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Clinical and Histopathological Aspects of Salivary Gland Tumors*

A Review

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A presumptive clinical diagnosis of salivary gland tumor can usually be made by taking an accurate history, performing a careful clinical examination, and utilizing essential radiographic and sialographic aids. Once a tumor is identified, differential diagnosis between benign and/or malignant involvement, and the exact tumor type becomes more formidable, frequently requiring histological diagnosis. Since optimum treatment is dependent upon an accurate differential diagnosis and surgical management according to tumor type, the clinical and histological aspects of salivary gland tumors are reviewed. A thorough knowledge of these characteristics allows an accurate diagnosis and provides the indications for proper treatment.

Major and minor salivary gland tumors differ in incidence, cell type, growth characteristics and method of treatment.[1,2,3]

About 80% of salivary gland tumors occur in the major salivary glands, most frequently in the parotid, submandibular and sublingual glands respectively. Primary neoplasms of these glands must be differentiated from salivary gland enlargement due to nutritional deficiency, sialolithiasis, sialadenitis, lymphadenitis, lipomas, cysts, mumps, Boeck's Sarcoid, tuberculosis, lymphoma, Mikulicz's syndrome (malignant lymphoma, leukemia), benign masseteric hypertrophy, carotid body and artery aneurysms and metastatic disease.[4-9]

The most common primary neoplasm of the major salivary glands is the benign pleomorphic adenoma or mixed tumor. Approximately 70% of all major salivary gland tumors are of this histological type with the parotid being affected approximately 10 times as often as the submaxillary gland.[8,10] The sublingual gland is almost never primarily involved by this neoplasm. Other less frequently occurring benign neoplasms of the major salivary glands include papillary cystadenoma lymphomatosum (Warthin's tumor),

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benign lymphoepithelial lesion (Mikulicz's disease), and the oxyphilic cell adenoma (onkocytoma) (see Table I).

Malignant tumors comprise the remaining 20 to 30% of the major salivary gland tumors and, as with the benign lesions, the incidence of occurrence is highest in the parotid, submaxillary and sublingual glands respectively.[11] The most common malignant tumor is the mucoepidermoid type. The adenocarcinomas, adenoid cystic carcinoma (cylindroma), epidermoid carcinoma, malignant mixed tumor and acinic cell carcinoma occur less frequently in approximately this order (see Table I).[12,13]

Although tumors of the minor salivary glands are less common than those of the major glands, comprising approximately only 20% of salivary glands neoplasms, they occur in more diverse areas such as the lip, tongue, tonsil, cheek, floor of the mouth, hard and soft palate, alveolar ridge, pharynx, larynx, nasal cavity and paranasal sinuses. Also, a significantly higher proportion of these tumors are malignant compared to those of the major salivary glands. Reynolds *et al* have recently reported that 70% of minor salivary gland tumors in their series were malignant, which is just the converse of the malignant-benign ratio incidence of that found in the major salivary glands.[1]

As in the major salivary glands, the most common benign tumor of the minor salivary glands is the pleomorphic adenoma or mixed tumor. Of the malignant tumors, the adenoid cystic carcinoma (cylindroma), adenocarcinoma and mucoepidermoid carcinoma are encountered most commonly.

Discussion

Salivary glands are composed of an acinar or glandular component, ductal component and an interspersed connective tissue stroma. The acinar component varies from gland to gland, but basically is composed of serous and mucous elements. Stained with hematoxylin and eosin, the serous portion appears as clusters (acini) of dark staining cells with numerous zymogen granules within the cytoplasm. Some acini have dark staining crescent-shaped serous cells, called demilunes, about their periphery. The mucous

Table I
Classification and Incidence of Major Salivary Gland Tumors

I.	BENIGN	80%
	A. Pleomorphic adenoma (mixed tumor)	
	B. Papillary cystadenoma lymphomatosum (Warthin's tumor)	
	C. Benign lymphoepithelial lesion (Mikulicz's disease)	
	D. Oxyphilic cell adenoma (onkocytoma)	
II.	MALIGNANT	20%
	A. Mucoepidermoid	
	B. Adenocarcinoma	
	C. Adenoid cystic carcinoma (cylindroma)	
	D. Epidermoid carcinoma	
	E. Pleomorphic adenoma	
	F. Acinic cell carcinoma	

component or acini appear microscopically as a circular arrangement of light or clear triangular-shaped cells with their nuclei at the outer circumference. Around the circumference of the mucous acini are myoepithelial cells which contract and aid in the expulsion of the mucous. In glandular structure, the parotid gland is serous, the submaxillary is primarily serous with mucous components, the sublingual is primarily mucous, and the minor salivary glands are primarily composed of mucous acini.

A. Benign Major Salivary Gland Tumors

1. The most common benign salivary gland tumor is the pleomorphic adenoma.

Recently Carl-Magnus Eneroth published the results of an extensive (1,102 major salivary gland tumors) histopathological and clinical study on mixed tumors of the major salivary glands.[10] Prior to his work there were many different views as to whether mixed tumors were benign, semimalignant or malignant. In 1924, Masson classified them on the basis of the conditions of encapsulation: The benign tumor was completely encapsulated, the semimalignant infiltrated and penetrated the capsule, and the malignant not only infiltrated and penetrated the capsule but herniated into the surrounding tissues, causing infiltrative destructive changes.[14] Although other investigators have assigned importance to histologic criteria (such as cylindromatous structures and a high degree of cellularity), Eneroth demonstrated that neither dominance of the epithelial component, high degree cellularity, nor cylindromatous structure implied an increased degree of malignancy. Furthermore, although others had shown that the histologic aspects of the tumor-capsule relations were important, Eneroth directly correlated the histologic capsule criteria with a long-term clinical follow-up. From his retrospective study of 681 mixed tumors of the major salivary glands, he concluded that penetration of the capsule and incomplete encapsulation were not associated with any signs of increased malignancy in the form of metastasis or death from tumor disease. Consequently, he rejected the concept of semimalignancy. However, about 3% of his cases did exhibit infiltrative destructive growth into the surrounding tissues. It was in these cases that metastasis and death from tumor were found.[10]

On these grounds, Eneroth classified mixed tumors on the basis of the relation between the tumor tissue, capsule and surrounding tissues into two distinct groups: (1) benign, comprising 97% of all mixed tumors in his study, without histologically identifiable infiltrative destructive growth into the surrounding tissues, and (2) malignant, comprising 3% of mixed tumors, with infiltrative destructive growth into surrounding tissues. Earlier investigators reported that about 10% of these tumors were malignant.[11,12]

The incidence of benign tumors in males is approximately equal to that in females. About 95% occur in the parotid gland with peak incidence in the fifth decade. Patients have usually been aware of the tumors for two to three years. Most often located in the superficial lobe, these tumors grow very slowly, are nonpainful, and freely movable. When removed they always are found to have a fibrous capsule.

Histopathologically, the neoplastic element is the epithelial cell and not the mesenchymal component. On this basis, the name "mixed tumor" is somewhat misleading.

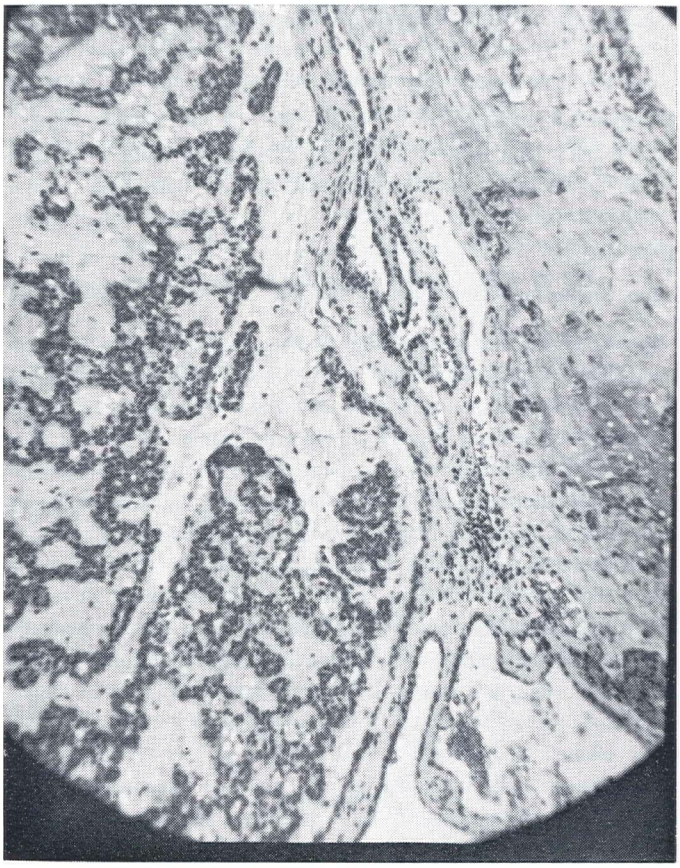

Figure 1
Pleomorphic adenoma

Smith feels that the epithelial neoplastic element is derived from the mature ductal cell within the salivary gland, although definite proof is lacking.[15] Characteristically, the tumors exhibit pleomorphism, with no characteristic cellular pattern, with the squamouslike cells occurring in sheets, strands, trabeculae, glandlike structures and even singly. The epithelial component is thought to induce the stromal cell production of the pleomorphic loose myxoid matrix, pseudocartilage and scirrhous tissue (see Figure 1).

In contrast, the malignant mixed tumor generally has a much more rapid growth rate, is fixed, is sometimes painful and occurs later in life. Histologically, there often are only small areas of malignancy, with most of the tumor being indistinguishable from its benign counterpart.

Surgical excision is the treatment for these tumors, with an adequate margin of surrounding normal tissue. This usually means superficial lobectomy in the parotid and total excision in the submaxillary gland. Recurrence is not uncommon following lesser

treatment. Radiation therapy has not been shown effective in the treatment of benign mixed tumors.[10]

2. The second most common benign major salivary gland tumor is the papillary cystadenoma lymphomatosum (Warthin's tumor). Unlike the pleomorphic adenoma for which it is often mistaken clinically, this lesion is benign and has no malignant counterpart or tendency to become malignant. Much more common in males than in females, the tumor is almost always found within the superficial parotid gland. It is a firm, nonpainful, circumscribed and nonfixed mass. It occurs most frequently during the fifth decade of life. Occasionally it occurs in the minor salivary glands and has been reported, multicentrically and bilaterally, in the major salivary glands.[16]

Histopathologically it is thought that this tumor develops from the epithelial ducts and that the lymphoid element represents a passive part of the lesion. The lesion is associated with lymphoid hyperplasia, a fact that has been explained on the basis (1) that the lymphoid tissue, embryologically associated with the developing major salivary

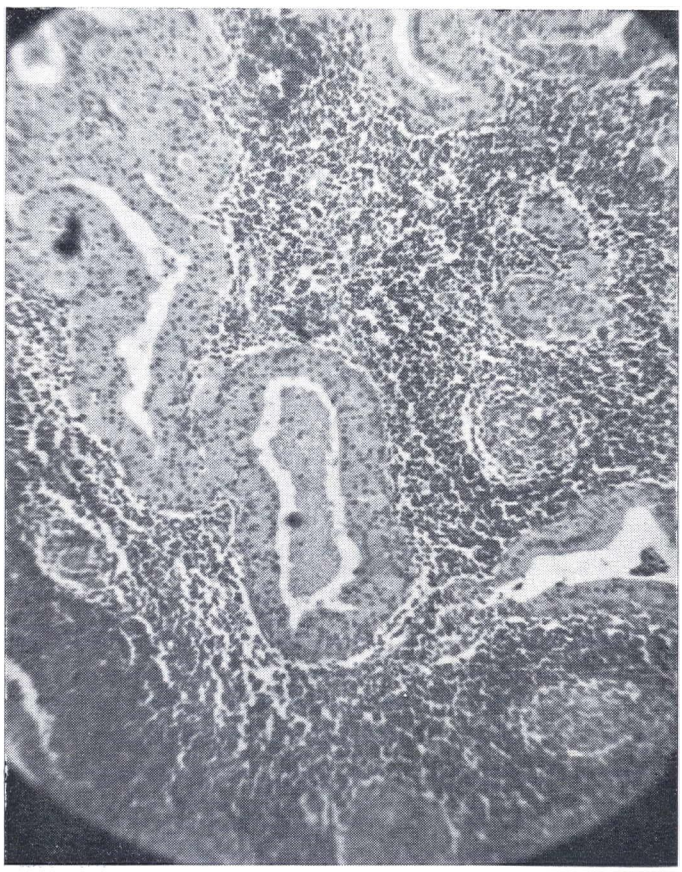

Figure 2
Papillary cystadenoma lymphomatosum

glands, undergoes induction hyperplasia,[15] and/or (2) that scattered foci of lymphocytes, present in the adult salivary gland, become hyperplastic.[17] Characteristically, epithelial cells are found in double rows lining cystic areas, with the inner cells most often being columnar and the outer cells cuboidal. The cystic linings normally exhibit papillarylike projections into the cavities, with diffuse lymphoid hyperplasia surrounding them. When stained with hematoxylin and eosin, these cavities usually contain a pink, granular coagulum. Germinal centers are sometimes seen within the areas of lymphoid hyperplasia (see Figure 2).

As with the benign pleomorphic adenoma, excision is the treatment of choice. Similarly, like the pleomorphic adenoma, recurrence is not uncommon following incomplete excision. Foote and Frazell reported that over 10% of such tumors recurred in their series.[11] Radiation has no proven value in the treatment of these tumors.[18,19]

3. A second benign neoplasm of the major salivary glands associated with lymphoid hyperplasia is the benign lymphoepithelial lesion or Mikulicz's disease. As with most other benign salivary gland lesions, this condition also occurs characteristically in the fifth or sixth decade of life, and most frequently involves the parotid glands. However, unlike the others, it often affects both the parotid and submaxillary glands bilaterally. Typically, the patient has had this lesion as a painless growth or diffuse "mumpslike" swelling many years prior to seeking treatment. In other instances there is a discrete mass present which is clinically indistinguishable from other benign salivary neoplasms. With long-standing disease there is sometimes a decrease in salivary flow.

Although this condition has been fraught with much misunderstanding, recent concensus is that Mikulicz's disease is an unusual inflammatory process, which is only a part of a greater symptom complex known as Sjögren's syndrome.[20-23] Two of the following factors must be present to diagnose Sjögren's syndrome: keratoconjunctivitis sicca, xerostomia, and rheumatoid arthritis.[23]

This tumor is thought by some to be an inflammatory lesion. Microscopically one sees an orderly infiltrative hyperplasia of lymphoid tissue into the salivary gland stroma with interspersed islands of proliferating ductal cells resembling metaplastic epithelium.[20] In time, the lymphoid element tends to replace much of the salivary gland stroma (see Figure 3). Distinct patterns of glandular involvement are noted by secretory sialography.[23]

In the simple or diffuse type of involvement no specific treatment is usually necessary, however when superimposed sialadenitis is present, duct ligation, radiation or gland excision may become necessary. When this condition presents as localized, tumorous growth surgery is usually indicated on a diagnostic basis.[21,24]

4. The oxyphilic cell adenoma or onkocytoma, a benign tumor, tends to occur chiefly in the parotid gland of persons over 65 years of age. It is considered by some not to be a true tumor but rather a change associated with aging.[15] Extremely rare, these tumors are usually firm, nodular masses which may fluctuate during growth. Like all benign salivary gland tumors, there is seldom pain associated with their growth.

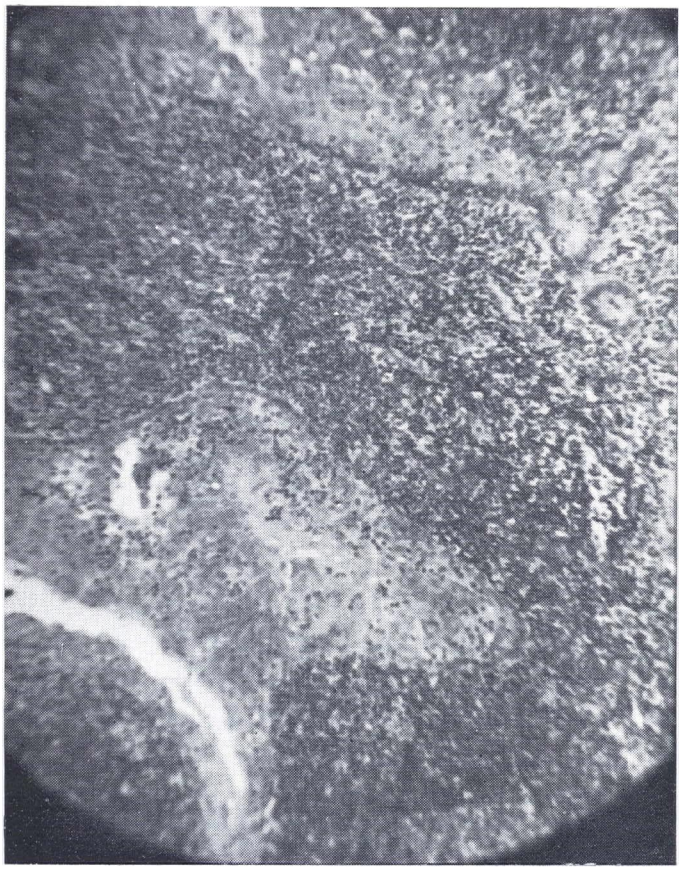

Figure 3
Benign lymphoepithelial lesion

Numerous onococytes, which are large cells with pink cytoplasm and round well-formed nuclei, are histopathologically characteristic of these lesions. They occur in the form of sheets, strands, glands, columns and most commonly as cords (see Figure 4).

Since this tumor is well encapsulated and seldom recurs, surgical excision affords adequate treatment. Radiation therapy has been tried in several cases without success.[25]

B. Malignant Major Salivary Gland Tumors

Malignant tumors, which comprise 20 to 30% of the major salivary gland tumors, present greater problems in diagnosis and treatment. General characteristics are (1) fixation to surrounding structures, (2) sudden and rapid increases in size, often after a stationary period, (3) pain, (4) enlargement of regional lymph nodes, (5) stony-hardness, (6) and, when located within the parotid gland, facial nerve (VII) involvement. In treatment and prognosis three factors must be considered: (1) cell type, (2) stage of disease when first seen, and (3) adequacy of treatment.[3]

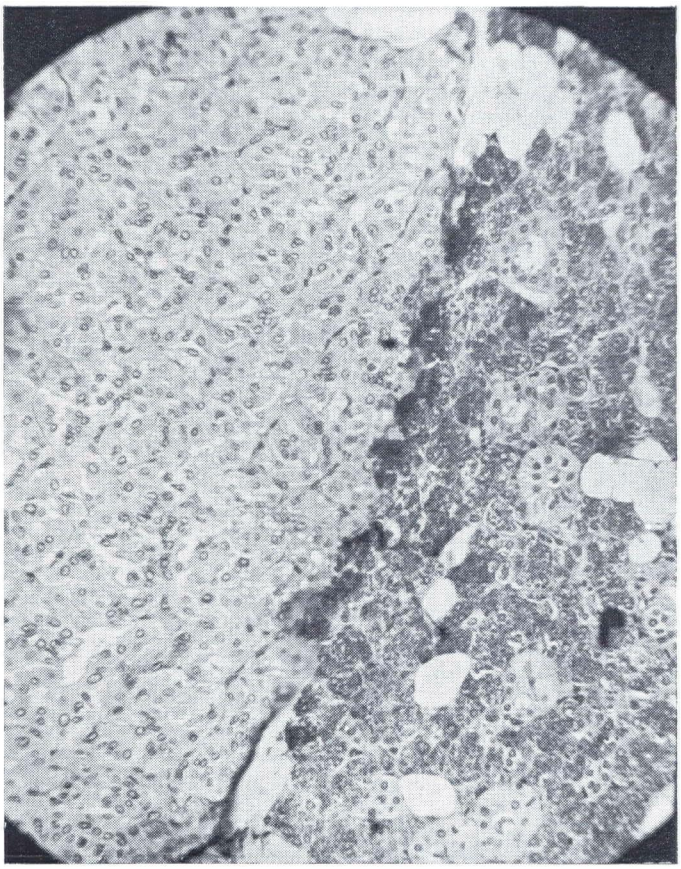

Figure 4
Oxyphilic cell adenoma

1. Of the malignant tumors, the most common is the mucoepidermoid carcinoma.[12,26] In the past these tumors have been classified as both benign and malignant neoplasms. This is because there is a spectrum of activity for these tumors from (1) those which do not metastasize, to (2) low-grade malignant types, to (3) the highly malignant type which manifest themselves early with regional and systemic metastasis. The tendency is to categorize these as either low or high-grade malignant tumors. Clinically, the low-grade type usually presents signs and symptoms similar to benign tumors. The high-grade type presents manifestations typical of malignant disease as described.

Histopathologically, the epidermoid component arises from the ductal cells of the interlacunar and interlobar ducts, and the mucous-secreting cells arise from the epithelial elements within the ductal cells.[15] In addition, there is often a third cell type that is smaller and considered intermediate to the mucous epidermoid cells. Generally, when the cellular elements are predominantly epidermoid and intermediate, the tumor

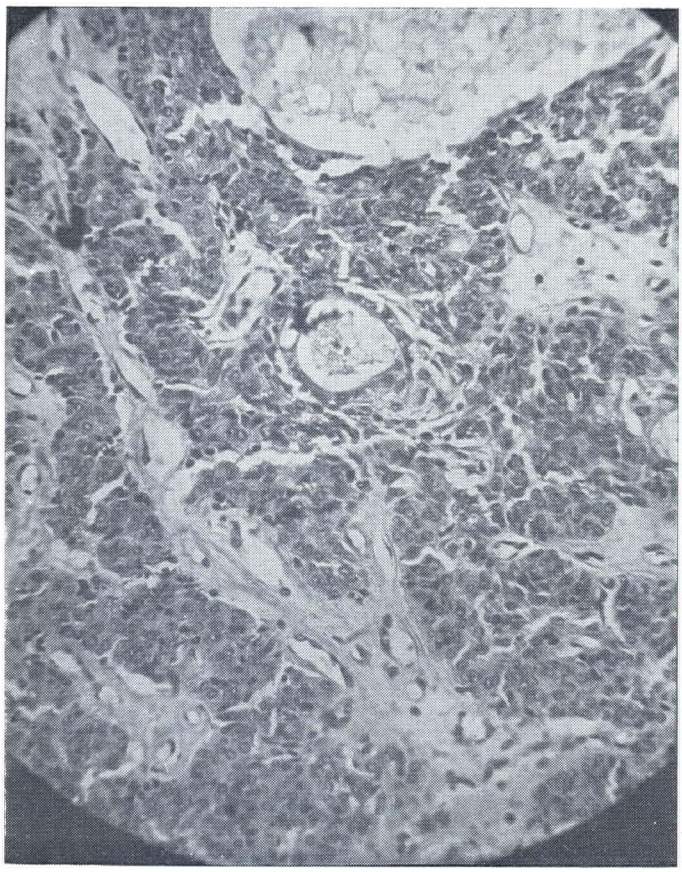

Figure 5
Mucoepidermoid carcinoma

is highly malignant. In low-grade tumors, on the other hand, mucous-secreting cells predominate (see Figure 5).

In early (small lesion without regional metastasis) low-grade mucoepidermoid carcinoma, local excision of the involved gland without radical neck dissection is often curative. In more advanced low-grade and in high-grade tumors, gland excision with radical neck dissection is indicated.[3,9] There is some evidence that preoperative radiation therapy is beneficial in temporarily inhibiting their reproductive capacity,[27] and post-operatively in cases in which complete removal is in doubt.[28]

2. The adenocarcinomas, which include the cylindromas and acinic cell carcinoma, are sometimes considered a separate group consisting of what Foote and Frazell have called the "miscellaneous forms" of adenocarcinoma.[12] These include the trabecular, anaplastic, mucous cell and pseudoadamantine adenocarcinomas. Generally these are rapid growing, aggressive, infiltrative tumors with early local metastasis.

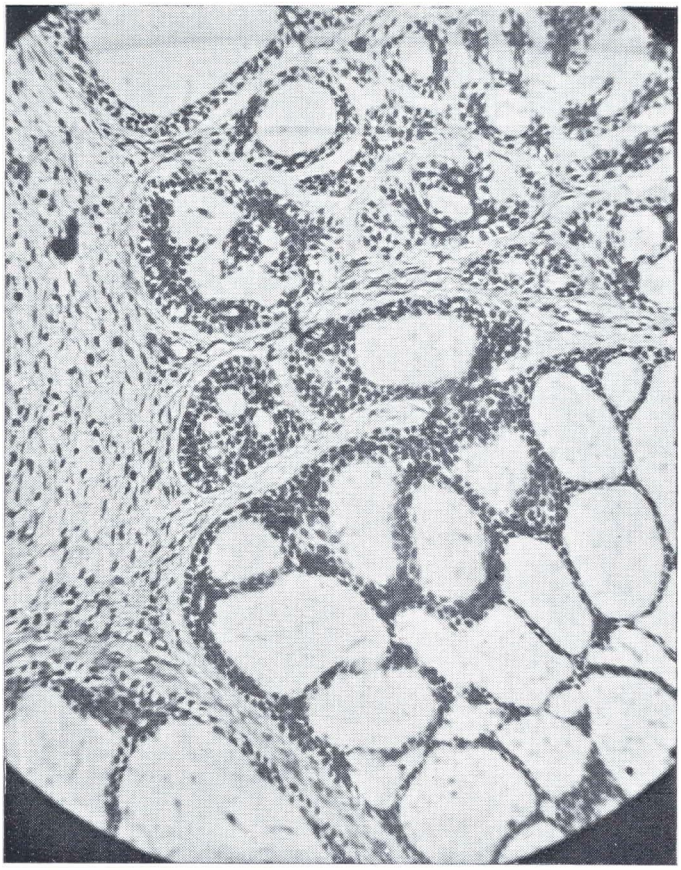

Figure 6
Adenoid cystic carcinoma

3. The adenoid cystic carcinoma or cylindroma, although a type of adenocarcinoma, behave quite differently. Unlike all other major salivary gland tumors, they occur most often in the minor salivary glands, and with equal frequency in the parotid and submaxillary gland. They usually occur in the fourth decade and can be mistaken for benign tumors because they grow slowly and often alternate between decreased and increased growth periods. Other features, however, are characteristic of malignant tumors. They spread first to regional lymph nodes and later to the lungs, bones and viscera. In addition, there is frequently neural sheath involvement and spread, a factor accounting for the high proportion of facial nerve paralysis and incomplete excision of these tumors.

Cylindromas arise from mature ductal cells which appear as small, dark staining basal like cells with little cytoplasm.[15] These cells are arranged in cords and cellular aggregates which surround multiple cysticlike spaces filled with mucous like material. Between the cystic like structure a loose fibrous tissue stroma exists (see Figure 6).

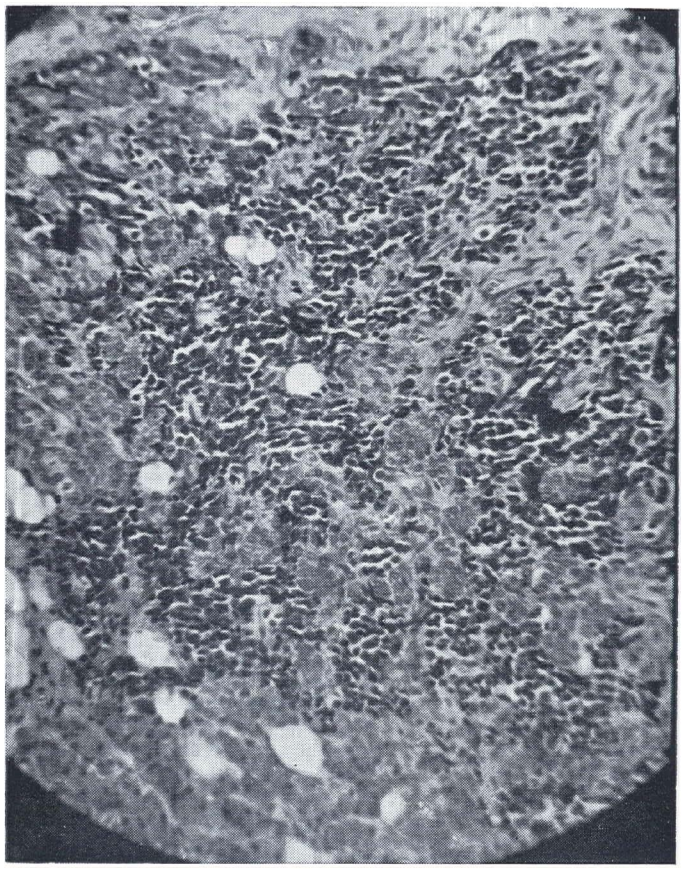

Figure 7
Epidermoid carcinoma

When the diagnosis of cylindroma is made, adequate surgical excision is indicated. Due to the nature of their insidious and perineural spread this is often difficult, however the use of frozen sections at the time of surgery is helpful.[29] Ackerman and DelRegato report that some of these tumors are not only radiosensitive, but radiocurable.[28] This has not been the experience of others who report that this mode of treatment offers no hope of cure and effects only temporary regression.[29]

4. The fourth most common malignant tumor of the major salivary glands is the epidermoid or squamous cell carcinoma. Because these are quite rare as primary tumors in the major salivary glands, a careful search should be made to rule out the possibility of extension from overlying skin, adjacent tissue, or metastasis from a distant focus. The histology is essentially identical with epidermoid carcinomas of other sites and the tumors are thought to arise from squamous metaplasia of the ductal epithelium.

Epidermoid carcinomas occur most often in the parotid gland in the fifth to sixth decade, most frequently in males. They are indurated, firmly fixed to surrounding

structures, ulcerated in about 50% of the cases, and metastasize to the regional lymph nodes more rapidly than do other malignant salivary gland tumors. These tumors often have a rapid clinical course and although death from distant metastasis may occur, the majority of patients die from uncontrollable local and regional disease. Nevertheless, the prognosis of these tumors is also dependent upon their cell type, the better differentiated being less malignant.

Histopathologically they vary from well-differentiated squamous cell carcinoma (with typical epidermoid cells, intercellular bridges and pearl formation), to very anaplastic, undifferentiated carcinoma in which the diagnosis is extremely difficult (see Figure 7).

The available evidence justifies the use of radiotherapy as a primary procedure prior to surgery, or when total surgical excision is uncertain, or whenever surgical treatment is contraindicated.[28]

5. The acinic cell carcinoma, a third "type" of adenocarcinoma, is unique in that it occurs almostly solely within the parotid gland. It is a histologically distinct tumor which may appear benign or of extremely low-grade malignancy. However, in a recent long-term study of 1,678 parotid tumors, 2.2% were acinic cell carcinoma and had a relatively high rate of local recurrence and distant metastasis.[30]

Women are affected by this tumor much more frequently than are men. Mean age of detection is about 45. The patients in most instances are asymptomatic apart from a noticeable swelling in the parotid region. In about 25% of the instances however, the tumors cause pain and/or facial nerve paralysis.[30]

Histologically acinic cell carcinomas are almost always encapsulated and not initially infiltrative. Unlike other salivary gland tumors, which arise from the epithelial ductal cells, this carcinoma arises from the acinar cells proper. The classic cellular pattern of these tumors is represented by solid epithelial sheets of rounded or polygonal cells with basophilic, granulated cytoplasm and small, eccentric nuclei (see Figure 8).

In view of the malignant nature of this tumor, Eneroth believes that local surgical intervention can justifiably be complemented by neck dissection and postoperative irradiation.[30] The feeling of others is that subtotal or total parotidectomy is the initial treatment of choice.

In addition to the malignant major salivary gland tumors mentioned, Silver and Goldstein have recently reported a tumor (believed to be the first case) of primary sebaceous cell carcinoma of the parotid.[31]

C. Minor Salivary Gland Tumors

Clinical-histopathological studies of minor salivary gland tumors have been limited. In 1960, Fine *et al* reviewed the subject and compiled over 1,000 reported minor salivary gland tumors.[32] To this they added their series of 79 benign and malignant minor salivary gland tumors. They reported that approximately 50% of these tumors were malignant.

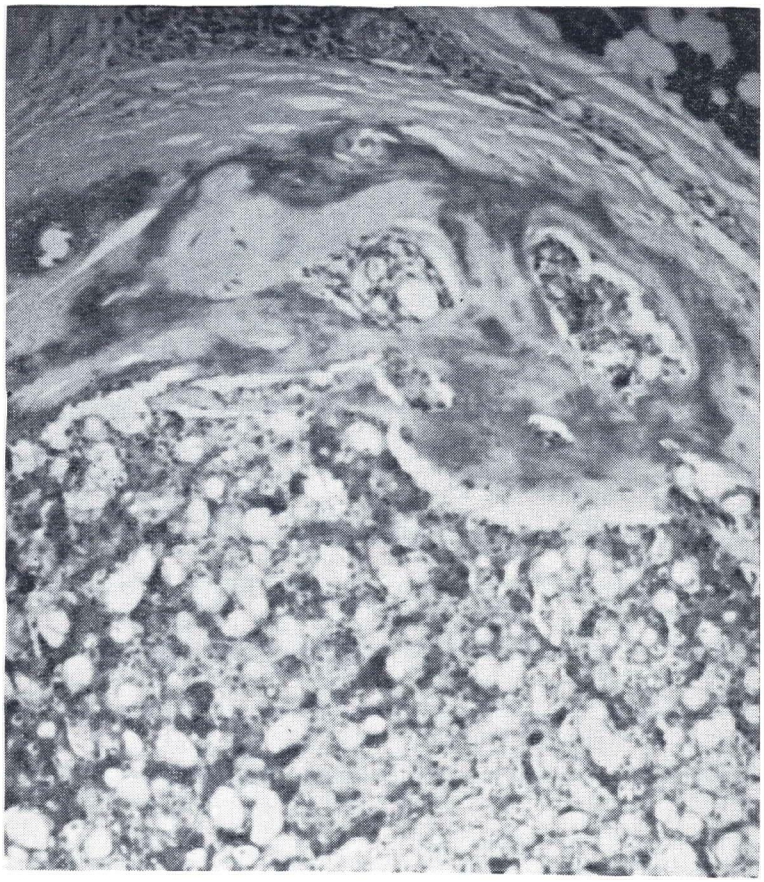

Figure 8
Acinic cell carcinoma

Table II*
Classification and Incidence of Minor Salivary Gland Tumors

I.	BENIGN	
	A. Pleomorphic adenoma (mixed)	31%
II.	MALIGNANT	
	A. Adenoid cystic carcinoma	27%
	B. Adenocarcinomas	21%
	C. Mucoepidermoid carcinoma	12%
	D. Malignant mixed	9%

*Adapted from Reynolds *et al*

More recently, Reynolds, McAuley and Rogers related their experience with tumors of the minor salivary glands.[1] In reviewing 49 cases, these authors reported that approximately 70% were malignant, a finding in agreement with the reports from Brown *et al* and Chaudhry *et al*.[33,34] These studies indicate that minor salivary gland tumors exhibit almost a reversal of the bening-malignant ratio noted in major salivary gland tumors (see Table II).

The palate (53%) is the most commonly affected area, with the cheek, lips, tongue and floor of the mouth being involved less frequently.[34,35] The detailed histological aspects need no further description. However, several important clinical points concerning malignant minor salivary gland tumors merit attention: (1) Their growth pattern is primarily one of local penetration and/or invasion resulting in multiple recurrences if initial surgical excision is inadequate, and (2) there appears to be no significant tendency to metastasize to regional nodes or specific distant sites.

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