Normal Anatomy

The major salivary glands are the paired parotid, submandibular (submaxillary), and sublingual glands. The parotid gland weighs 14–28 g, the submandibular gland weighs 7–8 g, and the sublingual gland weighs 3 g. The main duct of the parotid gland (Stensen duct) empties into the oral cavity opposite the crown of the second maxillary molar. The main ducts of both the submandibular glands (Wharton duct) and sublingual glands (Bartholin duct) open in the floor of the mouth, on each side of the frenulum of the tongue. Several minor sublingual gland ducts (Rivinus ducts) drain into the main duct or empty into the oral cavity along the plica sublingualis on either side of the frenulum.

The parotid gland is composed of a broad superficial lobe and a smaller deep lobe, with the facial nerve running between, and artificially separating, the two lobes. Variations of this anatomy and the distribution of the facial nerve occur.

Minor salivary gland tissue is present in many other locations in the head and neck region, where it may give rise to inflammatory conditions, benign tumors, and malignant tumors. They are found in the lips (more in the upper than the lower lip), gingiva, floor of mouth, cheek, hard and soft palates, tongue, tonsillar areas, oropharynx, and upper respiratory tract.

Microscopically, salivary glands are compound exocrine glands composed of a ductal and an acinar portion, the latter of either serous or mucinous type. 1 The parotid gland is exclusively serous, the submandibular gland is mixed with serous predominance, and the sublingual gland is mixed with mucinous predominance. Minor salivary glands can be pure mucinous (anterior tongue, palate), pure serous (posterior tongue), or mixed (lip, buccal, sinonasal tract, nasopharynx). The intercalated ducts and acini represent the terminal portion of the system (ductoacinar unit). Under normal conditions, rare sebaceous glands are annexed to the duct system in the parotid and, less commonly, the submandibular glands. The reserve cells of the intercalated ducts are the source of regeneration of the acinar tissue and the terminal duct system and are thought to be the progenitors (together with the closely apposed myoepithelial cells) of most salivary gland tumors. 2 However, it has been pointed out that basal

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Abstract
This chapter reviews the normal anatomy and histology of the three paired major salivary glands and the minor salivary glands. Inflammatory disorders and developmental disorders of salivary glands are briefly discussed. Salivary gland tumors make up for most of the chapter content, using the general classification adopted by the WHO. However, certain neoplasms are discussed together as they relate to differential diagnosis.

Keywords
salivary gland neoplasms,
salivary gland inflammation
and luminal cells at all levels of the duct system and even acinar cells are capable of DNA synthesis and mitosis, and therefore they all have the potential to give rise to neoplasms.1

Immunohistochemically, the luminal cells stain for low-molecular-weight keratin (including CK7), CD117, carcinoembryonic antigen (CEA), and epithelial membrane antigen (EMA). The intercalated duct luminal cells are also positive for lysozyme but not for S-100 protein.2 Serous acinar cells are positive for low-molecular-weight keratin and DOG-1.3 The myoepithelial cell component can show some minor differences in its immunohistochemical profile depending on its location, but this is an inconsistent finding: in the parotid gland the myoepithelial cells express mainly calponin and h-caldesmon; in the submaxillary glands they also express smooth muscle actin; and in the minor salivary glands there is an additional expression of smooth muscle myosin heavy chain. Myoepithelial cells also stain for p63, p40, CD10, and maspin, as do the basal cells.4

The lymphoid tissue of the parotid region is represented by small nodes located near or within the parotid gland and by scattered lymphoid cells located in the connective tissue around the acini and ducts. The latter are part of the mucosa-associated lymphoid tissue (MALT).5 Periparotid lymph nodes often contain benign salivary gland inclusions. No lymph nodes are present within the submandibular or sublingual glands.

**Heterotopia**

Heterotopia of salivary gland tissue has been divided into *intranodal* and *extranodal* types.6 The intranodal variety is more frequent. Almost all lymph nodes located within or near the parotid gland in infants contain salivary gland tissue. The finding is not as prevalent in adults, but it is still very frequent. The salivary gland tissue is usually located in the medullary portion of the node and is predominantly composed of intercalated and intralobular ducts; it may also contain acini (mainly of serous type) and small ducts of immature type.7

Extranodal heterotopia has been divided into *high* and *low* forms, depending on its location in the head and neck region. Sites of high heterotopia include the mandible, ear, palate tonsil, mylohyoid muscle, pituitary gland, and cerebellopontine angle; these are probably all the result of abnormalities in the embryonic migration of the salivary glands. Low heterotopia is related to the branchial pouches and is found in association with cysts and sinuses in the lower neck and in the thyroid gland.8 The most common location is along the medial border of the right sternomastoid muscle near the sternoclavicular joint. In this location, the ectopic glands can secrete saliva onto the skin during feeding.

Heterotopic salivary tissue is subject to the same pathologic changes as its orthotopic counterpart, including cystic formation, oncocytic metaplasia, ductal hyperplasia, and neoplasms.9 Among the latter, Warthin tumor is the most frequent, but several other benign and malignant types have been described.10

**Sialolithiasis**

Calcui may form in the major ducts of the submandibular, sublingual, and parotid glands, sometimes in a multicentric and bilateral fashion.11 They are more common in the submandibular gland than in the parotid gland, presumably because in the former the saliva is more saturated with calcium salts and the duct is longer with a sharp upward angle prior to its termination onto the floor of the mouth (Fig. 6.1).12 Rarely, they affect minor salivary glands.13 Some of the stones have a foreign body or bacterial nidus. Others do not have an identifiable nidus, are laminated, and are composed of the crystalline compound carbonate apatite.14 The formation of calculi blocks secretion and produces swelling of the distal salivary gland tissue. If ductal obstruction persists, the gland becomes inflamed and atrophic as acinar tissue is destroyed. With obstructed ducts of the submandibular and sublingual glands, marked induration can occur in the floor of the mouth that may be mistaken for neoplasm by palpation. The duct orifices become erythematous and swollen. Radiographic examination may demonstrate a radiopaque mass, and sialography will show partial or total blockage of the duct. The stones can also be demonstrated by ultrasound.15 Microscopic examination of glands that have been affected by stones shows dilation of ducts with intraluminal neutrophils, at times squamous metaplasia of the epithelium, moderate to prominent chronic inflammation, and a variable destruction of acinar tissue (Fig. 6.2). Degenerative changes in the secretory and myoepithelial cells are also apparent at the immunohistochemical and ultrastructural levels.16

The treatment of symptomatic sialolithiasis consists of surgical removal or disintegration of the calculus. The latter is achieved with techniques such as intracorporeal or extracorporeal shock-wave lithotripsy.17 In most cases the gland can be preserved, but surgical resection is occasionally necessary.18

**Sialadenitis**

Acute sialadenitis can be localized to one salivary gland (usually parotid or submandibular) or be the expression of a systemic infection. Viral sialadenitis (rarely seen as a surgical specimen or biopsy) can be caused by paramyxovirus (mumps), cytomegalovirus, Epstein–Barr virus (EBV), coxsackievirus, and influenza A and parainfluenza viruses.19 Acute supplicative sialadenitis is generally caused by *Staphylococcus aureus, Streptococcus* species, and gram-negative bacteria. Dehydration, malnutrition, immunosuppression, and sialolithiasis are
Benign Lymphoepithelial Cysts and HIV-Related Lesions

Benign lymphoepithelial cysts are lesions of the parotid or upper cervical lymph nodes characterized by unilocular or multilocular cystic formations lined by glandular or squamous epithelium surrounded by a florid lymphoid hyperplasia with prominent germinal centers. The amount of the lymphoid component is variable, and the cyst lining is often infiltrated by lymphocytes. This is likely an acquired process resulting from the proliferation of branchial pouch-derived or analogous epithelium (e.g. intranodal salivary gland inclusions) induced by the lymphoid hyperplasia, probably through a specific interaction between the epithelial cells and a subset of lymphocytes. Other examples of this phenomenon in the head and neck area are branchial cleft cyst, the branchial cleft cyst-like formations sometimes seen in Hashimoto thyroiditis, and multilocular thymic cyst.

Another salivary gland lesion that merits mention in this context is human immunodeficiency virus (HIV)-associated lymphoepithelial cyst (Fig. 6.5). The morphologic changes in

Sclerosing polycystic adenosis is characterized by the presence of a discrete mass (usually in the parotid gland) formed by fibro-hyaline stroma enclosing dilated and hyperplastic ductal and acinar structures (Fig. 6.4). Apocrine-like metaplasia and transluminal bridges with a cribriform pattern of growth are present. The appearance resembles that of sclerosing adenosis and fibrocystic disease of the breast. Some of the epithelial cells contain large, brightly eosinophilic cytoplasmic granules. The behavior is characterized by indolent. Although initially reported as a reactive inflammatory process, most authors now believe this is a low-grade neoplasm, and a study with the HUMARA technique has shown that the disease is of clonal nature.

Granulomatous sialadenitis is uncommon and can result from tuberculosis, fungal infection, sarcoidosis, or duct obstruction from calculi or malignant tumors. In the latter instance, the granulomas result from rupture of ducts and may contain small pools of mucin. A xanthogranulomatous variant of sialadenitis has also been described.

Kimura disease can involve the salivary glands (especially the parotid) by spread from adjacent lymph nodes.

### Benign Lymphoepithelial Cysts and HIV-Related Lesions

**Benign lymphoepithelial cysts** are lesions of the parotid or upper cervical lymph nodes characterized by unilocular or multilocular cystic formations lined by glandular or squamous epithelium surrounded by a florid lymphoid hyperplasia with prominent germinal centers. The amount of the lymphoid component is variable, and the cyst lining is often infiltrated by lymphocytes. This is likely an acquired process resulting from the proliferation of branchial pouch-derived or analogous epithelium (e.g. intranodal salivary gland inclusions) induced by the lymphoid hyperplasia, probably through a specific interaction between the epithelial cells and a subset of lymphocytes. Other examples of this phenomenon in the head and neck area are branchial cleft cyst, the branchial cleft cyst-like formations sometimes seen in Hashimoto thyroiditis, and multilocular thymic cyst.

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**Figure 6.2** Obstructive sialadenitis associated with submandibular gland sialolithiasis. The parenchyma is atrophic with mixed acute and chronic inflammation including intraluminal neutrophils.

**Figure 6.3** Gross appearance of suppurative sialadenitis.

**Figure 6.4** Sclerosing polycystic adenosis. Small tubules and epithelial nests composed of cells with apocrine cytology are present within a collagenous stroma. Note the eosinophilic cytoplasmic granules in the bottom left.
this condition include multiloculated lymphoepithelial cysts similar to those previously described, solid lymphoepithelial lesions (so-called epimyoepithelial islands) similar to those seen in Mikulicz disease (see next section), and a combination of both.44,45 These lesions can be unilateral but are often bilateral. The more prominent the combination of these changes, the more likely that HIV infection is the causative factor. Three-dimensional reconstructions have shown that the cysts arise from the intralobular duct system rather than from intraparotid lymph nodes.46

The lymphoid follicles of HIV-induced salivary gland disease show a prominent network of follicular dendritic cells and numerous intrafollicular CD8+ lymphocytes. The follicular dendritic cells show a strong expression of HIV-1 major core protein and HIV-1 RNA, indicating that there is active replication of the virus within them.47

There are two other polycystic diseases of the salivary glands that need to be mentioned here for differential diagnosis purposes. The first is polycystic (dysgenetic) disease, a developmental disorder so far reported only in females and characterized by bilateral parotid gland enlargement.48,49 The lesion is characterized by small epithelial cysts replacing most of the parotid gland parenchyma with small foci of residual acini interspersed throughout. The other is the already mentioned sclerosing polycystic adenosis. One should also keep in mind that some neoplasms of salivary gland may undergo prominent cystic changes. This is particularly true of mucoepidermoid carcinoma, acinic cell carcinoma, basal cell adenoma, sebaceous lymphadenoma, and, occasionally, benign mixed tumor.

**Lymphoepithelial Sialadenitis (Mikulicz Disease) and Sjögren Syndrome**

Lymphoepithelial sialadenitis (Mikulicz disease, benign lymphoepithelial lesion) most often presents as a slowly increasing and eventually striking enlargement of the salivary and/or lacrimal glands. This enlargement is usually bilateral and symmetric, but it can also be unilateral and localized, at least at the clinical level. If an infection develops, the process may subside only to recur when the infection is gone.

Grossly, the gland is enlarged and whitish, sometimes admixed with occasional cysts (Fig. 6.6A). Microscopically, the two cardinal changes are marked lymphoid infiltration and so-called epimyoepithelial islands.46 This combination of findings has been used to create a synonym for the disease associated with a catchy acronym, that is, myoepithelial sialadenitis (MESA), recently modified to lymphoepithelial sialadenitis (LESA).50 The lymphoid tissue contains numerous well-formed germinal centers and is composed of a mixed population of B and T lymphocytes, accompanied by scattered histiocytes and dendritic cells. The so-called epimyoepithelial islands appear as solid epithelial nests surrounded and infiltrated by lymphoid cells, which are mainly of monocytoid B type (see Fig. 6.6B). A hyaline substance is deposited between the cells, which is shown ultrastructurally to represent basement membrane material, including type IV collagen.51 The nature of the cells within the islands, that is, whether ductal, basal or myoepithelial, remains a controversial subject.51,52 Current evidence suggests a lack of myoepithelial cell participation, which—if true—would make the term "epimyoepithelial islands" inaccurate and the alternative "lymphoepithelial lesions" more appropriate.53

LESA can remain localized to the salivary gland but more often is a manifestation of a generalized symptom complex known as Sjögren syndrome, the other components of which are keratoconjunctivitis, xerostomia, rheumatoid arthritis, and hypergammaglobulinemia.54 In this condition, lymphoid infiltrates similar to those present in the major salivary glands are also seen in the lacrimal glands and minor salivary glands of the oral cavity. This fact is of diagnostic utility, in the sense that biopsy of the labial glands is often used to document the diagnosis of this condition.55 It should be noted, however, that so-called epimyoepithelial islands are usually scanty or absent at these sites. Occasionally, the lymphoid infiltrates extend to other organ systems, such as lymph nodes, lung, kidney, bone marrow, skeletal muscle, skin, or liver.56

The etiology of LESA, with or without Sjögren syndrome, remains enigmatic. The incidence of the disease is markedly increased in HIV-infected patients. As a matter of fact, there is a marked morphologic similarity (and probably a close pathogenetic relationship) between Sjögren syndrome as seen in this population and the HIV-related changes described in the previous section. Interestingly, a chronic lymphocytic sialadenitis morphologically very similar to Mikulicz disease occurs in hepatitis C virus (HCV)-related chronic liver disease.57
Other Non-Neoplastic Lesions

much difficulty in identifying it. The vexing problem is how to interpret the usual case of LESA that is composed of a morphologic mature (“benign-looking”) lymphocytic population, especially if a monotypic component has been detected with molecular techniques. Is it a reactive, possibly autoimmune process with a tendency to evolve into a recognizable malignant lymphoma, or is it a malignant lymphoma already? Some authors have taken the latter view and have placed LESA in the ever-expanding MALT lymphoma category, mainly on the basis of the molecular findings. It seems to us that to label a process as malignant at a stage at which it shows neither clinical nor morphologic signs of malignancy is neither conceptually nor medically sound. At the present state of knowledge, it is probably wiser to restrict the diagnosis of lymphoma to those cases showing some morphologic evidence of such. The most important feature in this regard is the number and distribution of the monocytoid B cells. The presence of these cells outside of the lymphoepithelial lesions, and especially as broad anastomosing strands, is in favor of lymphoma; the same is true for sheets of plasma cells, with or without Dutcher bodies. In fact, probably the earliest morphologic feature of MALT lymphoma arising in LESA is the presence of a “halo” of pale-staining sheets of monocytoid B cells surrounding the “epimyoepithelial” islands.

Irradiation Effect

The submandibular glands, which are often included in the field of irradiation for tumors of the oral cavity, swell and become firm as a result of the therapy. These changes may be mistaken clinically for metastatic carcinoma in submandibular lymph nodes and sometimes have led to unnecessary radical surgery. Not surprisingly, these changes are frequently seen in cervical lymph node dissection specimens in patients previously treated with radiation therapy. Microscopic examination shows atrophy of acinar elements with associated fibrosis and chronic inflammatory cells in the stroma. The lining of the duct epithelium may show prominent squamous metaplasia and degenerative-type atypia.

Other Non-Neoplastic Lesions

Lymphoid disorders of reactive nature can involve the intraparotid lymph nodes and be confused clinically with a primary salivary gland tumor. These include nonspecific follicular hyperplasia, healed abscesses, and granulomatous inflammations, such as those produced by cat-scratch disease. Amyloidosis may involve the salivary gland as part of a generalized process or as a localized pseudotumoral mass (“amyloid tumor”), and it may result in the sicca syndrome. Nodular fasciitis can present as a primary intraparotid or periparotid lesion; its microscopic appearance is identical to that of its more common soft tissue counterpart. Inflammatory pseudotumor is composed of a predominant population of myofibroblast-like cells in an edematous and inflammatory background. As in other sites where this entity occurs, there is a question as to whether it may represent a neoplastic condition, hence the alternative designation of inflammatory myofibroblastic tumor. Rosai–Dorfman disease (sinus histiocytosis with massive lymphadenopathy) can involve the major salivary glands, with or without accompanying lymph node enlargement. Intercalated duct hyperplasia of major salivary glands may coexist with salivary gland tumors of various types (especially epithelial–myoepithelial carcinomas) and with chronic parotitis. It is composed of intercalated duct epithelium and therefore different from the adenomatoid acinar hyperplasia found predominantly in intraoral salivary glands. It has been suggested that intercalated duct

Figure 6.6 A, Gross appearance of lymphoepithelial sialadenitis (LESA) of parotid gland. There is a combination of solid areas resulting from infiltration by lymphocytes and small cystic formations representing dilated ductal lumina. B, Prominent proliferation of duct epithelium in a patient with LESA disease.

The prevalent view is that LESA is a systemic autoimmune process. In the typical case the lymphocyte population is polyclonal, in keeping with a reactive process. However, this population may undergo small clonal expansions, detectable on Southern blots. In some cases, these evolve into full-blown lymphomas, whether in the salivary gland or in extraglandular locations. Some of these are large B-cell lymphomas (often with an immunoblastic appearance), whereas others are small lymphocytic lymphomas with or without plasmacytoid features (see later), and exceptional cases of Hodgkin lymphoma and peripheral T-cell lymphoma have been reported. When one of these lymphoma types develops, there is usually not...
hyperplasia may be a precursor lesion of some salivary gland neoplasms (see next section).

**Epithelial Tumors**

**Classification**

The classification of salivary gland tumors has proved a most difficult and frustrating exercise. If anything, it is even more complex than that of the somewhat related breast and sweat gland tumors. One of the major stumbling blocks is that most of the salivary gland tumors arise from—or differentiate toward—the same cell lines: epithelial (ductal and/or acinar) and abluminal (myoepithelial and/or basal cell). This results in a considerable overlap at all levels, compounded by the fact that each of these cells can undergo a variety of metaplastic changes (e.g. oncocytic, clear cell, sebaceous, squamous, chondroid). In addition, with some exceptions, these lesions are uncommon. The World Health Organization (WHO) classification stresses the distinction between benign and malignant tumors (i.e. adenomas and carcinomas). In this chapter, a somewhat different approach has been used. The tumors have been grouped, whenever possible, according to their predominant line of differentiation; this has been followed by a discussion of the benign and malignant members within each group.

**Tumors With Stromal Metaplasia**

**Pleomorphic Adenoma (Benign Mixed Tumor)**

Pleomorphic adenoma is the most common neoplasm of the salivary glands. It is most frequent in women in the fourth decade of life, but it can be seen in children and in elderly persons of either gender. It is approximately 10 times more common in the parotid than in the submandibular gland and is very rare in the sublingual gland. In the parotid gland, most tumors arise within the superficial lobe, from either the tail (50%) or the anterior portion (25%). The remaining 25% arise from the deep lobe and often present as a parapharyngeal mass. They are also seen in various minor salivary gland sites (e.g. palate).

Grossly, the tumor forms a rubbery, tan-white, firm mass with a bosselated surface and may grow to a large size but are usually between 2 and 5 cm (Fig. 6.7). The consistency depends on the relative amount of epithelial cells and stroma and the type of the latter. Although the tumor tends to be well circumscribed, small extensions (so-called pseudopodia) can often be seen protruding into the adjacent normal tissue. Islands of cartilage can be recognized by their glistening, translucent appearance. In rare cases, foci of mature bone are identified.

The typical pleomorphic adenoma has a biphasic appearance resulting from the intimate admixture of epithelium and stroma (Figs. 6.8 and 6.9). Most of the epithelial component is of a glandular nature, but foci of squamous metaplasia are common, sometimes accompanied by keratinized epithelial plugs in the lumen. The neoplastic glands have a lining composed of two cell types, the basally located cells displaying morphologic features of myoepithelial and basal cells. They may be cuboidal, oncocytic, clear, spindled, or "hyaline" (see Fig. 6.8). The latter cells are also referred to as plasmacytoid myoepithelial cells and are frequently seen in pleomorphic adenomas. The stroma may have a nonspecific myxoid appearance, sometimes containing abundant elastic tissue or extensive adipose tissue; however, areas of clear-cut cartilaginous differentiation are usually found. There is convincing morphologic, ultrastructural, immunohistochemical, and molecular evidence to suggest that these mesenchymal elements share the same origin as the epithelial cells and that they represent modified myoepithelial cells. Ultrastructurally, a continuum of cytoplasmic features from epithelial to mesenchymal cells is also present.

Additional stromal changes seen in pleomorphic adenoma include osseous metaplasia and areas of fibrosis. Cutaneous adnexal differentiation can be seen in pleomorphic adenomas, especially those arising in the palate and lip. This is most commonly manifest as trichilemmal differentiation, infundibulocystic structures, and trichohyalin granules. Other substances sometimes found in pleomorphic adenomas include tyrosine-rich crystalloids in the myxoid
Figure 6.8 Microscopic appearance of benign mixed tumor. Epithelial and myoepithelial cells can be easily distinguished.

Figure 6.9 Benign mixed tumor. The myoepithelial cells are undergoing cartilaginous metaplasia and appear to “melt” into the chondromyxoid stroma they are producing.

Figure 6.10 Benign mixed tumor with a markedly hypercellular appearance.

areas, collagenous spherules, calcium oxalate crystals, intraductal birefringent crystalloids of unknown chemical composition, and melanin. Some benign pleomorphic adenomas are extremely cellular, the tumor cells being either round or spindle shaped (Fig. 6.10). Others may show cytologic atypia in the form of scattered large hyperchromatic nuclei (which have been shown to be polyploid). Follow-up studies have indicated that these tumors do not behave differently from the ordinary variety. The rarity of mitotic figures and absence of necrosis aid in the differential diagnosis with true malignant neoplasms. Something similar can be said of pleomorphic adenomas with foci that superficially resemble the adenoid cystic carcinoma pattern. The presence of these foci does not influence the prognosis and therefore should be disregarded.

Immunohistochemically, the ductal epithelial component is positive for keratin, EMA, and CEA. The keratins most frequently expressed are CK7, CK8/18, and CK19 (with or without CK14) in the luminal cells of the tubular structures, and CK14 in the abluminal cells. The myoepithelial component is immunoreactive for low-molecular-weight keratins (CK7, CK8/18, and CK14), actin, myosin, other smooth muscle-specific proteins, p63, p40, and sometimes S-100 protein. The latter marker is also strongly expressed in the cartilaginous areas and in subpopulations of the epithelial ductal cells. The demonstration in some of the tumors of glial fibrillary acidic protein and astroprotein, two glial markers, is more difficult to explain; it has been suggested that it is the result of cross-reactivity with other intermediate filaments of similar structure and chemical composition. Regardless of the reason for this occurrence, it seems to be related to the capacity of this tumor for cartilaginous differentiation, and it therefore may be useful in the differential diagnosis with adenoid cystic carcinoma and basal cell adenoma, in which such a differentiation does not occur.

Cytogenetically, pleomorphic adenoma shows distinctive chromosomal translocations involving 8q12 or 12q13–15. The PLAG1 gene at 8q12 can be fused with CTNNB1 (β-catenin), LFIR (leukemia inhibitory factor receptor), or SII (transcription elongation factor SII), or is overexpressed due to intrachromosomal 8q rearrangements. The HMGA2 gene at 12q13–15 can be fused with FHT (fragile histidine triad) or NFIB (nuclear protein involved in transcriptional regulation). Overexpression of p53 or mutation in the TP53 gene is rare in pleomorphic adenoma, in contrast to its malignant counterpart.

The recurrence rate of pleomorphic adenoma depends almost entirely on the adequacy of the primary excision, as several classic studies have conclusively demonstrated. Recurrence is very high if the tumor is removed by a simple enucleation (Fig. 6.11). This is because small inconspicuous nodules (pseudopodia) attached by threadlike filaments of neoplastic tissue may be present surrounding the main mass. They may have the shape and appearance of lymph nodes and may be mistaken for nodal metastases by both the surgeon and the pathologist. If the tumor is enucleated, these small remnants may be left behind and will provide the nidus for recurrence. Most of these recurrences will appear during the first 18 months after surgery, but others supervene over an exceedingly long period (50 years or more). Because of this, long-term follow-up is essential. It has been proposed that patients with tumor spillage at operation or residual tumor left behind should have radiation therapy immediately to minimize the possibility of recurrence. Usually the microscopic pattern of the recurrent tumor exactly mimics that of the original neoplasm (Fig. 6.12). Surgery for recurrent tumor often fails. In approximately one-fourth of cases, further recurrences develop, often in the form of multiple foci. The proper therapy for pleomorphic adenoma is its total surgical removal, along with a margin of normal salivary tissue that surrounds it. For the tumors located in the superficial lobe of the parotid gland, which represent the majority, the standard surgery is a superficial parotidectomy with...
Major and Minor Salivary Glands

Malignant Mixed Tumor

Two major categories of malignant mixed tumor exist. The first and more common can be viewed as a malignant transformation of a preexisting pleomorphic adenoma (carcinoma ex pleomorphic adenoma). This complication occurs in approximately 5%–10% of these neoplasms. Clinical features that suggest this event in a long-standing tumor are sudden increase in growth, pain, and facial paralysis. Documentation that a malignant salivary gland tumor arose from a preexistent pleomorphic adenoma may be difficult to obtain. The clinical history, although suggestive of the process, is not by itself diagnostic. It is necessary to have microscopic evidence of a previously existing benign tumor or to have benign and malignant tumor in the same neoplasm. This may require thorough sampling of the tumor. Sometimes the preexisting benign lesion is represented only by a totally hyalinized round nodule surrounded by carcinoma. Features said to indicate a greater likelihood of malignant transformation of a pleomorphic adenoma are submandibular (as opposed to parotid) location, long duration, older patient age, large tumor size, and—at the microscopic level—prominent zones of hyalinization and a moderate degree of mitotic activity.

The malignant component of this tumor typically has an epithelial appearance usually comparable to that of the luminal cells, less commonly that of the myoepithelial cells, or both (Fig. 6.13). It has been stated that these malignant areas often assume the appearance of one of the well-recognized variants of salivary gland carcinoma (such as mucoepidermoid carcinoma or adenoid cystic carcinoma), but salivary duct carcinoma and adenocarcinoma, not otherwise specified (N.O.S.) type, appear to be the most common. For example, in the series of Tortoledo et al., the malignant component was classified as salivary ductal carcinoma in 13 cases, undifferentiated carcinoma in 10, terminal duct carcinoma in 9, myoepithelial carcinoma in 3, and unclassified in 2. Most of the tumors have a poorly differentiated appearance. As a matter of fact, whenever a high-grade adenocarcinoma that is difficult to classify is found in the salivary gland, the possibility of it having arisen from a pleomorphic adenoma should be considered. In a high percentage of early cases the malignant change is restricted to foci of intraductal carcinoma, with an intact layer of neoplastic myoepithelial cells on the outside.
In most cases, the immunohistochemical profile of the malignant cells is comparable to that of the ductal luminal cells of the benign component.\textsuperscript{137} In the malignant areas there is often overexpression of TP53 (as a result of mutation) and of HER2.\textsuperscript{138–140} However, this is also true in a small subset of pleomorphic adenoma lacking malignant change.\textsuperscript{141} Genetic alterations that mediate malignant transformation may include amplification of genes at 12q13–15 (including CDK4, HMGA2, MDM2), TP53 mutation, or HER2 amplification.\textsuperscript{142–144}

LiVolsi and Perzin\textsuperscript{129} have pointed out that if the cytologically malignant foci are found entirely within a pleomorphic adenoma (i.e. intracapsular or in situ) they are not associated with clinical malignancy if the tumor is completely excised. Only when invasion occurs beyond the capsule of the original neoplasm will the lesion potentially behave clinically in a malignant fashion. For invasive tumors, the extent of invasion beyond the capsule is of importance: minimally invasive (≤1.5 mm from the tumor capsule) versus widely or frankly invasive (<1.5 mm), as defined by the WHO.\textsuperscript{7} In one series, all patients whose malignant neoplasms extended for more than 8 mm beyond the capsule died of tumor.\textsuperscript{130} Therefore, the importance of thorough sampling cannot be overemphasized. The prognosis also depends on the histologic type of carcinoma, the microscopic grade (which is related to the former), and the proliferative index.\textsuperscript{130,145}

The most common sites of metastases are regional lymph nodes, lungs, bone (especially the vertebral column), and abdominal organs.\textsuperscript{146}

The second type of malignant mixed tumor has a biphasic composition similar to that of pleomorphic adenoma, but both the epithelial and the mesenchyme-like elements have a malignant appearance, the former often in the form of a ductal carcinoma and the latter in the form of chondrosarcoma or undifferentiated pleomorphic sarcoma. Because no preexisting benign tumor is found, the designation of carcinoma ex pleomorphic adenoma, which has been suggested as an alternative term for malignant mixed tumor, is inappropriate.\textsuperscript{133} Names such as true malignant mixed tumor and carcinosarcoma have been proposed instead.\textsuperscript{147–149} This is an aggressive, often rapidly lethal neoplasm.

### Tumors With Oncocytic (Oxyphilic) Change

Oncocytes or oxyphilic cells are large ductal epithelial cells with a granular, deeply eosinophilic cytoplasm crowded with mitochondria.\textsuperscript{150} Their number in the normal salivary gland increases with age, and their secretory activity is minimal, suggesting that they are the expression of a degenerative change.\textsuperscript{151} Sometimes one finds multiple parotid cysts lined by oncocytic epithelium, associated with tyrosine crystals in the lumen.\textsuperscript{152} In other instances, oncocyes form well-defined clusters scattered throughout the gland. It is not clear whether these clusters represent an exaggeration of the age-related hyperplastic process or the emergence of a neoplasm, an uncertainty reflected by the terms that have been used to designate this process: oncocytosis,\textsuperscript{153} multinodular oncocytoma,\textsuperscript{154} multinodular oncocytic hyperplasia, and multifocal adenomatous oncocytic hyperplasia.\textsuperscript{155,156}

The two major tumor types composed of oncocites are oncocytic adenoma and Warthin tumor.\textsuperscript{157,158} There are no transitional forms between these two tumors, suggesting that their pathogenesis is different.

### Oncocytic Adenoma and Oncocytic Carcinoma

Oncocytic adenoma (oncocytoma; oxyphilic adenoma) is defined, since the classic works of Hamperl, as a benign tumor exclusively composed of oncocytic cells.\textsuperscript{193} The majority occur in the parotid, but they are also well documented in the submandibular gland.\textsuperscript{160} In one large series, 20% of patients had either a history of radiation therapy to the region or of long-term occupational exposure.\textsuperscript{161} Grossly, the tumor presents as a solid, well-circumscribed mass, usually small and with a characteristic tan or brown color (Fig. 6.14). Microscopically, it is composed of large cells with small, central, round nuclei and abundant granular acidophilic cytoplasm (Fig. 6.15). Ultrastructurally, the cytoplasm is packed with mitochondria (Fig. 6.16). Mitotic figures are absent, and cellular transition from...
normal lining cells of the ducts may be seen. Occasionally, the cells undergo a clear change as a result of cytoplasmic glycogenation. The lumen of the glandular spaces formed by these tumors may contain psammoma bodies or tyrosine-rich crystals. Focal collections of oncocytes may be present in the adjacent normal gland. Local excision is usually curative. The tumor cells diffusely express keratin, and p63 highlights a subset of the cells in a distribution suggestive of basal-type cells. The latter is helpful in distinguishing oncocyto adenoma from metastatic renal cell carcinoma, which are always p63 negative.

The presence of cytoplasmic mucin or of mucin-containing cystic spaces is not a typical feature of oncocyto adenoma but can be seen occasionally; such a finding should raise the suspicion that the tumor is an oncocyto variant of mucoepidermoid carcinoma (see later). Occasionally, multiple oncocyto nodules, often with clear cell change, can be appreciated. In these cases, the term multinodular oncocyto hyperplasia is appropriate.

**Oncocyto carcinoma** (malignant oncocyto; oxyphilic carcinoma) is the malignant counterpart of oncocyto adenoma, a tumor type so rare as to represent a pathologic curiosity. It is characterized by cytologic atypia, mitotic activity, and infiltrative growth. These are typically high-grade neoplasms with aggressive clinical behavior.

**Warthin Tumor**

Warthin tumor (cystadenoma lymphomatous papilliferum) is found exclusively in the parotid gland and periparotid lymph nodes. Warthin tumor is more common in males, and a near-universal relationship with smoking has been found. It is often multicentric and is bilateral in 10%–15% of cases. It comprises 70% of all bilateral salivary gland neoplasms. Grossly, it appears as a lobulated brown mass and has a typical multicystic appearance, with fluid-filled spaces filled with dark brown fluid (often likened to motor oil) (Fig. 6.17). Occasionally the entire tumor undergoes necrotic changes consistent with hemorrhagic infarct. These changes can occur spontaneously but are more common following fine-needle biopsy.

Microscopically, lymphoid tissue is prominent, often with germinai centers; this has led to the time-honored suggestion that the lesion originates from excretory ducts located within intraparotid lymph nodes (Fig. 6.18). This lymphoid stroma is predominantly composed of B lymphocytes, but it also contains T lymphocytes, mast cells, and S-100 protein-positive dendritic cells. Covering the surface of this lymphoid tissue are large epithelial cells with oncocyto features, similar in most respects to those seen in oncocyto adenoma (Fig. 6.19). These cells are arranged in two layers, with some morphologic and immunohistochemical differences between them. The luminal cells are more columnar and the outer cells more polygonal. Both stain equally with keratin, and the outer cells are p63 positive, suggesting a basal cell phenotype. These oncocyto cells are also reactive for mitochondria-associated markers (Fig. 6.20). The keratins

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**Figure 6.16** Electron micrograph of oxyphilic adenoma showing cytoplasm packed with mitochondria (arrow). A portion of the nucleus (N) is at bottom right. (×31,000.)

**Figure 6.17** Gross appearance of Warthin tumor of parotid gland. The presence of multiple large cystic spaces is characteristic of this lesion. (Courtesy of Dr. J. Carvalho, Ann Arbor, MI.)

**Figure 6.18** Low-power appearance of Warthin tumor. Germinal centers are very prominent.
expressed are those typical for columnar differentiation, that is, CK7, 8, 18, and 19.177 Mucin-secreting cells and groups of sebaceous cells may also be present.178,179 There is no evidence for a myoepithelial cell component.180 Occasionally, the lymphoid component is scanty or absent.181 By electron microscopy, the cytoplasm of the granular epithelial cells is packed with mitochondria.

The cases associated with infarct-like necrosis may exhibit focal squamous metaplasia (see Fig. 6.19B), sometimes with features analogous to those of necrotizing sialometaplasia in the oral cavity,112 and are just as likely to be overinterpreted as squamous cell carcinoma.143

The typical treatment of Warthin tumor is surgical excision; the incidence of local recurrence is extremely low.

Malignant transformation of Warthin tumor is a rare event but has been documented both in terms of the lymphoid component evolving into malignant lymphoma143-145 and the epithelial component evolving into adenocarcinoma, mucoepidermoid carcinoma, squamous cell carcinoma, oncocytic carcinoma, Warthin adenocarcinoma,146 or Merkel cell carcinoma.147-149

Warthin tumor has been generally regarded as a true neoplasm, hence its inclusion in this section. However, some have made the suggestion that it may belong instead to the group of acquired multicyastic reactive conditions of the head and neck that also includes benign lymphoepithelial cyst and other lesions of branchial pouch derivation.42 The fact that the epithelial component of this lesion has been found to be polyclonal and that it tends to be associated with salivary ductal inclusions in parotid lymph nodes support this contention.191,192 If this interpretation is correct, one should regard the parotid lesions having a multicyastic oncocytic-lined component but lacking a lymphoid stroma (oncocytic papillary cystadenomas) as belonging to a different category.166

“Monomorphic” Adenoma

The outdated term monomorphic adenoma was originally proposed for any benign epithelial salivary gland tumor other than pleomorphic adenoma. It therefore included tumors as disparate as oncocytic adenoma, Warthin tumor, sebaceous lymphadenoma, canalicular adenoma, and basal cell adenoma.193,194 The very inclusiveness of the term when so defined, and the fact that some people have used it instead as a synonym for only one member of the group (i.e. for basal cell adenoma), has resulted in confusion. Therefore it is probably advisable to regard monomorphic adenoma not as a specific pathologic diagnosis but rather as the expression of a nosologic grouping.195

The term “monomorphic adenoma” does not appear in the new WHO classification of salivary gland tumors and should not be used as a specific pathologic diagnosis.79

Basal Cell Adenoma and Adenocarcinoma

Basal cell adenomas usually occur in adult patients, and there is a slight predilection for females.186 Most cases occur in the
parotid but a few have been reported within periparotid lymph nodes, as well as in minor salivary gland sites. Grossly, these tumors are encapsulated and often cystic; as a group, they tend to be smaller than pleomorphic adenomas. Microscopically, they are composed of basaloid epithelial cells, arranged in a variety of architectural patterns, and lacking in cartilage and chondromyxoid stroma. This acknowledges the fact that pleomorphic adenomas and basal cell adenomas have overlapping histology. Most basal cell adenomas have scattered ductal structures filled with eosinophilic secretions. The ducts undergo cystic change. Surrounding the ducts are varying amounts of basaloid cells that may have a true basal cell immunophenotype, as well as true myoepithelial cells. Therefore, these tumors contain varying amounts of ductal, basal, and myoepithelial cells. An important distinguishing feature seen in most basal cell adenomas is the palisading at the periphery of the epithelial nests, also giving the tumor a “basaloid” appearance. The pattern of growth may be predominantly tubular, trabecular, cribriform, or solid. In a variant of the latter designated as membranous or dermal analogue tumor, there is deposition of abundant basal lamina material around and within the epithelial nests, in a pattern nearly identical to that of the cutaneous sweat gland tumor known as eccrine dermal cylindroma (Fig. 6.21). Actually, there have been cases of multiple dermal cylindromas coexisting with multiple parotid tumors with the same microscopic appearance. Furthermore, the same cytogenetic abnormality in the chromosome 16q region has been found in the two tumors. The mutated gene involved in this syndrome (Brooke–Spiegler syndrome) is the CYLD gene, which can also be mutated in sporadic basal cell adenomas.

**Basal cell adenocarcinoma** is the malignant counterpart of basal cell adenoma. Like its benign counterpart, it can arise either in the major or the minor salivary glands. It has a similar architecture and immunohistochemical profile, but it differs by virtue of its infiltrative quality, perineurial spread, and vascular invasion, as well as a variable degree of cytologic atypia and mitotic activity. Although most basal cell adenocarcinomas are cytologically low grade, high-grade examples do occur. It also tends to express p53, BCL2, and epidermal growth factor receptor (EGFR), but this is not necessarily helpful in the diagnosis. The parotid gland is the predominant site, and the peak incidence is in the sixth decade of life. Solid, membranous, trabecular, and tubular patterns of growth have been described. The aggressiveness of the tumor can be manifested by local recurrence or metastases to the lymph nodes and lung. Like its benign counterpart, it can be associated with dermal cylindromas in the Brooke–Spiegler syndrome.

### Canalicular Adenoma

Another tumor formerly considered a variant of monomorphic adenoma is characterized by the presence of bilayered strands or ribbons of columnar epithelial cells separated by a loose, well-vascularized, paucicellular-myxoid stroma. This has been referred to as canalicular adenoma and is now regarded as an entity separate from basal cell adenoma because of its unique morphology and immunophenotype and greater tendency to arise from intraoral minor salivary glands. The “canalicular” description stems from the appearance imparted by the bilayered epithelial cells alternately opposing each other (Fig. 6.22). In some tumors, nodules of basaloid cells are present in between the columnar epithelial cells. A unique feature of canalicular adenomas is diffuse S100 reactivity. They are strongly positive for cytokeratin and have weak and focal staining.

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**Figure 6.21** Basal cell adenoma of parotid gland. The appearance is reminiscent of that of a skin adnexal tumor (cylindroma).

**Figure 6.22** Canalicular adenoma of the buccal minor salivary glands. 

A, Parallel rows of columnar epithelial cells appose each other in areas imparting a beaded or canalicular pattern. The stroma is scant and predominantly myxoid. B, The columnar cells are uniform and cytologically bland.
with p63 and myoepithelial markers at most. A vast majority of canalicul ar adenomas occur in the upper lip (80%) and buccal mucosa (10%) of adults. They are benign neoplasms that rarely recur with complete excision.

The main differential diagnosis of basal cell adenoma is with basal cell adenocarcinoma (see later discussion), pleomorphic adenoma, and adenoid cystic carcinoma. Basal cell adenoma lacks the chondromyxoid mesenchyme-like component of pleomorphic adenoma. In contrast to adenoid cystic carcinoma, it is encapsulated and devoid of stromal and perineurial invasion. Immunohistochemically, the duct-lining cells express keratins and CEA with variable S-100 protein reactivity; the basloid cells in the trabecular and solid areas express vimentin, actin, and p63, indicative of myoepithelial cell participation. Basal cell adenoma behaves in a benign fashion, analogous to that of pleomorphic adenoma, and excision is curative. The recurrence risk is not as high as it is for pleomorphic adenomas with the exception of the membranous type in which up to 25% of tumors recur.

Malignant transformation of basal cell adenoma is a rare but well-documented event; the membranous type is said to be particularly at risk (up to 25%). In six cases of this phenomenon reported by Luna et al., the malignant component was diagnosed as adenoid cystic carcinoma in three and as basal cell adenocarcinoma in the other three.

**Tumors With Sebaceous Differentiation**

Cells of a sebaceous type are often found within otherwise normal parotid glands. They are also found in a variety of salivary gland tumors. They are relatively common in Warthin tumor but may also appear in pleomorphic adenoma, mucoepidermoid carcinoma, adenoid cystic carcinoma, and epithelial–myoepithelial carcinoma.

Benign tumors with a predominant sebaceous component have been designated as sebaceous adenoma when pure and sebaceous lymphadenoma when accompanied by a prominent lymphoid stroma (Fig. 6.23). The latter tumor may present as a unilocular cystic mass on gross inspection. When the tumor contains the same admixture of epithelial glandular cells and lymphocytes but lacks sebaceous differentiation, it is simply designated as lymphadenoma. Rare malignant counterparts of these tumors exist; these have been called sebaceous carcinoma and sebaceous lymphadenocarcinoma, respectively.

**Tumors With Myoepithelial Differentiation**

Myoepithelial cells are a component of many types of benign and malignant salivary gland tumors, particularly pleomorphic adenoma, epithelial–myoepithelial carcinoma, adenoid cystic carcinoma, and basal cell neoplasms. Benign neoplasms composed exclusively of myoepithelial cells are referred to as myoepitheliomas. Grossly, they are well circumscribed and typically encapsulated. A variety of morphologic types have been described: spindle cell, hyaline (plasmacytoid), epithelioid, and clear cell. However, it should be noted that combined and intermediate forms exist, and that the myoepithelial nature of the hyaline cell type has been questioned by some.

The spindle cell type tumors have a stromalike appearance and can be confused with lesions of fibroblasts, Schwann cells, or smooth muscle cells (Fig. 6.24). The epithelioid type is composed of uniform round cells with moderate amounts of cytoplasm. As with other myoepitheliomas, immunohistochemical demonstration of myoepithelial differentiation is required to confirm the diagnosis. In the variant known as oncocytic myoepithelioma, the cytoplasm has a granular oxyphilic quality. In all myoepitheliomas, collagen stroma is scanty, microcystic formations may be present, and various degrees of secondary myxoid change or lipomatosus metaplasia of the stroma may be seen. Collagenous crystalloids may be present in some tumors. Ultrastructurally and immunohistochemically, microfilaments of both actin and keratin type can be demonstrated (Fig. 6.25). Most myoepitheliomas also demonstrate p63 and p40 reactivity, whereas S100 can be positive or negative. The hyaline (plasmacytoid) cell–type tumors are composed of cells with eccentric nuclei, some degree of pleomorphism and hyperchromasia, but scanty or no mitotic activity. The cytoplasm is abundant, with a diffuse eosinophilia that is very different from the fine granular quality seen in oncocytes. The cell margins are polygonal and sharply outlined (Fig. 6.26). The appearance of hyaline cells may simulate that of neoplastic plasma cells or even skeletal muscle cells. Ultrastructurally, their main feature is the presence of abundant, uniformly dispersed microfilaments measuring 50–100 Å in diameter. Although this type has ultrastructural evidence of myoepithelial differentiation, they are typically negative for traditional myoepithelial markers (actin, p63) but do stain with keratin and S-100. The clear cell type tumors are composed of sheets or nests of small cuboidal cells with moderate amounts of...
of clear cytoplasm. These clear cells contain variable amounts of glycogen but no fat or mucin.

Immunohistochemically, in general, the neoplastic myoepithelial cells show reactivity for keratin, both forms of S-100 protein, p63, p40, actin, and, in some cases, vimentin, calponin, and myosin. Although most myoepitheliomas are reportedly negative for EWSR1 rearrangements, clear cell myoepithelial carcinomas show EWSR1 gene rearrangements in approximately 40% of cases.

Tumors With Clear Cell Change

As is true in most other organs, clear cell–containing neoplasms of the salivary gland do not constitute a homogeneous or specific type. In the presence of such feature, the differential diagnosis should include clear cell myoepithelioma and myoepithelial cell tumors with clear cell change. These tumors are not limited to specific gland sites and are not necessarily associated with any particular age group. They represent a spectrum of differentiation with both benign and malignant variants. The majority of cases with a hyaline cell morphology have behaved in a benign fashion, although well-documented exceptions exist. Many malignant examples of the spindle cell and particularly of the clear cell types have been described. Malignant tumors have been referred to as both malignant myoepithelioma and myoepithelial carcinoma. In general, these have been characterized by infiltrative growth, increased cellularity, mitotic activity, necrosis, and cytologic atypia. A frequent growth pattern is composed of large invasive lobules with central necrosis. These malignant myoepitheliomas can arise de novo or as a malignant transformation of a myoepithelioma, benign mixed tumor, or a basal cell adenoma. They are uncommon, accounting for approximately 2% of salivary gland malignancies. They are most common in the parotid gland but can be seen in all salivary gland sites. Although no formal grading system exists, tumors with high mitotic activity, necrosis, and pleomorphism tend to behave as high-grade carcinomas. Following treatment, approximately one-third of patients will die of disease, one-third will be alive with disease, and one-third will be alive and disease free. Although most myoepitheliomas are reportedly negative for EWSR1 rearrangements, clear cell myoepithelial carcinomas show EWSR1 gene rearrangements in approximately 40% of cases.

Figure 6.25 Electron micrograph of a myoepithelioma of parotid gland. Portion of a neoplastic myoepithelial cell illustrating (left to right) extracellular space with collagen fibrils and basement membrane, electron-dense attachment plaques on the cell membrane, linear arrays of 6-nm actin microfilaments, perinuclear bundles of tonofilaments (indicative of squamous metaplasia), and a portion of the nucleus. (×22,900.) (Courtesy of Dr. Robert A. Erlandson, Memorial Sloan-Kettering Cancer Center.)

Figure 6.26 Myoepithelioma composed of so-called hyaline cells. (A, H&E; B, keratin; C, S-100 protein.)
carcinoma (positive for glycogen), sebaceous neoplasms (positive for fat), mucoepidermoid carcinoma (positive for mucin), acinic cell carcinoma, clear cell change in oncocytic tumors, and metastatic renal cell carcinoma. There are some malignant salivary gland tumors composed of clear cells that cannot be placed into any of those categories and for which the descriptive term clear cell carcinoma has been used. Most of these tumors occur in the oral cavity rather than in the major salivary glands and are accompanied by a prominent fibrohyaline stroma (hence the proposed term hyalinizing clear cell carcinoma for them).

Epithelial–myoepithelial carcinoma is an uncommon salivary gland carcinoma that most often occurs in the parotid gland but can occur in other major salivary glands and minor salivary gland sites, especially the sinonasal region. As the name implies, they are composed of a dual population of eosinophilic ductal cells surrounded by myoepithelial cells that most often have prominent clear cytoplasm (Fig. 6.27). The proportions of ductal and myoepithelial cells varies from tumor to tumor. The stroma can be scant but often contains variable amounts of myxoid and/or basement membrane–type material. Because most are low-grade, demonstration of infiltrative growth is required to make this diagnosis. Some tumors can have significant mitotic activity, pleomorphism, and necrosis. The invasive lobules are typically solid, but papillary and cystic growth patterns are not uncommon. Several “variants” have recently been described, including double clear, oncocytic-sebaceous, and apocrine. In addition, some may arise in a preexisting pleomorphic adenoma (carcinoma ex pleomorphic adenoma). The ductal cells react with low-molecular-weight cytokeratin, whereas the myoepithelial cells react with high-molecular-weight cytokeratin, p63, p40, actin, and calponin. S-100 staining, as is often the case in salivary gland neoplasia, is unpredictable. Although approximately 40% of tumors recur, metastases are seen in only 15% (mostly cervical lymph nodes) and disease-related mortality is less than 10%, with 5-year survival rates of 80%.

Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma is the most common salivary gland malignancy. Most cases of mucoepidermoid carcinoma are located in the parotid gland, and half of cases occur in the major salivary glands (Fig. 6.28). They also arise from minor salivary gland sites with the palate, buccal mucosa, and tongue being relatively common sites. This lesion also represents the most common malignant salivary gland tumor in children. Microscopically, three main cell types can be identified: mucin-producing, squamous (epidermoid), and intermediate (Fig. 6.29). The intermediate cells tend to predominate and are characterized as small cuboidal cells with minimal eosinophilic cytoplasm, resembling basal cells. The three cell types are
present in variable proportions from tumor to tumor and can form sheets and nests with duct-like structures or cysts. The better differentiated forms present grossly as a relatively well-circumscribed mass with cystic areas containing mucinous material (Fig. 6.30). Microscopically, well-differentiated mucinous cells predominate in these low-grade lesions. The high-grade varieties are more solid and have a more infiltrative pattern of growth. In the high-grade tumors, squamous and intermediate predominate over the mucin-producing cells. It should be pointed out that marked nuclear atypia, frequent mitoses, extensive keratinization, and extensive necrosis are not typical of mucoepidermoid carcinoma of any grade. When these features are present, the alternative possibilities of poorly differentiated adenocarcinoma and adenocarcinoma should be considered.

Morphologic variants of mucoepidermoid carcinoma include forms with a component of sebaceous cells, cases with prominent oncotic change (oncotic mucoepidermoid carcinoma), tumors with extensive clear cell change, forms with intense sclerosis of the stroma (sclerosing mucoepidermoid carcinoma), and an extremely rare variant characterized by sclerosis, focal epidermoid features, and eosinophilic infiltration (sclerosing mucoepidermoid carcinoma with eosinophilia), the latter being similar to the homonymous tumor of the thyroid gland. In addition, cases of mucoepidermoid carcinoma with a dedifferentiated component have been reported, the change being accompanied by an accelerated clinical course.

When the mucin or keratin formed by mucoepidermoid carcinoma escapes into the interstitial tissue, it causes an inflammatory reaction. Although true post-traumatic sialoceles and mucoceles certainly occur, in the presence of mucin-filled cystic spaces in the parotid region the possibility of a well-differentiated mucoepidermoid carcinoma should always be ruled out by taking additional sections. Sometimes, extensive fibrosis accompanies the spillage of mucin.

Immunohistochemically, simple mucin-type carbohydrate antigens (T, Tn, and sialosyl-Tn) have been detected in this tumor. The mucins expressed by mucoepidermoid carcinoma include MUC1, MUC2, MUC4, MUC5AC, and MUC5B, but not MUC3 (which is expressed instead by adenoid cystic carcinoma; see later). Significantly, MUC1 predominates in the high-grade tumors, whereas MUC4 is more prevalent in low-grade tumors.

In terms of keratin expression, the usual profile of mucoepidermoid carcinoma is CK7+/CK14+/CK20−. The pattern of staining with these markers recapitulates that of normal striated duct cells. Myoepithelial cell markers are usually negative and focal with weak staining if present. The exception is p63, which is positive in the epidermoid and intermediate cells.

In a majority of cases of mucoepidermoid carcinomas, a distinctive chromosomal translocation t(11;19)(q21;p13), which fuses the CRTC1 (formerly known as MECT1) gene with the MAML2 gene, is found. The translocation results in activation of the Notch pathway. Of interest, mucoepidermoid carcinomas occurring in other sites, such as skin, breast, lung, and cervix, have also demonstrated the CRTC1 translocation. In 6% of cases, CRTC3–MAML2 gene fusion is present instead of CRTC1–MAML2. Mucoepidermoid carcinomas harboring CRTC1–MAML2 or CRTC3–MAML2 fusion exhibit a more favorable prognosis compared with those lacking the gene fusion.

There is a marked difference in prognosis depending on the grade of the tumor, whether one uses the traditional two-tier system (low grade and high grade) or the three-grade scheme proposed by the Armed Forces Institute of Pathology (AFIP) authors, which is the one currently favored. This is based on a weighted points system: cystic component less than 20%, 2 points; neural invasion, 2 points; necrosis, 3 points; four or more mitoses per 10 high-power fields, 3 points; anaplasia, 4 points. A total score between 0 and 4 defines a low-grade tumor, a score of 5–6 applies to an intermediate-grade tumor, and a score of 7 or more indicates a high-grade tumor.

In the series reported by Jakobsson et al., the determinate 5-year survival rate was 98% for the low-grade variety and 56% for the high-grade variety. Most of the latter tumors showed their malignant behavior within the first 5 years after surgery, in contrast with the continuous fall in survival rate over a 20-year period seen with adenoid cystic carcinoma and acinic cell carcinoma. In another series involving 69 cases, all but 2 of the 14 deaths and all 6 instances of distant metastases occurred in high-grade tumors, which were also associated with an increased incidence of local recurrence and regional lymph node metastases. A correlation has also been found between prognosis and the following parameters: age (better in younger patients), gender (better in females), location (better in the parotid than in the submandibular gland), extraglandular extension, vascular invasion, necrosis, mitotic rate, cell proliferation as measured by MIB-1 antibody, DNA ploidy, and activation of the ERK-1/ERK-2 pathway.

Acinic Cell Carcinoma and Mammary Analogue Secretory Carcinoma

Acinic cell carcinoma comprises 1%–3% of all salivary gland tumors. There is a male predominance and a peak incidence in the fifth decade of life, but there is a broad age distribution. In fact, following mucoepidermoid carcinoma, it the second most common salivary gland malignancy in children. It is the most common bilateral salivary gland malignancy. A few familial cases have been described. The majority (80%) are located in the parotid gland, but many examples in the minor salivary glands have been recorded.

Grossly, the tumor presents as an encapsulated round mass with a solid, friable, grayish-white cut surface, usually measuring less than 3 cm in diameter. Occasionally it undergoes marked cystic degeneration.

The microscopic appearance shows considerable variation from case to case. The pattern of growth may be predominantly solid, microcystic, papillary–cystic, or follicular. There is also marked variability in the appearance of the tumor cells. The most characteristic cell, known as acinic, has a cytoplasmic appearance (granular and basophilic) and ultrastructural morphology analogous to that of acinic cells of normal salivary glands (Fig. 6.31). The cytoplasmic granules demonstrate periodic acid–Schiff (PAS) positivity that is...
Acinic cell carcinoma. The cells have an abundant cytoplasm filled with basophilic zymogen granules.

A particularly ominous but fortunately rare event in acinic cell carcinoma is the emergence of an anaplastic (dedifferentiated) component in the form of a high-grade adenocarcinoma, poorly differentiated carcinoma, or undifferentiated carcinoma. This development is associated with aneuploidy on flow cytometry, appearance of peculiar helioid inclusions at the ultrastructural level, and an accelerated clinical tempo. TP53 gene mutation and HER2 amplification have not been detected in dedifferentiated acinic cell carcinoma.

Mammary analogue secretory carcinoma is a recently described salivary gland carcinoma that was frequently diagnosed as acinic cell carcinoma but is now known to be a distinct entity that is identical to secretory carcinoma of the breast, confirmed by the morphologic, immunohistochemical, and genetic similarities between the two entities. The entity was reported by Skalova et al., taking advantage of the fact that mammary secretory carcinoma is associated with the t(12;15)(p13;q25) translocation leading to the ETV6–NTRK3 gene fusion. Given the histologic similarity to acinic cell carcinoma, a key question, of course, was whether acinic cell carcinoma of salivary glands carried the same translocation. Reis-Filho et al. working with 14 suitable cases, found the same cytogenetic aberration in all of them (but not in conventional acinic cell carcinomas or other salivary gland tumors). On the basis of this remarkable finding, the authors postulated the existence of a distinct entity among salivary gland tumors that they proposed to call mammary analogue secretory carcinoma of salivary glands (MASC). Most occur in the parotid gland, but intraoral minor salivary gland sites can also be involved. Morphologically, the cases representing this new entity are characterized by the presence of microcystic and glandular spaces with abundant eosinophilic secretion positive for PAS, mucicarmine, MUC1, MUC4, and mammaglobin (Fig. 6.32). The cells have an apocrine appearance with vacuolated, eosinophilic cytoplasm and uniform vesicular nuclei with small nucleoli (Fig. 6.33). Similar to mammary secretory carcinoma of the breast, the cells are positive for cytokeratin, S-100 protein, BRST-2, and mammaglobin but negative for androgen receptor, p63, and DOG-1. They are low-grade carcinomas that recur in approximately 30% of cases but only rarely metastasize or result in death. Rare examples with high-grade transformation (dedifferentiation) have been described and behave more aggressively.
Adenoid Cystic Carcinoma

Adenoid cystic carcinoma is a generally slow-growing but highly malignant neoplasm with a remarkable capacity for recurrence. In the parotid gland it is less common than mucoepidermoid carcinoma and acinic cell carcinoma, but in the minor salivary glands it is the most common malignant tumor.

Grossly, it usually has a solid appearance and an infiltrative pattern of growth, although some examples can be well circumscribed. Microscopically, the typical adenoid cystic carcinoma has a pattern described as cribriform: nests and columns of cells of rather bland appearance are arranged concentrically around glandlike spaces ("pseudocysts") filled with homogeneous eosinophilic PAS-positive material or granular myxoid material (Figs. 6.34 and 6.35). Most of these are not true glandular spaces; they represent instead extracellular cavities containing reduplicated basal lamina material and mucin produced by the tumor cells (Fig. 6.36). Small true glandular lumina are also formed. Indeed, identification of both pseudocysts and true glandular lumina is required to make a diagnosis of adenoid cystic carcinoma. The rare small glandular lumina are lined by a monolayer of eosinophilic epithelial cells. These are surrounded by varying amounts of small myoepithelial cells with scant cytoplasm and hyperchromatic, angulated nuclei. This tumor has a remarkable tendency for invasion of perineurial spaces, to the degree that the diagnosis of adenoid cystic carcinoma should be questioned if an adequate sample taken from the periphery of the tumor does not exhibit this feature (Fig. 6.37).

Some adenoid cystic carcinomas have a predominantly tubular pattern of growth, whereas others are mainly solid and yet others (exceptionally rare) are sclerosing. The solid pattern is characterized by overgrowth of the epithelial (glandular) component and frequently displays more mitotic activity with increased cytologic atypia with or without small foci of necrosis. Combined patterns of growth are common, whether in the original tumor or in the recurrences (Fig. 6.38).

Immunohistochemically, the tumor cells located in recognizable duct structures express a phenotype similar to that of the intercalated duct (positive for keratin, CEA, lysozyme, lactoferrin, α1-antichymotrypsin, S-100 protein, and CD117 [c-KIT]), and those around pseudocysts have a phenotype suggestive of myoepithelial cell differentiation (positive for S-100 protein, p63, and actin and variably positive for keratin).

Cytogenetically, there is a high incidence of loss of heterozygosity (LOH) at chromosome 6q23–35. Alterations of TP53 are
uncommon, except in dedifferentiated cases (see later). A microarray analysis has demonstrated the common expression of genes indicative of myoepithelial differentiation, transcription factors 50 \times 4 and AP-2\(\gamma\), and members of the Wnt/β-catenin signaling pathway. A proportion of cases (approximately 30%) of adenoid cystic carcinomas exhibit a distinctive chromosomal translocation resulting in MYB–NKIB fusion.

The differential diagnosis with benign mixed tumor can be difficult. Important points to remember are that adenoid cystic carcinoma is invariably invasive and often associated with perineural invasion, and that chondromyxoid stroma and foci of squamous metaplasia are consistently absent. In addition, papillary growth and true cyst formation are not a feature of adenoid cystic carcinoma.

Another important differential diagnosis is with polymorphous low-grade adenocarcinoma, which is rendered easier by the realization that the latter is almost nonexistent in the major salivary glands. At the microscopic level, the nuclei of adenoid cystic carcinoma tend to be hyperchromatic and angulated rather than bland and uniform. Furthermore, as already stated, adenoid cystic carcinoma is usually strongly immunoreactive for CD117 (c-KIT), whereas polymorphous low-grade adenocarcinoma is either negative or shows a lesser intensity of staining. The latter fact makes this stain suboptimal as a distinguishing feature. In contrast, diffuse S-100 protein staining would support a diagnosis of polymorphous low-grade adenocarcinoma over adenoid cystic carcinoma, whereas strong p63 staining would support the latter.

Because the prognosis of adenoid cystic carcinoma is greatly influenced by its pattern of growth, this feature has been used as a grading system. In one series, the recurrence rate was 59% for the tubular tumors, 89% for the classic cribriform lesions, and 100% for the solid variety. In another series in which a somewhat similar grading system was used, the cumulative survival rates at 15 years were 39%, 26%, and 5%, respectively. The solid or anaplastic type of adenoid cystic carcinoma is associated with a higher incidence of metastases and a rapid clinical course.

Based on these findings, adenoid cystic carcinomas can be graded as follows: grade 1—tubular or mixed cribriform and tubular; grade 2—pure cribriform or those with a solid component less than 30%; grade 3—tumors with 30% or more solid component. A behavior just as aggressive (if not more so) is to be expected in the rare instances in which a conventional adenoid cystic carcinoma undergoes dedifferentiation or high-grade transformation, an event that is accompanied by TP53 gene mutation. Other factors that influence the prognosis of adenoid cystic carcinoma are stage (very important), presence of tumor at the margins, anatomic site, size of the primary lesion, degree of atypia, and lymph node metastases.

Adenoid cystic carcinomas frequently metastasize to the lungs. These metastases are usually silent, and it is not unusual to find multiple nodules in the chest x-ray film of a totally asymptomatic individual. Lymph node metastases are rare, at least at the time of the initial presentation; many of them seem to represent direct extension from the perinodal soft tissues rather than true embolic deposits.

In the treatment of adenoid cystic carcinoma, a radical surgical approach should be used, no matter how well differentiated the tumor appears under the microscope. Cures after tumor recurrence are very difficult to achieve. Radiation therapy is rarely curative, but it may improve results when combined with surgery, and it may produce excellent temporary regression of inoperable recurrences.

### Salivary Duct Tumors

**Salivary duct papilloma** usually arises within minor salivary glands, but a few cases have been reported in the parotid.

**Salivary duct carcinoma** is usually seen in elderly males, most commonly in the parotid gland but also in the submandibular gland. Some cases develop on the basis of a preexisting pleomorphic adenoma and salivary duct carcinoma is the most common carcinoma seen in carcinoma ex pleomorphic adenoma. Microscopically, it resembles high-grade in situ and invasive apocrine ductal carcinoma of the breast, whether comedo, solid, cribriform, papillary, invasive micropapilllary, mucinous (mucin-rich), the usual invasive form, or even sarcomatoid (Fig. 6.39). In other words, it spans the same wide range of differentiation as its more common mammary counterpart. The immunohistochemical profile is similar to that of a ductal-type adenocarcinoma and just as diverse as its morphologic appearance. There is expression of keratin (including low- and high-molecular-weight keratins), HER2/neu (approximately 40% of cases), CEA, and EMA. It also frequently expresses androgen receptors (approximately 90%) but negative for estrogen receptor. Some tumors express CD117 (c-KIT), GDFP-15 (especially in the intraductal component), and prostate-specific antigen and other prostate-related markers.
Polymorphous Low-Grade Adenocarcinoma

Polymorphous low-grade adenocarcinoma is usually restricted to the minor salivary glands of the oral cavity and is therefore discussed in Chapter 4.397–399 Those occurring in the major salivary glands nearly always arise against a background of benign mixed tumor,400,401 but rare primary examples do occur.402,403 The main differential diagnosis is with adenoid cystic carcinoma and benign mixed tumor.402,403

Cystadenocarcinoma (Papillary Cystadenocarcinoma)

Cystadenocarcinoma comprises less than 3% of all parotid tumors, but they also occur in the sublingual gland.363,404 It may grow large and be accompanied by hemorrhage and necrosis. Similar cases have been described in the oral cavity.405,406 The presence of invasive cystic nodules with well-defined papillary structures is the most important distinguishing feature. Mucin production is usually present, but there are no squamous or intermediate...
components (Fig. 6.42). If there is a prominent papillary component, the tumors can be designated as (papillary) cystadenocarcinoma. Sometimes the malignant papillary component is a focal feature in an otherwise benign-looking mucinous cystadenoma. The differential diagnosis includes mucoepidermoid carcinoma, acinic cell carcinoma, the papillary subtype of polymorphous low-grade adenocarcinoma, and metastatic carcinoma, particularly from the thyroid. Blanck et al. divided their cases into high- and low-grade varieties based on the presence or absence of stromal invasion. The former had a poor prognosis, comparable with that of adenoid cystic carcinoma, whereas the latter did not differ prognostically from low-grade mucoepidermoid carcinoma.

**Squamous Cell Carcinoma**

Most squamous cell carcinomas in the parotid region represent metastases in the intraparotid lymph nodes of tumors located in the oral cavity, some other region in the upper aerodigestive tract, or the skin.

True pure squamous cell carcinomas of the salivary gland are very rare. Some represent the malignant component of a mixed tumor; others are predominantly squamous cell types of high-grade mucoepidermoid tumors, as shown by their focal positivity for mucin stains. An in situ malignant ductal component has been occasionally encountered and can support the concept of primary salivary gland squamous cell carcinoma but could also represent secondary invasion from a metastasis. These tumors grow rapidly and infiltrate surrounding structures. The treatment of choice is radical surgery, but radiation therapy is also effective. The overall 5-year survival rate in a series of 18 cases from the Mayo Clinic was 50%.412

**Small Cell Carcinoma and Other Neuroendocrine Carcinomas**

There are malignant tumors of the salivary gland that are entirely composed of a solid population of small cells with a darkly staining nucleus, high mitotic activity, and scanty cytoplasm. Some of these tumors are indistinguishable from small cell carcinomas of the lung. They may be pure or associated with areas of glandular or squamous differentiation. Ultrastructurally, dense-core granules consistent with endocrine differentiation are found in most but not all of the cases. Immunohistochemically, all of the cases studied by two groups of authors expressed one or more neuroendocrine markers, such as Leu7, neuron-specific enolase (NSE), chromogranin, or synaptophysin. Keratin (often dot-like pattern) and EMA are also regularly expressed.

In approximately half of the cases these tumors have been found to have features analogous to those of Merkel cell carcinoma of skin, including immunoreactivity for CK20 and polyomavirus. Rarely, small cell carcinoma can be the malignant component arising in a background Warthin tumor (Fig. 6.43). On the basis of the above findings, some authors have proposed to divide small cell carcinomas of salivary glands into Merkel cell type and pulmonary type, the latter being negative for CK20. It remains to be seen whether this distinction carries a clinical significance, but preliminary studies suggest that the Merkel cell type is associated with a better survival. Overall, recurrence and metastasis occur in more than half of patients, with 5-year survival ranging from 15% to 50%.

**Lymphoepithelioma-Like Carcinoma**

Lymphoepithelioma-like carcinoma is the preferred term for a type of salivary gland carcinoma that has also been reported as a malignant lymphoepithelial lesion and lymphoepithelial carcinoma. This tumor is particularly frequent among Eskimos and Chinese, in whom it may show evidence of familial clustering. It presents as a unilateral mass, in either the parotid or submaxillary glands, in adult patients without any of the peripheral manifestations of Sjögren syndrome. Its low-power appearance is reminiscent of Mikulicz disease because of the mixture of epithelial solid islands and lymphoid tissue. However, high-power examination shows that the islands have malignant cytologic features throughout. The appearance is that of a nonkeratinizing large cell carcinoma, with occasional spindle-shaped areas, analogous by light and electron microscopy to the nasopharyngeal tumor classically known as lymphoepithelioma. That the analogy may be more than morphologic is suggested by the fact that many of these patients have serologic evidence of EBV infection and that EBV DNA has been found in the tumors by in situ hybridization and other molecular techniques. Perineural invasion may be present. Immuno-histochemically, there is strong positivity for keratin. The reactive lymphoid tissue forms germinal centers and may exhibit focally a starry sky pattern. Regional lymph node metastases are very common, and distant metastases (particularly to the lung, liver, and bone) also occur. Wide variations in mortality rates have been reported, but the overall outcome in the better documented cases seems to
be relatively good, with 5-year survival rates ranging from 75% to 85%.427,455

**Other Primary Carcinomas**

Some adenocarcinomas of salivary gland combine features of two histologically distinct types. They are referred to as hybrid carcinomas, and one of the two components is often of myoepithelial nature, but any combination of histologic subtypes is possible.436,437 Other adenocarcinomas do not fit into any of the previously described patterns and are referred to as adenocarcinoma, N.O.S.438,439 Following the description of salivary duct carcinoma, polymorphous low-grade adenocarcinoma, MASC, low-grade cribriform cystadenocarcinoma, and epithelial–myoepithelial carcinoma, the number of adenocarcinomas, N.O.S. has shrunk considerably.438

**Malignant Lymphoma**

Malignant lymphoma in the parotid region may arise from an intraparotid lymph node or in the gland itself. In the former instance, the histologic features and natural history of the disease are those of nodal lymphoma in general. When the salivary gland tissue is involved, this may represent the expression of disseminated involvement or, more commonly, a primary process of this organ. The large majority of primary lymphomas of salivary gland involve the parotid gland, but the submaxillary gland can also be affected.440–443 Clinically, most present as unilateral masses. The large majority of salivary gland lymphomas are of B-cell derivation, most commonly MALT lymphoma, followed by follicular lymphoma and diffuse large-B-cell lymphoma.440,442,444

Some salivary gland lymphomas are of follicular type and feature the t(14;18) characteristic of follicular lymphoma.444–445 Some have sclerosing features and simulate chronic sclerosing sialadenitis (Kuttner tumor; but see later).446 Others—the majority—are composed of small lymphocytes and cells resembling monocytoid B cells. These tumors are currently regarded as belonging to the MALT/marginal zone type.447,448 They often arise against a background of Mikulicz disease or other immune-mediated diseases (see earlier).449 They are characterized by a very slow evolution and an excellent long-term prognosis;446,447,449; it is not unusual for recurrent disease to supervene in the contralateral parotid, skin, or in some other location a decade or more after the initial diagnosis.450 In contrast, lymphomas composed of large cells run a rapidly progressive clinical course.451

Cases of malignant lymphoma have also been observed in association with Warthin tumor.452,453 in transplant recipients.454 and following chronic sclerosing sialadenitis (Kuttner tumor).455

Isolated cases of plasmacytoma of the salivary gland have been reported, some later developing typical radiographic bone changes of multiple myeloma.456

T-cell lymphomas of the salivary gland are rare but well documented.457 These include tumors of T/natural killer cells. They may show prominent lymphoepithelial lesions and cannot therefore be reliably distinguished from B-cell tumors on morphologic grounds.458

Hodgkin lymphoma presenting as a primary salivary gland neoplasm is very rare.459 Most cases so diagnosed in the past would probably be reclassified today.

**Other Primary Tumors**

Benign vascular tumors of blood vessel and lymph vessel type (lymphangiomata) occur in the parotid gland.460

Infantile (juvenile) hemangioma is the most common salivary gland tumor in infants and children.461 It is often congenital and usually involves the parotid gland. It forms a diffuse soft mass without fixation to the overlying skin. Microscopically, it is made up of anastomosing thin-walled capillaries growing between salivary ducts and acini (Fig. 6.44). The solid proliferation of endothelial cells and the presence of mitotic figures may lead to a mistaken diagnosis of malignancy.462 These lesions practically never become malignant and can regress spontaneously. Some of the cases have been associated with the Kasabach–Merritt syndrome.463 Immunohistochemical reactivity for GLUT1 distinguishes this lesion from its mimics, particularly vascular malformations, because the former demonstrate diffuse cytoplasmic reactivity.464 This distinction is important because infantile hemangiomas can be followed clinically without surgical intervention. Vascular malformations, in contrast, need to be treated because they tend to grow slowly over time.

Lipoma rarely involves the region of the parotid salivary gland.465 It should be distinguished from lipomatosis, which is a diffuse nontumoral deposition of adipose tissue throughout the gland accompanied by enlargement of the organ. The latter has been seen in association with diabetes, cirrhosis, chronic alcoholism, malnutrition, and hormonal disturbances.466 In some cases, this has been preceded by hypertrophy of the serous acinar cells, interstitial edema, and ductal atrophy, a process known as sialosis or sialadenosis.467

Schwannoma can arise from one of the fine radicles of the facial nerve and present clinically as a primary salivary gland tumor.468 It is grossly encapsulated, and its microscopic appearance is similar to that of schwannomas elsewhere. Failure to recognize this neoplasm as benign may result in needless sacrifice of the facial nerve.

Adult rhabdomyoma often presents in the soft tissues of the submandibular area, but the gland itself is rarely affected.469

Solitary fibrous tumor has been reported in the parotid and in the submandibular gland.470,471 Its histology and clinical course is similar to that of its soft tissue counterpart.

Sialolipoma is a benign tumor composed of mature adipose tissue and glandular elements, which are probably entrapped.472

Granular cell tumor has been reported within the parotid gland.473

Sialoblastoma (embryoma) is a term used for an extremely rare, highly cellular epithelial parotid tumor of neonates and infants having an embryonal or “blastomatous” appearance.474–477 The neoplastic cells typically are reactive for keratin, p63, S-100, and actin. The biologic behavior is difficult to predict on histologic
grounds. Some of the sialoblastomas have recurred locally, several had regional lymph node involvement, and one case resulted in lung metastases.478

Salivary gland anlage tumor is another congenital tumor of minor salivary gland type that has been described only in the nasopharynx.479

Sarcomas are very rare and need to be distinguished from epithelial, myoepithelial, and melanocytic tumors with a spindle cell pattern.480 The types described in adults include malignant peripheral nerve sheath tumor, fibrosarcoma, synovial sarcoma, Kaposi sarcoma, angiosarcoma,481 Ewing sarcoma/primitive neuroectodermal tumor (PNET), desmoplastic small round cell tumor,482 and undifferentiated malignant fibrous histiocytoma.480,483–486 In children, embryonal rhabdomyosarcoma can arise in the parotid region and can secondarily invade the gland.487

Metastatic Tumors

Most metastatic tumors to this region are centered in intraparotid or submandibular lymph nodes.488 As the tumor grows, it closely mimics a primary neoplasm of the salivary gland. It should be remembered that the most common malignant tumor in the submandibular and parotid gland region is a metastatic carcinoma in the submandibular or parotid lymph nodes rather than a primary salivary gland carcinoma. The most common types are squamous cell carcinoma (from the upper aerodigestive tract or skin) and malignant melanoma (including the desmoplastic variant).488–490 Of the distant tumors metastasizing to the major salivary glands, lung, kidney, and breast tumors are the most common.488,492,493 Other reported sites include prostate and large bowel.490,494

General Features of Salivary Gland Tumors

Relative Incidence and Malignancy

Salivary gland tumors are 12 times more frequent in the parotid than in the submandibular gland, a difference that cannot be explained on the basis of gland size alone. The majority are benign and largely represented by the pleomorphic adenoma.495,496

In a series of 2632 salivary gland tumors reported by Eneroth,497 the incidence of malignancy was 17% for the parotid gland, 38% for the submandibular gland, and 44% for the palate. The incidence of malignancy is highest for tumors of the sublingual gland and benign sublingual gland neoplasms are exceedingly uncommon.498–500 Most tumors of major salivary glands are unilateral and single. Bilaterality and multiplicity are common only in Warthin tumor but can also be seen with pleomorphic adenoma and acinic cell carcinoma.499 Acinic cell carcinoma is the most common bilateral salivary gland malignancy.

Tumors of minor salivary glands can be found anywhere in the oral cavity, including the hard and soft palate, cheek, gingiva, tonsillar area, and tongue.499 Their frequency seems to be approximately proportional to the amount of normal glandular tissue in this area, which may explain their marked predilection for the hard palate. They can also occur in the lip (particularly upper lip), nasal cavity and paranasal sinuses, ear, jaw, pharynx, larynx, trachea, and bronchi. Furthermore, tumors of the salivary gland type may arise from a variety of glandular structures, particularly breast and sweat glands.

Finally, salivary gland tumors of various types have been described as arising from lymph nodes located in or around the parotid gland, presumably on the basis of ectopic salivary tissue. Warthin tumor is by far the most common type, but examples of sebaceous lymphadenoma, pleomorphic adenoma, basal cell adenoma, acinic cell carcinoma, and mucoepidermoid carcinoma have also been reported.497,500

Little is known about the etiology of salivary gland tumors, and high-risk populations have not been identified except for the rare lymphoepithelioma-like carcinoma.501 An increased incidence of benign mixed tumors and other neoplasms has been observed following therapeutic childhood irradiation,502,503 and a possible increase in carcinomas (particularly of mucoepidermoid type) has been noted among atomic bomb survivors.504

In children, the most common salivary gland tumor is benign mixed tumor, but the proportion of malignant tumors is higher than in adults. Among the malignant neoplasms, mucoepidermoid carcinoma, adenoid cystic carcinoma, and acinic cell carcinoma are the most common.496,501–507

Clinical Diagnosis

Benign tumors of the salivary glands usually can be distinguished from the high-grade malignant varieties on the basis of their clinical and gross characteristics. The presence of facial nerve paralysis is almost diagnostic of malignancy. These criteria do not apply for the low-grade acinic cell carcinomas and mucoepidermoid carcinomas because their clinical presentation is usually indistinguishable from that of benign neoplasms. The reverse also may be true, although only in rare cases. Warthin tumor, for instance, may be clinically thought to be malignant because of its adherence to the skin.

Staging

A clinical staging system using the TNM classification scheme for major salivary gland tumors has been established. It is based on: size of the primary tumor, local extension with involvement of adjacent structures (bone, skin, ear canal, facial nerve, skull base, pterygoid plates, carotid artery), involvement of the regional lymph nodes (number, size, and laterality), and the presence or absence of distant metastases. Importantly, extraglandular extension is based on gross or clinical evidence and not microscopic evidence alone. Salivary gland carcinomas of minor salivary glands are staged according to the site from which they arise.

Biopsy and Cytology

Tumors of the submandibular gland are usually treated by removal of the gland without previous biopsy. For tumors of the parotid glands, several choices are available depending on the size and location of the tumor, clinical features, and expertise of the pathologist. Tumors involving the superficial parotid lobe lacking clinical features of malignancy can be properly handled by a superficial lobectomy with frozen section, any subsequent therapy depending on the diagnosis of the frozen section. Obviously malignant tumors with skin invasion can usually be diagnosed with a small incisional biopsy and treated accordingly. Other options are core needle biopsy and fine-needle aspiration. Although the former usually provides diagnostic material, the possibility of implantation along the needle track and the difficulty sometimes encountered in the differential diagnosis (particularly among adenoid cystic carcinoma, monomorphic adenoma, and benign mixed tumor) have resulted in a less than enthusiastic response from clinicians and pathologists. Instead, fine-needle aspiration has been used successfully by several European institutions (particularly the Karolinska Institute in Sweden) and has now become widespread in the United States (Figs. 6.45 and 6.46). The overall accuracy rate has been greater than 90% in most reported series.498,505 The fine-needle aspiration procedure can induce necrotic and reparative changes in the tumor, particularly if composed
of oncocytes, however, the subsequent microscopic evaluation of the case is not significantly compromised.

**Frozen Section**

Intraoperative examination of salivary gland tumors is an accurate procedure that can help the surgeon determine the extent of the surgery needed, particularly for parotid neoplasms. Obviously, the usefulness of this procedure depends on the expertise of the pathologist in providing accurate diagnoses and the wisdom of the surgeon in applying this information.

**Treatment**

The extent of surgical treatment of parotid tumors is determined by their microscopic type, histologic grade, and the anatomic peculiarities of the parotid gland, particularly its intimate relationship with the facial nerve.

Fortunately, most parotid pleomorphic adenomas arise from the superficial lobe, so a superficial or partial parotidectomy with preservation of the nerve can be performed; actually, the nerve can be preserved in selected cases even if the entire gland is removed.

Most low-grade malignant tumors of mucoepidermoid or acinic cell type can be treated in a similar fashion. If the carcinoma is advanced and/or high grade, total parotidectomy with sacrifice of the facial nerve is usually necessary. If there is clinical evidence of nodal involvement, this procedure needs to be coupled with selective or radical neck dissection. Elective wide dissection should be considered in malignant tumors that are of high grade and/or larger than 4 cm.

The surgical treatment of submandibular tumors, whether benign or malignant, is total removal of the gland. The recurrence rate of carcinomas of this particular gland is relatively high because of the close relation of the gland to the mandible.

Patients who develop postoperative recurrence of high-grade malignant salivary gland tumors do poorly; most have a relatively short survival, and subsequent treatment is effective in only one of four cases.

Radiation therapy has been used as the primary form of therapy in inoperable tumors and as a postoperative modality in cases selected on the basis of the microscopic features and surgical procedure. There is evidence that this may result in a decrease in the incidence of local recurrence.

**Prognosis**

The prognosis of salivary gland tumors is determined by the clinical staging, location, and microscopic features. Malignant tumors of the submandibular gland have a higher incidence of recurrence and metastases than parotid tumors of the same type. For adenoid cystic carcinoma, the prognosis is best when located in the palate, intermediate when in the parotid gland, and worst in the submaxillary gland. For parotid malignant tumors, the presence of facial nerve paralysis is an ominous prognostic sign. In regard to microscopic types, the prognosis is best for the low-grade variants of mucoepidermoid and acinic cell carcinoma and worst for the high-grade variants of these tumors and for adenoid cystic carcinoma, malignant mixed tumor, salivary duct carcinoma, and squamous cell carcinoma. Additional prognostic parameters are discussed in connection with the respective tumor types.

Amplification of HER2 oncogene and p53 oncoprotein expression have been claimed to correlate with aggressive behavior, but it is not clear that these parameters represent independent prognostic determinators.
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Figure 6.47 Survival rates in malignant salivary gland tumors. (From Eneroth CM, Hamberger CA. *Principles of treatment of different types of parotid tumors*. Laryngoscope. 1974;84:1732–1740.)
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