemotherapy. Cis-platinum, doxorubicin, and 5-fluorouracil were the most effective agents. Definite regression of disease was seen in some patients. However, the long clinical course of this disease precluded any conclusions regarding influence upon survival. Adenocarcinoma, acinous cell carcinoma, and carcinoma ex-mixed tumor also responded to this combination. Squamous cell carcinoma and mucoepidermoid carcinoma appeared to be more responsive to methotrexate and cis-platinum. They suggest that these two groups may reflect the histogenesis of these tumors with respect to the bicellular theory. Tannock and Sutherland reported 17 patients with adenoid cystic carcinoma who received 34 trials of chemotherapy. Five objective responses were noted. Most responses were 5-fluorouracil. They recommend this agent in patients with symptomatic or life-threatening adenoid cystic carcinomas that do not respond to local treatment.

Treatment for Tumors of the Submandibular Gland

Tumors involving the submandibular gland are usually contained within the gland, and the resection is confined to the gland and surrounding fat or lymph nodes. If a malignant tumor is invading tissue, the procedure is expanded to include involved structures with an appropriate tumor-free margin. Structures excised often include the marginal mandibular branch of the facial nerve and the hypoglossal and lingual nerves, as well as the mandible, tongue, floor of the mouth, and skin.

Preoperative evaluation of a submandibular gland tumor, as in tumor of the parotid gland, begins wit a careful history and examination. As with the parotid gland, most neoplasms arising within the submandibular gland are asymptomatic. However, if the patient has evidence of neural involvement with loss of marginal mandibular nerve or hypoglossal function or loss of sensation and taste, or both, aggressive malignant disease is probable. Palpation of the mass, both externally and bimanually, aids in localization of the mass. At times, however, one has difficulty differentiating the gland from one or several enlarged lymph nodes overlying the gland. It may also be difficult to differentiate tumors from inflammatory disease, especially if the patient has not had symptoms suggestive of recurrent sialadenitis. Evaluation for reduced salivary flow through the orifice of Wharton's duct and palpation for ductal stones may support inflammatory gland disease. Discovery of additional adenopathy may indicate nodal spread from a primary gland tumor or may represent nodal spread from a more distal site or lymphoma. Once again, in cases in which confusion exists, application of the needle aspiration technique may help solve a dilemma. The gland is quite accessible and easily aspirated. If necessary, the gland may be presented into the neck by placing the finger intraorally and pushing the gland to a more specific location. Aspiration may help determine whether the mass is within the gland or represents a lymph node and is also useful in differentiating inflammatory from neoplastic disease.

In selected cases, imaging techniques may be helpful, particularly to assess spread beyond the gland. Views of the mandible, including occlusal views, may be obtained when searching for bone erosion. CT scans usually do not yield additional information, since all surrounding soft tissue spaces can be palpated or visualized without difficulty. Submandibular sialography is somewhat difficult to perform because of the small ductal orifice. The risk of overinjection and attendant patient discomfort does not justify the routine application of this procedure. For suspected tumors, delineation of the ductal system does not aid in surgical

decision-making.

Submandibular Gland Excision

The technique of submandibular gland excision should be performed under a general anesthetic unless the patient's medical status requires local anesthesia. The incision is routinely placed 2 to 3 cm below the inferior border of the mandible and should be hidden in a skin crease if possible. The skin incision may be injected for hemostasis with caution to avoid superior infiltration if an anesthetic is used with the vasoconstricting agent. The anesthesiologist should avoid using paralyzing agents if at all possible. The incision usually measures approximately 5 cm in length and is carried down through the platysma. The capsule of the gland and surrounding soft tissue should be left intact over the gland when excision is being carried out for suspected neoplasm. Since this technique puts the marginal mandibular nerve at greater risk, the facial vein and artery should be located as close to the gland as possible immediately and after transection should be elevated superiorly to reflect the marginal mandibular nerve from the field. If adenopathy is present over the gland, the marginal mandibular nerve often passes directly over or around these facial nodes, and the surgeon must carefully dissect the nerve from the nodes. The gland and surrounding soft tissue may then be safely dissected from the undersurface of the mandible. The inferior border of the gland is then elevated from the digastric muscle. The facial artery, if transected superiorly, will again be transected posterolaterally as one nears its origin from the external carotid artery. The gland is then reflected laterally to expose the mylohyoid muscle. as the superficial portion of the gland is dissected from this muscle, the posterolateral border is encountered. A retractor is inserted, and the free edge of the mylohyoid is retracted medially. This maneuver allows exposure of three important structures in the floor of the submandibular triangle - the lingual and hypoglossal nerves and Wharton's duct. With gentle downward traction on the gland, the lingual nerve is usually noted as a downward curving band with the apex at the midpoint of the gland. This attachment of the lingual nerve to the gland represents the parasympathetic supply to the gland. The duct lies inferior to the lingual nerve and is often surrounded by sublingual glands and may not be seen well initially. The hypoglossal nerve is more inferior yet and is always accompanied by at least one large vein, the ranine vein. The presence of this vein may aid in the identification of the nerve, which often is immediately adjacent to or beneath this vessel. Both the nerve and the accompanying vein emerge from beneath the digastric muscle and pass anterosuperiorly into the tongue. When all structures are identified, the duct and branch of the lingual nerve to the gland are ligated and transected. The gland and contiguous soft tissue may then be dissected free and removed. A rubber ribbon drain is inserted deep to the platysma, and the wound is closed in layers.

If a neck dissection is indicated, this procedure is performed in continuity with the gland excision. Tumors may exhibit local invasive behavior as evidenced by alteration of nerve function, fixation to deep structures, or skin involvement. In these cases, the margin of resection may include the lingual, hypoglossal, or marginal mandibular nerves, the floor of the mouth, tongue, mandible, or skin. A careful preoperative evaluation will alert the surgeon to the necessity of extensive surgical procedures in this area and he or she will therefore be prepared for adequate reconstruction.

Complications of submandibular gland excision are few. The most common postoperative finding is marginal mandibular weakness. This paresis often occurs when the nerve is dissected from an underlying adenopathy. Weakness also may occur from persistent traction on the upper flap. Complete return of function is the rule but may require several months. Loss of lingual and hypoglossal nerve function is rare unless these nerves are included in the resection.

Principles of Management of Malignant Salivary Gland Neoplasms

Histologic grade and clinical staging are the two most important determinants of survival. By combining the T classification and the histopathologic diagnosis we have developed a schema for management of malignant salivary gland neoplasms. Four groups are identified for each location. As we pass from group 1 to group 4, increasing severity of disease is matched with progressively more aggressive therapy (Table 10).

Table 10. Principles of Management of Salivary Gland Tumors

	Tumor type Parotid gland Submandibular gland
Group 1	T_1 and T_2 low-grade; mucoepidermoid low-grade; acinic cell Superficial or total parotidectomy; preservation of seventh cranial nerve (CN VII) Submandibular triangle resection
Group 2	T_1 and T_2 high-grade adenocarcinoma; malignant mixed; undifferentiated squamous cell Total parotidectomy with resection of neck dissection for N^+ neck only; postoperative radiation Wide excision of submandibular triangle; preserve nerves unless involved; postoperative irradiation.
Group 3	T_3N_0, N^+, and any recurrent tumors not in group 4 Radical parotidectomy; sacrifice of CN VII with immediate reconstruction; neck dissection for N^+ neck only; postoperative irradiation Radical neck dissection to include CN XII and lingual nerve
Group 4	T_4 Radical parotidectomy with resection of skin, mandible, muscles, and mastoid tip, as indicated; sacrifice of CN VII with immediate reconstruction; neck dissection for N^+ neck only; postoperative irradiation Surgery to fit disease extent.

For parotid gland malignancies, group 1 includes smaller tumors in the T_1 and T_2 classifications (less than 4 cm in diameter) with histologic cell types that are associated with slow growth, that is, low-grade muco-epidermoid and acinic cell carcinoma. A parotidectomy (superficial or total) with an adequate margin of normal tissue is sufficient therapy. The seventh cranial nerve is preserved in all cases. At the time of the parotidectomy, nodes adjacent to the parotid gland are inspected and referred for pathologic consultation if metastatic involvement is suspected. If the final pathologic diagnosis demonstrates clear margins without metastatic adenopathy, and no tumor spillage occurred during the operative procedure, radiotherapy is not necessary.

In group 2, we have tumors in the T_1 and T_2 categories with histopathologic diagnoses that suggest more aggressive behavior and associated poorer survival rates. These pathologic cell types include adenoid cystic carcinoma, squamous cell carcinoma, adenocarcinoma, high-grade mucoepidermoid carcinoma, and carcinoma ex-mixed tumor. For these tumors, we feel a total parotidectomy is indicated, including the upper cervical nodes. Again, the seventh cranial nerve is preserved unless direct invasion is encountered. If the facial nerve is involved, resection is carried to clear margins that are confirmed by frozen section and then the nerve is grafted immediately. The neck is dissected if nodes show tumor cells by frozen section or the surgeon's clinical judgment perceives them. Postoperative radiotherapy is delivered to the parotid region and the neck, with the treatment ports dictated by the size and location of the tumor as well as the extent of nodal disease.

In group 3, we have placed T_3 tumors and all patients with nodal metastasis or recurrent tumors who are not placed in group 4 (T_{4a} and T_{4b}). In these tumors, a radical parotidectomy with sacrifice of the facial nerve is usually required for a sufficient tumor-free margin. The nerve is grafted immediately, and a concomitant neck dissection is performed when metastatic nodal disease is present. Frozen section analysis is required for intraoperative assessment of facial nerve involvement. Temporal bone exploration is indicated if extratemporal biopsy specimens indicate an inadequate margin. Postoperative radiotherapy is delivered to the appropriate regions.

Group 4 includes T_4 lesions - those greater than 6 cm (T_{4a}) or tumors exhibiting aggressive local behavior (T_{4b}). The magnitude of excision will be dictated by the extent of disease. Neighboring structures that may be resected include the mandible, maxilla, temporal bone, muscles of mastication, and skin, as well as the facial nerve. Neck dissection is indicated for palpable metastatic disease. Reconstruction is often complex. A variety of procedures may be required to give satisfactory facial contour and support as well as soft tissue and skin coverage. Various static and dynamic slings as well as pedicled and free microvascular flaps have been used for these reconstructive challenges. Postoperative radiotherapy is delivered when healing is complete.

The principles presented for parotid gland malignancies may also be applied to submandibular gland neoplasms. In group 1, resection of the submandibular triangle is sufficient surgery for the small, low-grade malignancies. A clean plane of dissection between nerves and tumor is usually possible, allowing preservation of these structures. Radiotherapy is not required for malignancies in this group. In group 2 tumors, a wider excision is required for an adequate margin. Nerves are not resected unless they are directly involved with tumor or cannot be cleanly dissected free from the tumor. Postoperative radiation is recommended.

In group 3 tumors, the lingual and hypoglossal nerves must be sacrificed in most cases, particularly in recurrent tumors. A neck dissection is routinely performed for tumors in this category. Radiotherapy should follow the surgical excision. Surgery for tumors placed in group 4 will be tailored to fit the extent of disease. A marginal or segmental resection of the mandible may be required for these large, aggressive carcinomas. Portions of the tongue, floor of the mouth, and skin may be included with the tumor and associated nerves. A neck dissection and postoperative radiotherapy are included in the standard management of these tumors. Reconstruction may require transfer of both soft tissue and skeletal elements to reconstitute function and cosmesis.

The extent of surgery is based upon tumor size and local extension. For parotid gland malignancies, the facial nerve is preserved unless directly involved; neck dissection is performed only when tumor cells are found, and radiotherapy is recommended for all but small, low-grade tumors. With submandibular carcinomas, the basic approach is similar, with neck dissection used for all larger aggressive lesions.

More than three decades ago, Foote and Frazell introduced an acceptable classification system that has permitted scientific study of the treatment and course of salivary gland malignancies. Advances in pathologic and radiologic diagnosis, particularly in the area of CT scanning and cytologic examination, allow accurate pre-surgical assessment. Precise and well-constructed surgical procedures are possible, allowing maximal extirpation of disease with preservation of function. Adjunctive radiotherapy has provided improved local control with reduced surgical morbidity, particularly with respect to facial nerve function. Chemotherapy for these neoplasms is still in its infancy, but with distant metastases becoming more common as local control improves, this area of therapy becomes increasingly important. The protracted clinical course observed in patients with salivary gland neoplasms necessitates long-term follow-up before the role of these adjuvant therapies can be fully assessed.