Table 16-4 Histologic Classification and Incidence of the Most Common Benign and Malignant Tumors of the Salivary Glands

Benign	Malignant
Pleomorphic adenoma (50%) (mixed tumor)	Mucoepidermoid carcinoma (15%)
Warthin tumor (5%-10%)	Adenocarcinoma (NOS) (10%)
Oncocytoma (1%)	Acinic cell carcinoma (5%)
Other adenomas (5%-10%) Basal cell adenoma Canalicular adenoma	Adenoid cystic carcinoma (5%) Malignant mixed tumor (3%-5%) Squamous cell carcinoma (1%)
Ductal papillomas	Other carcinomas (2%)

NOS, Not otherwise specified.
Data from Ellis GL, Auclair PL: Tumors of the Salivary Glands. Atlas of Tumor Pathology, Fourth Series. Washington, DC, Armed Forces Institute of Pathology, 2008.

benign and malignant tumors is listed in Table 16-4; not included are the rare benign and malignant mesenchymal neoplasms.

As indicated in Table 16-4, a small number of neoplasms makes up more than 90% of salivary gland tumors, and so our discussion is restricted to these. Overall, these neoplasms are relatively uncommon and represent less than 2% of all tumors in humans. About 65% to 80% arise within the parotid, 10% in the submandibular gland, and the remainder in the minor salivary glands, including the sublingual glands. Approximately 15% to 30% of tumors in the parotid glands are malignant. In contrast, approximately 40% of submandibular, 50% of minor salivary gland, and 70% to 90% of sublingual tumors are cancerous. Thus, **the likelihood of a salivary gland tumor being malignant is more or less inversely proportional to the size of the gland.**

These tumors usually occur in adults, with a slight female predominance, but about 5% occur in children younger than age 16 years. Warthin tumors occur much more often in males than in females, perhaps reflecting the historically higher prevalence of smoking, a predisposing factor, among men. The benign tumors most often appear in the fifth to seventh decades of life. The malignant ones tend to appear somewhat later. Whatever the histologic pattern, neoplasms in the parotid glands produce distinctive swellings in front of and below the ear. In general, when they are first diagnosed, both benign and malignant lesions range from 4 to 6 cm in diameter and are mobile on palpation except in the case of neglected malignant tumors. Although benign tumors are known to have been present usually for many months to several years before coming to clinical attention, cancers are generally detected more quickly because of their rapid growth. Ultimately, however, there are no reliable clinical criteria to differentiate benign from malignant lesions.

Pleomorphic Adenoma

Pleomorphic adenomas are benign tumors that consist of a mixture of ductal (epithelial) and myoepithelial cells, and therefore they show both epithelial and mesenchymal differentiation. Because of their remarkable histologic diversity, these neoplasms have also been called *mixed tumors.* They represent about 60% of tumors in the parotid, are less common in the submandibular glands, and are relatively rare in the minor salivary glands. They reveal epithelial elements dispersed throughout the matrix along with varying degrees of myxoid, hyaline, chondroid (cartilaginous), and even osseous tissue. In some tumors the epithelial elements predominate; in others they are present only in widely dispersed foci.

Little is known about the origins of these neoplasms, except that radiation exposure increases the risk. Equally uncertain is the histogenesis of the various components. A currently popular view is that all neoplastic elements, including those that appear mesenchymal, are of either myoepithelial or ductal reserve cell origin (hence the designation *pleomorphic adenoma*). A high fraction of cases are associated with chromosomal rearrangements involving *PLAG1*, a gene encoding a transcription factor that is overexpressed as a result of these rearrangements. PLAG1 overexpression appears to upregulate expression of a number of genes that increase cell growth, such as components of growth factor receptor signaling pathways.

MORPHOLOGY

Most pleomorphic adenomas present as rounded, well-demarcated masses rarely exceeding 6 cm in the greatest dimension (Fig. 16-15). Although they are encapsulated, in some locations (particularly the palate) the capsule is not fully developed, and expansile growth produces protrusions into the surrounding gland, which may lead to recurrences if the tumor is merely enucleated. The cut surface is gray-white with myxoid and blue translucent areas of chondroid (cartilage-like).

The dominant histologic feature is the great heterogeneity mentioned. The epithelial elements resembling ductal cells or myoepithelial cells are arranged in duct formations, acini, irregular tubules, strands, or sheets of cells. These elements are typically dispersed within a mesenchyme-like background of loose myxoid tissue containing islands of cartilage and, rarely, foci of bone (Fig. 16-16). Sometimes the epithelial cells form well-developed ducts lined by cuboidal to columnar cells with an underlying layer of deeply chromatic, small myoepithelial cells. In other instances there may be strands or sheets of myoepithelial cells. Islands of well-differentiated squamous epithelium may also be present. In most cases there is no epithelial dysplasia or evident mitotic activity. There is no difference in biologic behavior between the tumors composed largely of epithelial elements and those composed largely of seemingly mesenchymal elements.

Clinical Features. These tumors present as painless, slow-growing, mobile, discrete masses within the parotid or submandibular areas or in the buccal cavity. The recurrence rate (perhaps months to years later) with parotidectomy is about 4% but, with simple enucleation approaches 25%.

A carcinoma arising in a pleomorphic adenoma is referred to variously as a *carcinoma ex pleomorphic adenoma* or a *malignant mixed tumor.* The incidence of malignant transformation increases with time, being about 2% for tumors present less than 5 years and almost 10% for those present for more than 15 years. The cancer usually takes the form of an adenocarcinoma or undifferentiated carcinoma. Like cancers elsewhere, these malignancies are highly infiltrative and tend to completely overrun and replace the preexisting pleomorphic adenoma. This may make it difficult to substantiate the diagnosis of carcinoma