Salivary gland tumours can show a striking range of morphological diversity between different tumour types and sometimes within an individual tumour mass. In addition, hybrid tumours, dedifferentiation and the propensity for some benign tumours to progress to malignancy can confound histopathological interpretation. These features, together with the relative rarity of a number of tumours, can sometimes make diagnosis difficult, despite the abundance of named tumour entities. The increasing use of pre-operative fine needle aspiration biopsies also needs to be taken into account, as artifactual changes may be superimposed on the tumours. Unfortunately, the morphological variability of these tumours is mirrored by the immunohistochemical profiles, so that special stains are rarely useful in routine diagnosis of salivary gland epithelial neoplasms.
### WHO histological classification of tumours of the salivary glands

<table>
<thead>
<tr>
<th>Malignant epithelial tumours</th>
<th>8310/3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinic cell carcinoma</td>
<td>8550/3</td>
</tr>
<tr>
<td>Mucoepidermoid carcinoma</td>
<td>8430/3</td>
</tr>
<tr>
<td>Adenoid cystic carcinoma</td>
<td>8200/3</td>
</tr>
<tr>
<td>Polymorphous low-grade adenocarcinoma</td>
<td>8525/3</td>
</tr>
<tr>
<td>Epithelial-myoepithelial carcinoma</td>
<td>8562/3</td>
</tr>
<tr>
<td>Clear cell carcinoma, not otherwise specified</td>
<td>8310/3</td>
</tr>
<tr>
<td>Basal cell adenocarcinoma</td>
<td>8147/3</td>
</tr>
<tr>
<td>Sebaceous carcinoma</td>
<td>8410/3</td>
</tr>
<tr>
<td>Sebaceous lymphadenocarcinoma</td>
<td>8410/3</td>
</tr>
<tr>
<td>Cystadenocarcinoma</td>
<td>8440/3</td>
</tr>
<tr>
<td>Low-grade cribriform cystadenocarcinoma</td>
<td>8440/3</td>
</tr>
<tr>
<td>Mucinous adenocarcinoma</td>
<td>8480/3</td>
</tr>
<tr>
<td>Oncocytic carcinoma</td>
<td>8290/3</td>
</tr>
<tr>
<td>Salivary duct carcinoma</td>
<td>8500/3</td>
</tr>
<tr>
<td>Adenocarcinoma, not otherwise specified</td>
<td>8140/3</td>
</tr>
<tr>
<td>Myoepithelial carcinoma</td>
<td>8982/3</td>
</tr>
<tr>
<td>Carcinoma ex pleomorphic adenoma</td>
<td>8941/3</td>
</tr>
<tr>
<td>Carcinosarcoma</td>
<td>8980/3</td>
</tr>
<tr>
<td>Metastasizing pleomorphic adenoma</td>
<td>8940/1</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>8070/3</td>
</tr>
<tr>
<td>Small cell carcinoma</td>
<td>8041/3</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>8012/3</td>
</tr>
<tr>
<td>Lymphoepithelial carcinoma</td>
<td>8082/3</td>
</tr>
<tr>
<td>Sialoblastoma</td>
<td>8974/1</td>
</tr>
<tr>
<td><strong>Basal cell adenoma</strong></td>
<td>8147/0</td>
</tr>
<tr>
<td><strong>Warthin tumour</strong></td>
<td>8561/0</td>
</tr>
<tr>
<td><strong>Oncocytoma</strong></td>
<td>8290/0</td>
</tr>
<tr>
<td><strong>Canalicular adenoma</strong></td>
<td>8149/0</td>
</tr>
<tr>
<td><strong>Sebaceous adenoma</strong></td>
<td>8410/0</td>
</tr>
<tr>
<td><strong>Lymphadenoma</strong></td>
<td>8410/0</td>
</tr>
<tr>
<td><strong>Sebaceous</strong></td>
<td>8410/0</td>
</tr>
<tr>
<td><strong>Non-sebaceous</strong></td>
<td>8410/0</td>
</tr>
<tr>
<td><strong>Ductal papillomas</strong></td>
<td>8503/0</td>
</tr>
<tr>
<td><strong>Inverted ductal papilloma</strong></td>
<td>8503/0</td>
</tr>
<tr>
<td><strong>Intraductal papilloma</strong></td>
<td>8503/0</td>
</tr>
<tr>
<td><strong>Sialadenoma papilliferum</strong></td>
<td>8406/0</td>
</tr>
<tr>
<td><strong>Cystadenoma</strong></td>
<td>8440/0</td>
</tr>
<tr>
<td><strong>Soft tissue tumours</strong></td>
<td>9120/0</td>
</tr>
<tr>
<td><strong>Haemangioma</strong></td>
<td>9120/0</td>
</tr>
<tr>
<td><strong>Haematolymphoid tumours</strong></td>
<td>9120/0</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>9120/0</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>9680/3</td>
</tr>
<tr>
<td>Extramedial marginal zone B-cell lymphoma</td>
<td>9699/3</td>
</tr>
</tbody>
</table>

### Benign epithelial tumours

| Pleomorphic adenoma                                             | 8940/0                |
| Myoepithelioma                                                  | 8892/0                |

---

1. Morphology code of the International Classification of Diseases for Oncology (ICD-O) (821) and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.
# TNM classification of carcinomas of the salivary glands

<table>
<thead>
<tr>
<th>TNM classification</th>
<th>1,2</th>
</tr>
</thead>
<tbody>
<tr>
<td>T – Primary tumour</td>
<td></td>
</tr>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour 2 cm or less in greatest dimension without extraparenchymal extension*</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour more than 2 cm but not more than 4 cm in greatest dimension without extraparenchymal extension*</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour more than 4 cm and/or tumour with extraparenchymal extension*</td>
</tr>
<tr>
<td>T4a</td>
<td>Tumour invades skin, mandible, ear canal, or facial nerve</td>
</tr>
<tr>
<td>T4b</td>
<td>Tumour invades base of skull, pterygoid plates, or encases carotid artery</td>
</tr>
</tbody>
</table>

Note: *Extraparenchymal extension is clinical or macroscopic evidence of invasion of soft tissues or nerve, except those listed under T4a and 4b. Microscopic evidence alone does not constitute extraparenchymal extension for classification purposes.

| N – Regional lymph nodes## | |
| N0 | No regional lymph node metastasis |
| N1 | Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension |
| N2 | Metastasis as specified in N2a, 2b, 2c below |
| N2a | Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension |
| N2b | Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension |

<table>
<thead>
<tr>
<th>Stage Grouping</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2</td>
</tr>
<tr>
<td>Stage III</td>
<td>T3</td>
</tr>
<tr>
<td>T1, T2, T3</td>
<td>N1</td>
</tr>
<tr>
<td>Stage IV A</td>
<td>T1, T2, T3</td>
</tr>
<tr>
<td>T4a</td>
<td>N0, N1, N2</td>
</tr>
<tr>
<td>Stage IV B</td>
<td>T4b</td>
</tr>
<tr>
<td>Any T</td>
<td>N3</td>
</tr>
<tr>
<td>Stage IV C</td>
<td>Any T</td>
</tr>
</tbody>
</table>

Note: Midline nodes are considered ipsilateral nodes.

1 (947,2418).
2 A help desk for specific questions about the TNM classification is available at http://www.uicc.org/index.php?id=508.

## The regional lymph nodes are the cervical nodes.
Tumours of the salivary glands: Introduction

Anatomy
Salivary glands are exocrine organs responsible for the production and secretion of saliva. They comprise the three paired major glands, the parotid, submandibular and sublingual, and the minor glands. The latter are numerous and are widely distributed throughout the mouth and oropharynx and similar glands are present in the upper respiratory and sinonasal tracts, and the paranasal sinuses.

Secretory acinus
The functional unit of salivary glands is the secretory acinus and related ducts, and myoepithelial cells. Acini may be serous, mucous or mixed. Serous acini form wedge-shaped secretory cells with basal nuclei. They surround a lumen that becomes the origin of the intercalated duct. The cytoplasm of serous cells contains densely basophilic, refractile zymogen granules that are periodic acid Schiff positive and diastase resistant. Their principle secretion is amylase. Mucous acinar cells also have basally placed nuclei and their cytoplasm is clear and contains vacuoles of sialomucin. The secretions of these cells pass through the intercalated ducts. These are often inconspicuous in routine histological sections. They are lined by what appears to be a single layer of cuboidal cells with relatively large, central nuclei. They are continuous with the much larger striated ducts. The intercalated ducts are lined by a single layer of cuboidal cells with relatively large, central nuclei and are linked to the much larger striated duct. The latter are lined by tall, columnar, eosinophilic cells that are rich in mitochondria. They have parallel infoldings of the basal cytoplasm and are responsible for modifying the salivary secretions. The striated ducts join the interlobular excretory ducts, which are lined by pseudostratified columnar epithelium that often contains few mucous cells.

Myoepithelial cells
Myoepithelial, or basket cells, are contractile and are located between the basement membrane and the basal plasma membrane of the acinar cells. They are variable in morphology and are inconspicuous in H&E sections. They contain smooth muscle actin, myosin and intermediate filaments including keratin 14. Immunohistochemical stains for the proteins highlights their stellate shape. They have long dendritic processes that embrace the secretory acini. Myoepithelial cells also surround the intercalated ducts but their presence in striated ducts is not firmly established. Ultrastructurally, the cytoplasm of myoepithelial cells contains actomyosin microfilaments running parallel with the outer surface of the cell, glycogen granules and lipofuscin, and pinocytotic vesicles may also be a conspicuous feature.

Parotid gland
The parotid gland is almost purely serous and the parenchyma is divided into lobules by fibrous septa. There is abundant intralobular and extralobular adipose tissue which increases in relative volume with age. The parotid gland contains randomly distributed lymphoid aggregates and lymph nodes that range from one to more than 20 in number. Not infrequently the lymph nodes contain salivary gland ducts or occasionally acini (Neisse Nicholson rests). Sebaceous glands, either individually or in small groups, are commonly seen if the tissue is widely sampled.

Submandibular gland
The gland is mixed serous and mucous although the serous element predominates (~90%). In mixed acini the serous cells form caps, or demilunes, on the periphery of the mucous cells. The intercalated ducts are shorter and the striated ducts more conspicuous than those of the parotid gland.

Sublingual gland
The gland is also mixed but is predominantly mucous in type. The mucous acini form elongated tubules with peripheral serous demilunes.

Minor salivary glands
These are most numerous at the junction of the hard and soft palate, lips and buccal mucosa. The minor glands of the lateral aspects of the tongue, lips and buccal mucosa are seromucous whereas those in the ventral tongue, palate, glossopharyngeal area and retromolar pad are predominantly mucous. Salivary glands related to the circumvallate papillae (von Ebner’s glands) are serous in type. The minor glands are not encapsulated, and those in the tongue and lip especially can be deeply located in the musculature.

Epidemiology
The epidemiology of salivary gland tumours is not well documented (2053). In many studies the data are limited, as some are restricted to parotid gland neoplasms or tumours of major glands. In addition, most salivary gland tumours are benign and some cancer registries have only included malignant tumours. One study specifically excluded Warthin tumour, which is the second most common benign salivary neoplasm (698). In addition, several investigators felt that their quoted incidence figures were an underestimate, particularly for benign tumours (963,1471,2053).

The global annual incidence when all salivary gland tumours were considered varied from 0.4-13.5 cases per 100,000 population (669). The frequency of malignant
salivary neoplasms ranged from 0.4-2.6 cases per 100,000 population (1353,1960,2053,2503). In the United States, salivary gland malignancies accounted for 6% of head and neck cancers, and 0.3% of all malignancies (2167). There is also some geographic variation in the frequency of tumour types. In studies of patients from Denmark and parts of Pennsylvania, about 30% of all parotid tumours were Warthin tumours, a seven-fold increase of the expected frequency (1765,2075). The reported frequency of mucoepidermoid carcinomas among British patients (2.1%) is much lower than the worldwide range of 5-15% (703,704, 1772,2580). There was a very high reported incidence of salivary gland tumours in North American Inuits from 1950-1966 (1087,2255). This was almost exclusively due to lymphoepithelial carcinomas that formed 25% of all malignancies in this population. Since then there has been a significant decline in the relative frequency of this tumour. A survey of different ethnic groups in Malaysia showed a higher frequency of salivary tumours in Malays than Chinese or Indians (1551). Another study showed variations in the incidence of salivary tumours amongst different ethnic groups according to their city of residence (1705). It should be noted that in some series malignant lymphoma and metastatic disease represent about 9% of major gland tumours, highlighting the need to include these neoplasms in differential diagnostic considerations (669,1916).

Site, age and sex distribution
Between 64 and 80% of all primary epithelial salivary gland tumours occur in the parotid gland with most located in the superficial (lateral) lobe; 7-11% occur in the submandibular glands; fewer than 1% occur in the sublingual glands; and 9-23% occur in minor glands (669,679, 703,2301,2439). Benign tumours represent 54-79%, and 21-46% are malignant. The proportion of malignant tumours, however, varies greatly by site. Malignant tumours comprise 15-32% of parotid tumours, 41-45% of submandibular tumours, 70-90% of sublingual tumours, and 50% of minor gland tumours. Eighty to 90% of tumours that occur in the tongue, floor of mouth, and retromolar areas are malignant. Females are more frequently affected, but there is some gender variation according to the tumour type. The average ages of patients with benign and malignant tumours are 46 and 47 years, respectively, and the peak incidence of most of the specific types is in the sixth and seventh decades. However, the highest incidence of pleomorphic adenomas, mucoepidermoid carcinomas, and acinic cell carcinomas is in the third and fourth decades. In patients under 17 years of age, the frequency of mesenchymal tumours of the major glands is similar to that of epithelial tumours (1304,1413,2302,2337). In this age group, pleomorphic adenomas, mucoepidermoid carcinomas and acinic cell carcinomas account for about 90% of epithelial tumours, and the frequency of benign and malignant tumours is essentially equal.

Among all patients, the most common tumour type is pleomorphic adenoma, which accounts for about 50% of all tumours. Warthin tumour is second in frequency among benign tumours and, in most large studies, mucoepidermoid carcinoma is the most common malignant tumour (669,679,703,2301,2439). Most canalicular adenomas and polymorphous low-grade adenocarcinomas arise from minor glands whereas nearly all Warthin tumours occur in the parotid gland or parotid lymph nodes.

Etiology
Viruses
A number of viruses have been implicated in the pathogenesis of salivary gland tumours. There is a strong association between Epstein Barr virus (EBV) and lymphoepithelial carcinomas (2253, 2636), but this appears to be largely restricted to Asian patients (1173) and Greenlandic Inuits (986). EBV has not been convincingly shown in other salivary gland carcinomas or neighbouring normal gland (2636). A recent study did not support an etiological role for EBV or cytomegalovirus in benign parotid tumours (1407). SV40 sequences have been demonstrated in human pleomorphic adenomas (1643) but there is no convincing association between human salivary gland tumours and other viruses, including polyoma virus and papilloma virus.

Radiation
There is compelling evidence implicating exposure to ionizing radiation and the development of salivary gland tumours. Long-term follow-up studies of the survivors of the atomic bomb explosions in Hiroshima and Nagasaki show an increased relative risk of 3.5 for benign, and 11 for malignant salivary neoplasms (193,194,2543,2544). The risk was directly related to the level of exposure to ionizing radiation. There was a high frequency of both mucoepidermoid carcinomas and Warthin tumours in these patients (2229).

Therapeutic radiation, particularly of the head and neck region, has been linked with a significantly increased risk of developing salivary gland cancers (1725,1754,2197,2268). There appears to be a risk from iodine131 used in the treatment of thyroid disease, as the isotope is also concentrated in the salivary glands (1111). There is evidence that exposure to routine dental radiographs is associated with an increased risk of salivary gland carcinoma (2088,2089). Exposure to ultraviolet radiation has also been implicated (1832,2451,2452). There appears to be no excess risk in those exposed to radon (1733), or the microwaves of cellular telephones (92,1224).

Occupation
It has been shown that workers in a variety of industries have an increased incidence of salivary gland carcinomas. These include rubber manufacturing (1127,1620), exposure to metal in the plumbing industry (1730) and nickel compounds (1127), woodworking in the automobile industry (2512) and employment in hairdressing and beauty shops (2513,2514). An increased risk of salivary gland cancers was reported in people living in certain Quebec counties where asbestos was mined, and the risk was inversely proportional to the distance from the mines (935).

Lifestyle and nutrition
No association was found between tobacco use and alcohol consumption and salivary gland cancers in a case/control study (1801), confirming previous findings (1295,2792). One study showed an elevated risk in men but not women (1127). However, there is a strong association between smoking and Warthin tumour (Section on Warthin tumour). Exposure to silica dust and kerosene as a cooking fluid increased
the risk of developing salivary malignancy in a Chinese population [2902], and a higher level of risk of parotid carcinomas was associated with exposure to nickel, chromium, asbestos and cement dust in a European study [603]. An increased level of risk has been postulated in those with a high cholesterol intake [1128].

Hormones
Endogenous hormones have been reported in normal and neoplastic salivary glands, but some of the results have been conflicting. Estrogen receptors were found in nearly 80% of normal glands in males and females and four out of eight salivary tumours in women had estrogen receptor levels similar to those of "hormonally dependent" breast carcinomas [606]. However, more recent studies have not confirmed this finding and questioned the methodology [616]. Estrogen receptors have been reported in a minority of cases of acinic cell carcinoma, mucoepidermoid carcinoma [1214] and salivary duct carcinoma [134], but were not detected in adenoid cystic carcinoma [616, 1214, 1732, 2335]. Estrogen or estrogen receptors have been reported in pleomorphic adenomas in some studies [1214, 1764, 1946], but in others, estrogen receptors were absent [1851].

Progesterone receptors have been reported in normal salivary glands [892, 2335]. They have been detected in a minority of pleomorphic adenomas [892, 1214] but high levels of expression were reported in recurrent pleomorphic adenomas and this was thought to be a prognostic factor [892]. However, a recent study failed to show progesterone receptors in all the benign salivary tumours examined [1851].

Progesterone receptors were seen in 2/10 acinic cell carcinomas and 3/10 mucoepidermoid carcinomas [1214] but were not detected in salivary duct carcinoma [134]. They have been reported in adenoid cystic carcinomas in some studies [1214, 1965] but in others they were absent, or present in only a few tumours [616, 1214].

Androgen receptors are present in over 90% of salivary duct carcinomas [711, 712, 1265]. A recent study showed immunoreactivity for androgen receptors in all their cases of salivary duct carcinoma, carcinoma ex pleomorphic adenoma and basal cell adenocarcinoma [1851]. There was also staining for the receptors in a fifth of their cases of acinic cell carcinoma, mucoepidermoid carcinoma and adenoid cystic carcinoma.

Diagnostic imaging
Plain radiography and sialography are useful for ductal inflammatory disease, but computed tomography (CT), ultrasonography, CT sialography, and magnetic resonance imaging (MRI) are usually better for evaluation of suspected neoplastic disease. MRI is particularly useful when inflammatory disease is not suspected. It does not have the risks of radiation exposure nor complications with intraductal injection of contrast media, and it is often superior in demonstrating the interface of tumour and surrounding tissues. T1-weighted images of normal parotid have an image signal intermediate between fat and muscle whereas submandibular tissue is closer to muscle in intensity. With advanced age and fatty infiltration, the signal intensity of parotid tissue approaches fat. Most salivary gland tumours are brighter on T2 than T1 images but this difference is minimal in prominently cellular tumours. Lesions with higher water content, such as human immunodeficiency virus related parotid cysts, Warthin tumours, cystadenomas and cystadenocarcinomas, and cystic mucoepidermoid carcinomas, have a bright T2 signal.

Fine needle aspiration biopsy
Fine needle aspiration biopsy (FNA) can provide clinicians with rapid, non-surgical diagnoses. It can be performed at the time of initial consultation. Correlation of the clinical impression, cytologic diagnosis and radiographic imaging studies can then guide along different treatment pathways. FNA can be used both as a diagnostic test and as a screening tool to triage patients into different treatment groups i.e. surgical vs. medical management vs. to follow without intervention [2109]. FNA biopsy is useful in establishing whether a given lesion is inflammatory or neoplastic, is a lymphoma or an epithelial malignancy, or represents a metastasis or a primary tumour [424, 1585, 2892]. Unnecessary surgery can be avoided in approximately one third of cases [668] especially in: (1) patients whose salivary gland lesion is part of a more generalized disease process, (2) inflammatory lesions where a clinical suspicion of malignancy is low, (3) patients in poor health who are not good operative candidates, (4) patients with metastasis to a salivary gland or adjacent lymph node, (5) some examples of lymphoproliferative disease [763] or (6) in a primary soft tissue or skin appendage lesion arising in the area of a major salivary gland.

A number of series have examined the diagnostic accuracy of salivary FNA [26, 495, 2474, 2887] with false positive and false negative rates ranging from 1-14%. The rate of correctly establishing a diagnosis as benign or malignant ranges from 81-98% in most recent reports. However, a specific diagnosis can only be made in approximately 60-75% of cases [668]. False negative diagnoses due to inadequate sampling appear to be the most frequent error.

Frozen section examination
When considering all head and neck sites, the accuracy of frozen section diagnoses of the salivary gland is the most controversial. A review of 2460 frozen sections from 24 series revealed an overall accuracy rate for a benign or malignant diagnosis, excluding deferred diagnoses, of 96% [379, 900, 1697, 2170, 2900]. False-positive rates (benign tumours initially diagnosed as malignant) were 1.1%, false-negative rates (malignant tumours initially diagnosed as benign) were 2.6%, and 2% of cases were deferred. If one subdivides the salivary gland lesions into benign and malignant groups, the accuracy rate (98.7%, excluding deferred diagnoses) is excellent for the benign lesions, which compose 80% of the frozen sections. However, in the malignant tumour group, the accuracy rate (85.9%) is suboptimal [900].

The most common benign tumour over-diagnosed as malignant was pleomorphic adenoma. This was frequently called mucoepidermoid carcinoma or adenoid cystic carcinoma [904]. Mucoepidermoid carcinoma is the malignancy most frequently associated with a false negative benign frozen section diagnosis, while acinic cell carcinoma, adenoid cystic carcinoma, carcinoma ex pleomorphic adenoma and an occasional lymphoma have also caused difficulty.

Staging
Staging of carcinomas of the major salivary glands is based on tumour size,
local extension of tumour, metastasis to regional nodes, and distant metastases (see TNM classification). Recent changes in the staging system include a revision in the definition of T3 and the division of T4 into tumours that are resectable (T4a) and unresectable (T4b) [947,2418]. According to TNM rules, tumours arising in minor salivary glands are classified according to the criteria for other carcinomas at their anatomic site of origin, e.g., oral cavity. Spiro and co-workers have successfully applied the criteria used for squamous cell carcinoma of the oral cavity, pharynx, larynx, and sinus to mucoepidermoid carcinoma [2305,2863].

Genetics
The goal of the molecular biological studies of salivary gland tumours is to define objective markers that may supplant the subjective phenotypic evaluation in the diagnosis, biological assessment and therapeutic stratification of patients with these tumours. The following molecular genetic events tentatively characterize some of these tumours:

1. Chromosomes 3p21, 8q12 and 12q13-15 rearrangements and the PLAG-1 and HMGI-C genes in pleomorphic adenomas
2. Translocations of chromosomes 11q21 and 19p13 in both Warthin tumour and mucoepidermoid carcinoma.
3. Structural and molecular alterations at 6q, 8q, 12q in adenoid cystic and carcinoma ex-pleomorphic adenoma.
4. Elevated HER-2 gene expression and gene amplification in mucoepidermoid, salivary duct and adenocarcinomas.

EGFR
Several studies have shown high expression of EGFR/HER-2/neu family members in mucoepidermoid and adenoid cystic carcinoma. The data suggest a biological role for members of this pathway in these tumours and their potential use as a target for therapy [887].

C-erbB-2/HER-2/neu
This is an oncogene that encodes for a transmembrane glycoprotein receptor involved in cell growth and differentiation. The gene is a member of the EGFR signal transduction family and has been shown to be overexpressed in aggressive breast cancer. Studies in salivary gland adenocarcinoma, including salivary duct and mucoepidermoid carcinoma, point to a general consensus on the association of HER-2 overexpression and adverse clinicopathologic features [725, 884,1058,2086,2198,2465].

C-Kit
This is a proto-oncogene that encodes a transmembrane receptor type tyrosine kinase that belongs to the colony-stimulating factor-1 (CSF-1) and platelet-derived growth factors (PDGF;4-6). Upon binding to its ligand, a signalling cascade is initiated to stimulate growth and differentiation of haematopoietic cells [835]. Studies of C-kit in salivary gland tumours have largely focused on adenoid cystic carcinoma and findings vary considerably. C-kit expression appears to be restricted to adenoid cystic carcinoma [1215,2006] and myoepithelial carcinomas [1215] but absent in polymorphous low-grade adenocarcinoma [2006] and other types of salivary gland tumours [1215].

None of the highly expressed tumours manifested genetic mutations at exons 11 & 17. The results confirm a previous study and underscore that a mechanism for gene activation and other genetic alterations may play a role [1117]. A more recent study of this gene indicates high expression in other types of salivary gland neoplasms as well (adenoid cystic carcinoma, polymorphous low-grade adenocarcinoma and monomorphic types of adenoma) [636].

TP53
TP53 is a tumour suppressor gene located at the short arm of chromosome 17. The protein product acts as a transcription factor for cell differentiation, proliferation and death [636,1117,1485]. The role of this gene in salivary gland tumorigenesis remains unknown. Studies of different tumours have yielded variable results [554,1327,2198]. The incidence of p53 expression in other benign, malignant and hybrid tumours is low and does not correlate with recurrence [1823]. At present there is insufficient information on the correlation between p53 and outcome. These unsettling results reflect the lack of technical and interpretative uniformity in assessing this marker [2421].

Expression profiles
A study of nine benign (4 Warthin tumours and 5 pleomorphic adenomas) and three carcinomas (2 mucoepidermoid and one clear cell carcinoma), using cDNA of 19,000 human expressed sequence tags, identified a small set of genes that separate mucoepidermoid and clear cell carcinomas from normal and benign counterparts. Genes identified in carcinomas were apoptosis related [802].
A study of adenoid cystic carcinoma using oligonucleotide array platform for 8920 human genes was recently reported [818]. The study identified a set of genes that included basement membrane and extracellular matrix-related genes and genes encoding transcription factors SOX4 and AP-2a and members of the Wnt/β-catenin signalling pathway. A recent study of the gene expression in a cohort of pleomorphic adenomas and in spectrum of malignant tumours has also delineated a potential genetic profile that may be used in the biological investigation of these tumours [1652].

Genetic susceptibility
There is no evidence of familial clustering. An association has been reported with dermal cylindromatosis in the setting of Brooke-Spiegler syndrome [1248].

Prognosis and predictive factors
Prognosis correlates most strongly with clinical stage, emphasizing the importance of early diagnosis. The microscopcic grade and tumour type have been shown to be independent predictors of behaviour and often play an important role in optimizing treatment [1264,1918,2440,2447,2449,2519]. Locoregional failure of some types of salivary carcinomas results in a greater likelihood of distant metastasis indicating a need for aggressive initial surgery [2441]. As might be expected, there is often a positive correlation between grade and clinical stage.
Acinic cell carcinoma

**Definition**
Acinic cell carcinoma is a malignant epithelial neoplasm of salivary glands in which at least some of the neoplastic cells demonstrate serous acinar cell differentiation, which is characterized by cytoplasmic zymogen secretory granules. Salivary ductal cells are also a component of this neoplasm.

**ICD-O code**
8550/3

**Synonyms**
Acinic cell adenocarcinoma, acinous cell carcinoma. Acinic cell tumour is an inappropriate synonym since the malignant biologic behaviour of this neoplasm is well-established [2304].

**Epidemiology**
Slightly more women than men are affected. There is no predilection for any ethnic group. Affected patients range from young children to elderly adults with a fairly even distribution of patients from the second to the seventh decades of life. Four percent of the patients are under 20 years old [668,1304,1954].

**Localization**
The overwhelming majority, almost 80%, of acinic cell carcinomas occur in the parotid gland, and about 17% involve the intraoral minor salivary glands. Only about 4% develop in the submandibular gland, and less than 1% arise in the sublingual gland [668,2711,2886].

**Clinical features**
They typically manifest as slowly enlarging, solitary, unfixed masses in the parotid region, but a few are multinodular and/or fixed to skin or muscle. A third of patients also experience pain, which is often vague and intermittent, and 5-10% develop some facial paralysis. While the duration of symptoms in most patients is less than a year, it can be up to several decades in some cases [478,668,670,1435,2445].

**Macrosopcy**
Most are 1-3 cm in largest dimension. They are usually circumscribed, solitary nodules, but some are ill-defined with irregular peripheries and/or multinodularity. The cut surface appears lobular and tan to red. They vary from firm to soft and solid to cystic.

**Tumour spread**
Usually, acinic cell carcinomas initially metastasize to cervical lymph nodes and subsequently to more distant sites, most commonly the lung [670,960].

**Histopathology**
While serous acinar cell differentiation defines acinic cell carcinoma, several cell types and histomorphologic growth patterns are recognized. These are acinar, intercalated ductal, vacuolated, clear, and non-specific glandular and solid/lobular, microcystic, papillary-cystic, and follicular growth patterns [161,478,668,1492,2290,2304].

Acinar cells are large, polygonal cells with lightly basophilic, granular cytoplasm and round, eccentric nuclei. The cytoplasmic zymogen-like granules are PAS positive, resistant to diastase digestion, and weakly stained or non-stained with mucicarmine. However, the PAS positivity can sometimes be very patchy and not immediately obvious. Intercalated duct type cells are smaller, eosinophilic to amphophilic, cuboidal with central nuclei, and surround variably sized luminal spaces. Vacuolated cells contain clear, cytoplasmic vacuoles that vary in number and size. The vacuoles are PAS negative. Clear cells are similar in size and shape to acinar cells but have non-staining cytoplasm that is non-reactive with PAS staining. Non-specific glandular cells are round to polygonal, amphophilic to eosinophilic cells with round nuclei and poorly demarcated cell borders. They often develop in syncytial sheets.

Tumour cells are closely apposed to one another in sheets, nodules, or aggregates in the solid/lobular growth pattern. Numerous small spaces that vary from several microns to a millimetre or more in size characterize the microcystic pattern. Prominent cystic lumina, larger than the

---

G. Ellis  
R.H.W. Simpson
Acinic cell carcinoma

Microcystic spaces that are partially filled with papillary epithelial proliferations characterize the papillary-cystic pattern. This variant, in particular, may be very vascular and haemorrhagic and sometimes phagocytosis of haemosiderin by luminal tumour cells is a conspicuous feature. In the follicular pattern, multiple, epithelial-lined cystic spaces are filled with eosinophilic proteinaceous material, which produces a thyroid follicle-like appearance. Psammoma bodies are occasionally seen and are sometimes numerous. They are not restricted to the papillary-cystic variant and have been reported in FNA specimens.

Although a single cell type and growth pattern often dominate, many tumours have combinations of cell types and growth patterns. Acinar cells and intercalated duct-like cells often dominate while the other cell types seldom do. Clear cells are seen in only 6% of all acinic cell carcinomas [670]. They are usually focal and only rarely cause diagnostic confusion. The solid/lobular and microcystic patterns are most frequent, followed by the papillary-cystic and follicular patterns.

A prominent lymphoid infiltrate of the stroma is associated with many acinic cell carcinomas [83,1717]. Whereas a heavy lymphoid infiltrate by itself has no prognostic significance, some tumours are well-circumscribed masses arranged in a microfollicular growth pattern and with a low proliferation index. They are completely surrounded by the lymphoid infiltrate (with germinal centre formation) and a thin fibrous pseudocapsule. These tumours appear to constitute a subgroup that behaves far less aggressively than other acinic cell carcinomas [1717].

Immunoprofile

Although the immunoprofile is non-specific, acinic cell carcinomas are reactive for cytokeratin, transferrin, lactoferrin, alpha 1-antitrypsin, alpha 1-antichymotrypsin, IgA, carcinoembryonic antigen, Leu M1 antigen, cyclooxygenase-2, vasoactive intestinal polypeptide, and amylase. The zymogen granules in the neoplastic acinar cells are often non-reactive with anti-α-amylase immunostain, an enzyme in zymogen granules of normal serous acinar cells. Reactivity for oestrogen receptor, progesterone receptor, and prostate-specific antigen has been described in some tumours [338, 429,995,1031,1049,1214,2230,2296,2529,2571]. Approximately 10% of tumours are positive for S-100 protein [2529].

Electron microscopy

Multiple, round, variably electron dense, cytoplasmic secretory granules characterize acinar type cells. The number and size of the granules varies. Rough endoplasmic reticulum, numerous mitochondria, and sparse microvilli are also typically. Some cells contain vacuoles of varying size and shape. Basal lamina separates groups of acinar and ductal

Fig. 5.2 Acinic cell carcinoma. A Clear cells in acinic cell carcinoma are similar in size and shape to acinar-type cells but have non-staining cytoplasm. Some cells have a variable amount of eosinophilic cytoplasm. B The cytoplasmic granules in serous acinar-type cells in acinic cell carcinoma stain with PAS and are resistant to diastase digestion. C Sheets of tumour cells, acinar-type cells in this case, with few or no cystic spaces characterize a solid growth pattern in acinic cell carcinoma. D Often acinar type cells are scattered among nonspecific glandular cells. They are often inconspicuous with H&E-stain but highlighted with PAS stain (PAS stain).
tumour cells from the stromal tissues. The light microscopically clear cells are the result of artefactual changes or dilatations of rough endoplasmic reticulum, lipid inclusions, enzymatic degradation of secretory granules, and intracytoplasmic pseudolumina [398,539,543,971].

Histogenesis
Most investigators consider that these tumours arise from neoplastic transformation of the terminal duct cells (intercalated duct cells) with histodifferentiation toward serous acinar cells. It has been shown [539,540], however, that normal serous acinar cells undergo mitotic division, and some acinic cell carcinomas could arise from transformation of these cells.

Genetics

Cytogenetics
Multiple structural and numerical abnormalities of these tumours have been reported but no consistent or specific alterations can be defined. Deletions of chromosome 6q, loss of Y and trisomy 21 have been reported [2238]. A recent report of multiple analyses from one tumour showed various structural abnormalities, suggesting a polyclonal derivation [1218].

Molecular genetics
In the largest molecular analysis of these tumours 21 (84%) of the 25 tumours studied showed LOH in at least one of the 20 loci on chromosomes 1,4,5,6 and 17 [1526]. The most frequently altered regions were noted at chromosomes 4p, 5q, 6p and 17p regions. Chromosomes 4p15-16, 6p25-qter and 17p11 showed the highest incidence of alterations.

Another study of multiple spatially obtained samples from one tumour showed evidence for polyclonality suggesting different origins for this tumour [1218].

Prognosis and predictive factors
The average among several studies is a recurrence rate of about 35% and a metastatic rate and disease-associated death incidence of about 16% [441,478,670,960,1060,1112,2886]. Distant recurrences and metastasis to cervical lymph nodes indicate a poor prognosis. Distant metastasis is associated with very poor survival. While tumours in the submandibular gland are more aggressive than those in the parotid gland, acinic cell carcinomas in minor salivary glands are less aggressive than those in the major salivary glands [340,864,1112,2886].

Attempts at histological grading have been controversial and inconsistent. Features that are often associated with more aggressive tumours include frequent mitoses, focal necrosis, neural invasion, pleomorphism, infiltration, and stromal hyalinisation [161,650,670,960,2017,2445]. Occasional cases of dedifferentiation from a low-grade to a high-grade malignancy have been reported. These tumours are characterized by cytological pleomorphism, increased mitotic and proliferation indices and have a worse prognosis [594,1063,1191,2459].

Staging is often a better predictor of outcome than histomorphologic grading. Large size, involvement of the deep lobe of the parotid gland, and incomplete resection indicate a poor prognosis. The cell proliferation marker Ki-67 has shown the most promise as a predictor of biological behaviour. No recurrences of acinic cell carcinomas were seen when the percentage of positively immunostained tumour cells was below 5% whereas most patients with tumour indices above 10% had unfavourable outcomes [1060,2388].
**Definition**
Mucoepidermoid carcinoma is a malignant glandular epithelial neoplasm characterized by mucous, intermediate and epidermoid cells, with columnar, clear cell and oncocytoid features.

**ICD code** 8430/3

**Synonyms**
Mixed epidermoid and mucus secreting carcinoma. Mucoepidermoid tumour is an inappropriate synonym since the malignant biologic behaviour of this neoplasm is well established.

**Epidemiology**
Mucoepidermoid carcinoma (MEC) is the most common primary salivary gland malignancy in both adults and children (1650,2681,2711).

MEC demonstrates a wide, nearly uniform age distribution, with diminution in paediatric and geriatric life (456,1850).

Mean patient age is approximately 45 years. Sixty percent of palate lesions are in patients under 40. Tongue neoplasms are reported at an older average age. There is a 3:2 female predilection, but higher female predominance for tongue and retromolar pad tumours (668).

**Localization**
Approximately half of tumours (53%) occur in major glands. The parotid glands predominate, representing 45%, with 7% for submandibular glands and 1% in sublingual glands. The most frequent intra-oral sites are the palate and buccal mucosa.

**Clinical features**

**Signs and symptoms**
Most tumours present as firm, fixed and painless swellings. Sublingual gland lesions may demonstrate pain in spite of small size. Superficial intraoral neoplasms may exhibit a blue-red colour and mimic a mucocele or vascular lesion. The mucosa overlying palatal tumours can be papillary. Cortical bone is sometimes superficially eroded. Symptoms can include pain, otorhoea, paraesthesia, facial nerve palsy, dysphagia, bleeding and trismus (703).

**Macroscopy**
Tumours are firm, smooth, often cystic, tan, white or pink with well-defined or infiltrative edges.

**Tumour spread and staging**
Parotid gland tumours spread to adjacent pre-auricular lymph nodes, then to the submandibular region. Submandibular gland neoplasms spread to submandibular and the upper jugular lymphatic chain. Palatal lesions may extend into the upper respiratory tract and skull base. Lip lesions invade submental nodes and intraoral tumours metastasize to submandibular, post auricular and upper accessory nodes in neck level II. With advancing disease, levels III, IV and V may become involved. Distant metastases may be widespread to lung, liver, bone, and brain.

**Histopathology**
Mucoepidermoid carcinoma is characterized by squamoid (epidermoid), mucus producing and cells of intermediate type. The proportion of different cell types and their architectural configuration (including cyst formation) varies in and between tumours.

<table>
<thead>
<tr>
<th>Histopathologic feature</th>
<th>Point value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic component &lt; 20%</td>
<td>2</td>
</tr>
<tr>
<td>Neural invasion</td>
<td>2</td>
</tr>
<tr>
<td>Necrosis</td>
<td>3</td>
</tr>
<tr>
<td>4 or more mitoses / 10 hpf</td>
<td>3</td>
</tr>
<tr>
<td>Anaplasia</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumour Grade</th>
<th>Point Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0 - 4</td>
</tr>
<tr>
<td>Intermediate</td>
<td>5 - 6</td>
</tr>
<tr>
<td>High</td>
<td>7 or more</td>
</tr>
</tbody>
</table>

**Table 5.1** Histopathologic features, point values and point scores used in grading mucoepidermoid carcinoma

**Fig. 5.5** Mucoepidermoid carcinoma. A Low-grade. B Intermediate grade.
They are usually multicystic with a solid component and sometimes the latter predominates. Some tumours have defined borders but infiltration of gland parenchyma is evident. Cystic spaces are lined by mucous cells with basaloid or cuboidal intermediate cells interspersed, and to a lesser degree, polygonal epidermoid cells, but keratinization is rare. Mucous cells are large, with pale cytoplasm and peripherally displaced nuclei. They typically constitute less than 10% of the tumour. Sialomucin content is demonstrated by mucicarmine or Alcian blue staining. Intermediate cells usually predominate. Clear, columnar and/or oncocytic cell populations may be present and occasionally are prominent [985, 1198, 1996]. Clear cells demonstrate minimal sialomucin, but are diastase-sensitive periodic acid-Schiff positive, indicating glycogen content [666]. Focal sclerosis and/or mucus extravasation with inflammation is common. A sclerosing variant has been described [2657]. Neural invasion, necrosis, increased mitoses or cellular anaplasia are uncommon. At the tumour edge, a lymphocytic infiltrate with possible germinal centre formation can mimic nodal invasion [83].

**Grading**

Several systems have been proposed to grade this neoplasm, but none has been universally accepted [86, 258, 695, 1850, 2443]. However, one recent system using five histopathologic features has been shown to be reproducible in defining low, intermediate and high-grade tumours [86, 972, 1766]. In the submandibular gland low-grade tumours tend to behave more aggressively [921].

**Immunoprofile**

Squamoid cells may be sparse in mucoepidermoid carcinoma and high molecular weight cytokeratins can help identify them.

**Differential diagnosis**

Differential diagnosis includes necrotizing sialometaplasia [263], inverted ductal papilloma, cystadenoma [2292], carcinomas composed of clear cells, adenosquamous carcinoma, squamous cell carcinoma and metastases.

**Genetics**

**Cytogenetics**

Several MECs have been reported to possess t(11:19) (q21;p13) translocation as the only abnormality (or with other structural and numerical alterations). This abnormality is also shared by acute leukaemia [655, 1130, 1904].

**Molecular genetics**

Molecular studies of these tumours are few and limited in number of cases. They show infrequent genetic loss at chromosomes 9p21, 8q, 5p, 16q and 12p [351, 1228, 2408]. Studies of the H-ras gene in these tumours have reported 18% mutations at codon 12 and/or 13 (one case) and no mutations at codon 61 [2858]. The mutations are mainly found in high-grade tumours [2859]. Recently molecular analysis of the t(11:19) (q21;p12) resulted in the identification of a fusion transcript resulting from the binding of exon-1 of a novel gene of unknown function, the mucoepidermoid carcinoma translocated gene-1 (MECT1), at 19p13 region with exons 2-5 of a novel member of the mastermind-like gene family (MAML2) at 11q21 region. This transcript activate the notch target genes.

**Prognosis and predictive factors**

Most patients have a favourable outcome. In one study, 8% of patients died of disease: 11% and 5% for major and minor gland tumours, respectively. Death correlated with high-grade histopathologic features in minor gland and parotid gland tumours, but not in patients with submandibular gland tumours [921]. Death resulted from unresectable locoregional tumour, distant metastases or complications of adjunctive therapy [2609]. The impact of grading on prognosis was described before and, additionally a MIB-1 index >10% correlates with high histopathologic grade, increased recurrence, metastasis and decreased patient survival [2387, 2905]. Currently, there are no prognostically useful genetic factors.
Adenoid cystic carcinoma

Definition
Adenoid cystic carcinoma is a basaloid tumour consisting of epithelial and myoepithelial cells in variable morphologic configurations, including tubular, cribriform and solid patterns. It has a relentless clinical course and usually a fatal outcome.

ICD code
8200/3

Epidemiology
Adenoid cystic carcinomas (AdCC) comprise approximately 10% of all epithelial salivary neoplasms and most frequently involve the parotid, submandibular and minor salivary glands. They comprise 30% of epithelial minor salivary gland tumours with the highest frequency in the palate, followed by the tongue, buccal mucosa, lip and floor of mouth. The tumour occurs in all age groups with a high frequency in middle-aged and older patients. There is no apparent sex predilection except for a high incidence in women with submandibular tumours [1663,1849,2016,2444].

Clinical features
The most common symptom is a slow growing mass followed by pain due to the propensity of these tumours for perineural invasion. Facial nerve paralysis may also occur [1849,2016,2444,2519].

Macroscopy
The carcinomas are solid, well-circumscribed but unencapsulated. They present as light-tan and firm masses of variable sizes. They are invariably infiltrative [161,1663,2439].

Histopathology
Tumours consist of two main cell types: ductal and modified myoepithelial cells that typically have hyperchromatic, angular nuclei and frequently clear cytoplasm. There are three defined patterns: tubular, cribriform and solid. In the tubular form, well-formed ducts and tubules with central lumina are lined by inner epithelial and outer myoepithelial cells. The cribriform pattern, the most frequent, is characterized by nests of cells with cylindromatous microcystic spaces. These are filled with hyaline or basophilic mucoid material. The solid or basaloid type is formed of sheets of uniform basaloid cells lacking tubular or microcystic formation. In the cribriform and solid variants small true ducts are invariably present but may not be immediately apparent. Each of these forms can be observed as the dominant component or more commonly as a part of a composite tumour [161,1663,1849,2016,2444,2519]. The stroma within the tumour is generally hyalinized and may manifest mucinous or myxoid features. In some tumours there is extensive stromal hyalinization with attenuation of the epithelial component. Perineural and to a lesser extent, intraneural invasion is a common and frequently conspicuous feature of AdCC. Tumours can extend along nerves for a considerable distance beyond the clinically apparent boundaries of the tumour. In addition, the tumour may invade bone extensively before there is

Table 5.2  Differential diagnosis of adenoid cystic carcinoma

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Pattern</th>
<th>Cellular features</th>
<th>Perineural invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal cell adenoma</td>
<td>Syncytial/ non-invasive</td>
<td>Uniform Basaloid</td>
<td>No</td>
</tr>
<tr>
<td>Epithelial-myoepithelial</td>
<td>Tubular/biphasic</td>
<td>Uniform, with clear outer cells</td>
<td>Rare</td>
</tr>
<tr>
<td>carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basaloid squamous cell carcinoma</td>
<td>Syncytial</td>
<td>Marked pleomorphism focal keratinization</td>
<td>Rare</td>
</tr>
<tr>
<td>Basal cell adenocarcinoma</td>
<td>Syncytial/invasive</td>
<td>Mild pleomorphism/ invasive</td>
<td>Yes</td>
</tr>
<tr>
<td>AdCC Solid</td>
<td>Syncytial</td>
<td>Mild pleomorphism</td>
<td>Yes</td>
</tr>
<tr>
<td>AdCC Tubular/cribriform</td>
<td>Ductal/ cylindromatous</td>
<td>Uniform biphasic</td>
<td>Yes</td>
</tr>
<tr>
<td>PLGA</td>
<td>Tubular papillary</td>
<td>Mild pleomorphism</td>
<td>Yes</td>
</tr>
<tr>
<td>pattern variable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellular PA</td>
<td>Syncytial</td>
<td>Uniform</td>
<td>No</td>
</tr>
</tbody>
</table>

AdCC: Adenoid cystic carcinoma; PLGA: Polymorphous low-grade adenocarcinoma; PA: Pleomorphic adenoma

Fig. 5.7  Adenoid cystic carcinoma. Cribriform pattern with mucopolysaccharide filled spaces.
radiographical evidence of osseous destruction.
Adenoid cystic carcinoma occasionally occurs with other different neoplasms (hybrid tumours) [505,1823,2297,2416]. Pleomorphic carcinomas and sarcomatoid transformation of adenoid cystic carcinoma have been reported, mostly in recurrent and metastatic disease [397, 418].

**Immunohistochemistry**

In differentiating between polymorphous low-grade adenocarcinoma and adenoid cystic carcinoma, Ki-67 immunostaining may be helpful [2680]. DNA content, C-kit and E-cadherin have been found to be associated with the biological behaviour of these tumours [636, 637, 1215, 1577]. Ki-67 and p53 have also been studied in these tumours [2844], but no clear association with outcome have been reported. C-kit overexpression and its biological implication remains unknown. None of these markers, however, have been validated. Estrogen and progesterone receptor positivity has been reported in adenoid cystic carcinoma but the biological significance is currently unknown.

**Differential diagnosis**

Pleomorphic adenoma, polymorphous low-grade adenocarcinoma, epithelial-myoeipithelial carcinoma, basal cell adenoma or adenocarcinoma and basaloid squamous carcinomas are the major entities to be differentiated from adenoid cystic carcinoma.

**Genetics**

**Cytogenetics**

The most consistent, although not exclusive, reported alterations have been at chromosomes 6q, 9p and 17p12-13 regions. The t(6;9) (q21-24;p13-23) has been reported in several tumours and is considered to be a primary event in at least a subset of these tumours [657, 1220, 1906, 2238].

**Molecular genetics**

Frequent losses at 12q (33%) 6q23-qter, 13q21-q22 and 19q regions (40%) have been reported [657]. A study of the 9p21 regions and the p16 gene found only one tumour with LOH at this region and no mutations of the gene [351]. A recent genomic study identified new markers that may be helpful in future investigation of these tumours. Promoter methylation of the p16 was found in 20% of these tumours [1653]. Studies of other genes have been equally non-conclusive. Alterations of the p53 and Rb genes have been reported but no alterations in the K-ras have been found [2843].

**Prognosis and predictive factors**

Factors that influence survival include histologic patterns, tumour site, clinical stage, bone involvement and status of surgical margins [1849, 2016, 2439, 2444, 2519]. Generally, tumours composed of tubular and cribriform patterns pursue a less aggressive course than those with greater than 30% of solid component [2519]. Along with the histologic pattern, clinical stage greatly affects prognosis. Other studies have failed to confirm the value of grading [2439, 2444] and underscored the significance of tumour size and clinical stage as the most consistent predictors of clinical outcome in patients with these tumours [2442, 2449]. The 5-year survival rate is approximately 35% but the long-term survival is poorer. Eighty to 90% of patients die of disease in 10-15 years [993, 2016]. The local recurrence rate ranges from 16-85% in several series of these tumours. Recurrence is a serious sign of incurability. Lymph node involvement is uncommon but has been reported to range from 5-25% and typically from tumours of the submandibular gland and is often due to contiguous spread rather than metastasis. The incidence of distant metastasis is estimated to range from 25-55%. The lung followed by bone, brain and liver are the common sites. Only 20% of patients with distant metastasis survive 5-years. The influence of perineural invasion on survival has been contradictory [860]. Wide local and radical surgical excisions with and without post-operative radiation is the treatment of choice [54, 339, 1849, 2439, 2444, 2519]. Radiation alone or with chemotherapy in the treatment of recurrent or metastatic disease has shown limited success. Radiotherapy, however, has been shown to improve local control in cases with microscopic residual disease [2670]. The value of chemotherapy in these tumours is limited and remains to be proven.

---

Fig. 5.8 Adenoid cystic carcinoma. A Tubular form, composed of inner epithelial ductal and outer myoepithelial cells. B Solid form. Tumour cells are small and basaloid with scanty cytoplasm.
Polymorphous low-grade adenocarcinoma

M.A. Luna
B.M. Wenig

Definition
A malignant epithelial tumour characterized by cytologic uniformity, morphologic diversity, an infiltrative growth pattern, and low metastatic potential.

ICD-O code 8525/3

Synonyms
Terminal duct carcinoma, lobular carcinoma

Epidemiology
PLGA is the second most common intraoral malignant salivary gland tumour, accounting for 26% of all carcinomas (2711). The female-to-male ratio is about 2:1. Patient age ranges from 16-94 years mean 59 years. Over 70% of the patients are between the ages of 50 and 70 years (342,697). To date, only two tumours have been reported in the pediatric population (2641).

Localization
Approximately 60% of the cases have involved the palate. Other intraoral locations are the buccal mucosa, retromolar region, upper lip, and the base of the tongue (342,697). Uncommon locations include major salivary and lacrimal glands, nasopharynx and nasal cavity (1299,2763).

Clinical features
A painless mass in the palate is the most common clinical sign. The duration of the lesion has varied from weeks to as much as 40 years (342). Bleeding, telangiectasia, or ulceration of the overlying mucosa occurs occasionally.

Macroscopy
PLGA usually appears as a firm, circumscribed, but non-encapsulated, yellow-tan lobulated nodule up to several centimetres in greatest dimension (average 2.2 cm) (342).

Histopathology
PLGA is characterized by cytologic uniformity, histologic diversity, and an infiltrative growth pattern. The tumour cells are small to medium size and uniform in shape with bland, minimally hyperchromatic, oval nuclei and only occasional nucleoli. Mitoses are uncommon and necrosis is not typical. The striking feature of these carcinomas is the variety of morphologic configurations between tumours and within an individual tumour. The main microscopic patterns are: 1) lobular, 2) papillary or papillary-cystic (typically focal), 3) cribriform areas sometimes resembling those in adenoid cystic carcinoma, and 4) trabecular or small, duct-like structures lined by a single layer of cuboidal cells. The cells form concentric whorls or targetoid arrangements around blood vessels or nerves. Foci of oncocytic, clear, squamous or mucous cells may be found. Stroma may show areas of mucinosis or hyalinization. Despite the innocuous cytologic appearance, the neoplasm always invades adjacent soft tissues and is unencapsulated. Neurotropism is common in PLGA. Invasion of adjacent bone may be seen in tumours of the palate or mandible.

Immunohistochemistry
The neoplastic cells of PLGA are immunoreactive with antibodies to cytokeratin (100%), vimentin (100%), S-100 protein (97%), carcinoembryonic antigen (54%), glial fibrillary acidic protein (GFAP) (15%), muscle specific actin (13%), and epithelial membrane antigen (12%) (342,2011,2763). Expression of galectin 3 has been reported to be significant in PLGA (2006). Bcl-2 is over expressed in most cases of PLGA (342,2011).

Differential diagnosis
The differential diagnosis includes pleomorphic adenoma (PA) and adenoid cystic carcinoma (AdCC), especially in small biopsy specimens. Unlike PLGA, PA is nearly always circumscribed and is composed of proliferating stromal, epithelial, and myoepithelial cells. It lacks the infiltrative, noncircumscribed character of PLGA. Although myxoid tissue is present in both tumours, the myxochondroid and chondroid areas present in PA are not evident in PLGA. Also, the typical benign plasmacytoid myoepithelial cells characteristic of palatal PA are seldom observed in PLGA. Staining with GFAP may be helpful in differentiating PA from PLGA. The distinction between PLGA and AdCC is based primarily on cytologic features. Cells in PLGA are cuboidal or columnar. They have vesicular nuclei and often conspicuous eosinophilic cytoplasm without the basaloid features characteristic of AdCC. Papillary and fascicular growth patterns are extremely rare in AdCC. Furthermore, PLGA does not have large cribriform pseudocystic spaces that contain pools of haematoxyphilic glycosaminoglycans. The solid cellular areas of PLGA lack nuclear pleomorphism, necrosis, increased mitotic activity, and the numerous tubular structures characteristic of the solid variant of AdCC. The potential discriminating value of immunohistochemistry between cases of PLGA and AdCC remains controversial (547), although some subtle differences may be apparent when series of these two neoplasms are studied (342,2006,2011,2391). Proliferative cell marker rates in PLGA are usually less than 6.4% (mean values 1.6% and 2.4%) (2391). However, a higher proliferative rate (average 7%) has been reported by others investigators (2011).

Genetics
Cytogenetic studies of this tumour are few. A total of 7 cases of which two were carcinoma ex-pleomorphic adenoma, have been reported. Alterations at 8q12 were found in two, 12q rearrangements in five, two showed a clonal t(6;9) (p21;p22) and one a monosomy 22 (1651). Cytogenetic alterations in PLGA have frequently displayed chromosome 12 abnormalities affecting the q arm and the p arm (1651).
Prognosis and predictive factors

The overall survival rate of patients with PLGA is excellent [164,342,696, 697,808]. A review of series with large numbers of cases and with long-term follow-up revealed a local recurrence rate between 9% and 17% and a regional metastases rate from 9-15% [342,697]. Distant metastases have seldom been reported [342,697]. Deaths attributed to tumour are unusual, and they occurred after prolonged periods [342,697]. In studies which accepted tumours with a predominant papillary configuration a higher incidence of cervical lymph node metastasis was reported [697]. The status of such tumours within the spectrum of PLGA is controversial. Dedifferentiation of PLGA has been reported and carries a less favourable prognosis. Such tumours should not be included under the rubric of typical PLGA [2368]. Treatment consists of complete surgical excision. Neck dissection should be added for those patients with cervical adenopathy.

Cribriform adenocarcinoma of the tongue

A possible variant is cribriform adenocarcinoma of the tongue, but it is not yet clear whether this represents a genuine entity or just an unusual growth pattern in PLGA, with which there appears to be some overlap [1718]. So far described only in one series, all cases presented with a mass in the tongue, usually the posterior part, and synchronous metastases in lateral neck lymph nodes, but no distant spread. There was an equal sex incidence and the mean age at presentation was 50.4 years (range 25-70).

The tumour grows beneath the surface epithelium and infiltrates soft tissue. It is divided by fibrous septa into lobules, which are solid or cribriform. A characteristic feature is that some nearly solid islands have a glomeruloid arrangement of broad microfollicular papillae separated from a layer of peripheral columnar cells by a narrow cleft. Small numbers of tubules are seen, and occasional spindling of tumour cells may occur. The nuclei are uniform, pale and often overlap, closely mirroring those of papillary carcinoma of the thyroid. Mitotic figures are sparse. No necrosis or significant haemorrhage is seen, and the stroma includes hyalinized areas, and rarely psammoma bodies. The tumours are positive for cytokeratin, and more patchily for S-100 protein. Myoepithelial markers, such as actin are either negative or only focally positive. Thyroglobulin staining is consistently negative.
Definition
A malignant tumour composed of variable proportions of two cell types, which typically form duct-like structures. The biphasic morphology is represented by an inner layer of duct lining, epithelial-type cells and an outer layer of clear, myoepithelial-type cells.

ICD-O code 8562/3

Synonyms
Adenomyoepithelioma (176), clear cell adenoma (494,2228), glycogen-rich adenoma (913), glycogen-rich adenocarcinoma (1758), clear cell carcinoma (407).

Epidemiology
Epithelial-myoepithelial carcinoma (EMC) represents around 1% of the salivary gland tumours. It is more prevalent in women (F: M=2:1). The patients range in age from 13 to 89 years, with the peak incidence in the 6th and 7th decades (436,493,614,784,1580). Only two cases have been reported in the paediatric group (436,1775).

Localization
EMC occurs mostly in major salivary glands, mainly in the parotid (60%), but also in the minor glands of oral mucosa and the upper (436,493,614,784,1580) and lower respiratory tract (610,1126,1174,2002).

Clinical features
EMC forms a painless, slow-growing mass. Tumours arising in minor glands frequently present as ulcerated, submucosal nodules and have less well-defined margins. Rapid growth, facial nerve palsy and/or associated pain are suggestive of concomitant high-grade areas.

Macroscopy
EMC is characteristically a multinodular mass, with expansive borders and lacking a true capsule. Cystic spaces may be present. Tumours of the minor glands are poorly circumscribed.

Histopathology
EMC has a lobulated growth pattern with a mixed tubular and solid architectural arrangement. Papillary and cystic areas can be identified in around 20% of the cases. Tumours from minor salivary and sero-mucinous glands show infiltration of surrounding tissues and there is ulceration of the overlying mucosa in about 40% of the cases. The hallmark of EMC histology is the presence of bi-layered duct-like structures: the inner layer is formed by a single row of cuboidal cells, with dense, finely granular cytoplasm and central or basal, round nucleus. The outer layer may show single or multiple layers of polygonal cells, with well-defined borders; the cytoplasm is characteristically clear and the nucleus is vesicular and slightly eccentric. The double-layered pattern is preserved in papillary-cystic areas but solid tumour areas may be exclusively formed by clear cells. PAS positive, hyaline, eosinophilic strands of basement membrane-like material surround the duct-like structures and, in solid areas, divide the clear cells into theques. Coagulative necrosis at the centre of tumour nodules is uncommon. In rare cases, squamous differentiation and spindle cells are observed as well as an oncocytic appearance in the inner cell layer of neoplastic ducts. Perineural and vascular invasion are frequent and bone invasion may occur. None to 1-2 mitoses per 10 HPF can be identified in the clear cell population of EMC. Rare cases of dedifferentiation have been reported (42,783).

Immunoprofile
Myoepithelial markers (smooth muscle actin, HHF35, p63 and/or calponin) stain the clear cell compartment. The luminal cells stain with cytokeratins.
**Differential diagnosis**

The differential diagnosis of EMC includes all primary salivary gland tumours that are predominantly formed by clear cells: pleomorphic adenoma, myoepithelioma, oncocytoma and mucoepidermoid carcinoma. Differential diagnosis with clear cell carcinoma, NOS relies on the demonstration of the peculiar amyloid-like quality of the stroma and on the absence of myoepithelial markers. Metastatic kidney and thyroid carcinoma may be distinguished using immunohistochemistry; CD10 and high-molecular weight cytokeratin in the former and thyroglobulin in the latter. EMC foci can be encountered within carcinoma ex pleomorphic adenoma as part of the carcinomatous component.

**Genetics**

A limited number of cases (6) have been karyotyped (656,1650,1751), half of them showing non-distinctive chromosomal alterations and the remaining normal karyotypes.

**Prognosis and predictive factors**

Recurrence occurs in around 40% of cases and metastasis in 14%. The most common metastatic sites are cervical lymph nodes, lung, liver and kidney. Death from disease complications occurs in less than 10% of the patients [436,493,614,784,1580]. Five- and 10 year overall survival rates are 80% and 72%, respectively [784]. Size and rapid tumour growth are associated with worse prognosis [42,783]. Margin status is a major pathological prognostic factor. Incomplete surgical excision is associated with recurrence and metastasis. The poorer prognosis associated with tumours located in minor salivary glands may be due to the higher frequency of recurrences due to incomplete surgery. Atypia is associated with unfavourable outcome [784] whenever present in more than 20% of tumour area. EMC is usually diploid [784,992]. Aneuploidy and high mitotic counts have been reported in cases with unfavourable prognosis [784]. Areas of dedifferentiation also predict poor outcome, with recurrence and metastasis in 70% of patients [42,783].

---

**Fig. 5.11** Epithelial-myoepithelial carcinoma. **A** Ductal tumour cells of inner layer predominance. **B** Solid growth of clear, myoepithelial-type cells.

**Fig. 5.12** Epithelial-myoepithelial carcinoma (EMC) of the parotid gland. **A** Dedifferentiated EMC. Low molecular weight cytokeratins emphasizes the loss of the biphasic pattern (lower). The differentiated component (upper) retains focal epithelial differentiation (CAM 5.2). **B** Immunostained for smooth muscle actin (SMA): the reverse image of that of the differentiated area is obtained, with intense staining of the outer layers. **C** Tumour cells of the outer layer are also strongly immunoreactive for calponin.
Clear cell carcinoma, not otherwise specified

**Definition**
Clear cell carcinoma, not otherwise specified (NOS), is a malignant epithelial neoplasm composed of a monomorphic population of cells that have optically clear cytoplasm with standard haematoxylin and eosin stains. Because many types of salivary gland neoplasms commonly or consistently have a component of clear cells, clear cell carcinoma is distinguished by the absence of features characteristic of these other neoplasms and its monomorphous population of clear cells.

**ICD-O code**
8310/3

**Synonyms**
Clear cell adenocarcinoma; hyalinizing clear cell carcinoma.

Clear cell carcinoma has been confused with epithelial-myoepithelial carcinoma (EMC), and EMC have been reported as clear cell carcinoma [407].

**Epidemiology**
The peak occurrence is in patients in the 40-70 year age range, and they are rare in children [668,2658]. There is no sex predilection.

**Localization**
Clear cell carcinomas are more frequent in the intraoral minor salivary glands than the major salivary glands [668,1728,1931,2179,2369,2716]. The palate is most frequently involved, but buccal mucosa, tongue, floor of the mouth, lip, and retromolar and tonsillar areas are also affected.

**Clinical features**
The only sign in most cases is swelling, but mucosal ulceration and pain occur with some tumours. Patients have reported the durations of their tumours as 1 month to 15 years [2369].

**Macroscopy**
Although the size of the primary tumour is usually 3.0 cm or less, the tumours usually are poorly circumscribed and infiltrate adjacent salivary gland, mucosa, soft tissues, bone, and nerves. The cut surface is greyish-white.

**Histopathology**
A monomorphous population of polygonal to round cells with clear cytoplasm characterizes clear cell carcinomas. In some cases, a minority of cells have pale eosinophilic cytoplasm. Nuclei are eccentric and round and frequently contain small nucleoli. PAS staining with and without prior diastase digestion of the tissue demonstrates cytoplasmic glycogen that varies from marked to not evident. The adjective glycogen-rich has been used by some to identify clear cell carcinomas with a prominent glycogen content [1028,2658]. With mucicarmine stain, intracytoplasmic mucins are usually absent. The tumour cells are arranged in sheets, nests, or cords, and ductal structures are absent. Mitotic figures are rare, but some tumours have a moderate degree of nuclear pleomorphism. In the hyalinizing type, the stroma is composed of thick bands of hyalinized collagen [727,1728], but in other tumours it consists of interconnecting, thin fibrous septa that may be cellular or loosely collagenous. Clear cell carcinomas are unencapsulated and infiltrative.

**Immunoprofile**
While tumours are immunoreactive for cytokeratin, at least focally, immunohistochemical studies have given variable results for S100 protein, glial fibrillary acidic protein, actin, and vimentin [1028,1728,1931,2348,2369,2658,2716]. Tumours that demonstrate histologic and immunohistochemical features of myoepithelial differentiation are best classified as clear cell variants of myoepithelioma or myoepithelial carcinoma [1719].

---

**Fig. 5.13** Clear cell carcinoma. A Polygonal cells with nonstaining cytoplasm and absence of ductal lumens characterize clear cell carcinoma. B This example is composed of a mostly solid sheet of tumour cells with little stroma.
Electron microscopy
Tight junctions, desmosomal attachments, tonofilaments, microvilli, and basal lamina are features of duct cell differentiation [399,1028,1728,1758,1931,2369,2716].

Histogenesis
Ultrastructural investigations have found features of ductal but not myoepithelial differentiation.

Prognosis and predictive factors
Prognosis is excellent. A few tumours have metastasized to cervical lymph nodes and, rarely, the lung, but no patients have succumbed to this neoplasm [155,948,1728,2716].

Fig. 5.14 Clear cell carcinoma. A Infiltration into adjacent lobules of normal parotid gland. B Clear cell carcinoma of the lip infiltrating skeletal muscle (top) and surrounding a peripheral nerve (lower centre). C PAS staining demonstrates a prominent cytoplasmic glycogen content. D Clear cell carcinoma of the parotid gland. Prominent hyalinized stroma separates nests of tumour cells.
**Definition**
Dominated by basaloid epithelial cells, basal cell adenocarcinoma is cytologically and histomorphologically similar to basal cell adenoma but is an infiltrative epithelial neoplasm with potential for metastasis.

**ICD-O code** 8147/3

**Synonyms**
Basaloid salivary carcinoma, carcinoma ex monomorphic adenoma, malignant basal cell adenoma, malignant basal cell tumour, and basal cell carcinoma [159, 408,698,1163,1340,1576]. Tumours in infants reported as basal cell adenoma/carcinoma or hybrids are best classified as sialoblastomas.

**Epidemiology**
There is no sex predilection. The average age of patients is 60 years, and only adults have been affected [668,673,1576,1792,2726].

**Localization**
Over 90%, of these tumours occur in the parotid gland, and they are rare in the minor salivary glands of the oral cavity [668,673,2703].

**Clinical features**
Rarely, patients complain of pain or tenderness; most tumours are asymptomatic except for swelling. The duration of tumours before excision ranges from weeks to years. Similar to some patients with basal cell adenomas, patients with basal cell adenocarcinomas may have a diathesis of multiple skin adnexal tumours and parotid basal cell adenocarcinomas [65,668,673,1163, 1576].

**Macroscopy**
Basal cell adenocarcinomas most frequently occur in the superficial (lateral) lobe of the parotid gland. The cut surface has variable coloration of grey, tan-white, or brownish. The texture is homogeneous although some tumours are focally cystic. They are unencapsulated, but some tumours appear well-circumscribed while others are obviously infiltrative.

**Histopathology**
Basaloid epithelial cells, which vary from small, dark cells to larger, paler stained cells, form histomorphologic patterns that are described as solid, membranous, trabecular and tubular. A solid pattern, in which variable sized and shaped nests are separated by thin septa or thick bands of collagenous stroma, is most frequent. In the membranous type, tumours produce excessive amounts of eosinophilic, hyalinized basal lamina material that forms intercellular droplets and peripheral membranes. Interconnecting bands of basaloid cells characterize the trabecular growth pattern. In the tubular type, there are luminal spaces among the basaloid cells. There are foci of squamous differentiation in some tumours. The nuclei of tumour cells along the interface with the collagenous stroma are often palisaded. The degree of cytologic atypia and the number of mitotic figures varies from one tumour to another but is often quite minimal. Infiltration of tumour cells into parotid parenchyma, dermis, skeletal muscle, or periglandular fat distinguishes basal cell adenocarcinoma from basal cell adenoma. Vessel or peripheral nerve invasion is evident in about a fourth of the tumours.

**Immunoprofile**
Immunohistochemical staining is variable among tumours. Tumour cells are reactive for cytokeratins and often focally reactive for S100 protein, epithelial membrane antigen, and carcinoembryonic antigen. Limited reactivity for smooth muscle actin and vimentin supports myoepithelial differentiation of some cells [2097,2793].

---

Fig. 5.15 Basal cell adenocarcinoma. A Basal cell adenocarcinoma, parotid gland. Invasive growth. B Abundant, prominently eosinophilic basal lamina material within and around nests of tumour is characteristic of the membranous pattern of basal cell adenocarcinoma.
Precursor lesions
Most basal cell adenocarcinomas probably develop de novo, but some arise by malignant transformation in basal cell adenomas (1576,1792).

Genetics
Cytogenetics
Chromosomal gains at 9p21.1-pter, 18q21.1-q22.3, and 22q11.23-q13.1 as well as losses at 2q24.2 and 4q25-q27 have been described (2612). The gain at 22q12.3-q13.1 is described as also common in adenoid cystic carcinoma.

Molecular genetics
A study of two familial cases and two sporadic basaloid tumours for alterations at the 16q12-13 regions showed high frequency (80%) of LOH in both sporadic and familial basaloid tumours and dermal cylindromas of the familial cases. The minimally deleted region contained the CYLD gene. This study indicates that these tumours share the same alterations as dermal cylindromas and implicates the CYLD gene in their development (437).

Prognosis and predictive factors
While they are locally destructive and often recur, basal cell adenocarcinomas only occasionally metastasize, and death of patients is rare (408,673,698,1163,1340,1576,1792,1799). Ki-67 and PCNA indices are low (782,2097).
Malignant sebaceous tumours

**Sebaceous carcinoma**

**Definition**
Sebaceous carcinoma is a malignant tumour composed of sebaceous cells of varying maturity that are arranged in sheets and/or nests with different degrees of pleomorphism, nuclear atypia and invasiveness.

**ICD-O code** 8410/3

**Epidemiology**
There is a bimodal age distribution with a peak incidence in the third decade and the 7th and 8th decades of life (range 17-93 years) [669,896,901]. The male and female incidence is almost equal. Unlike sebaceous neoplasms of the skin [1132, 2214], there is no increased risk of developing a visceral carcinoma in patients with a salivary gland sebaceous tumour.

**Localization**
Approximately 90% arise in the parotid area, with occasional tumours in the oral cavity, vallecula, sublingual gland, submandibular gland and epiglottis [107, 602,669,693,896].

**Clinical features**
Patients typically present with a painful mass with varying degrees of facial nerve paralysis and occasional fixation to the skin.

**Macroscopy**
Tumours have ranged from 0.6-8.5 cm in greatest dimension and vary from yellow, tan-white, greyish-white, white, to pale pink [896]. They are well circumscribed or partially encapsulated, with pushing or locally infiltrating margins.

**Histopathology**
Tumours are composed of multiple large foci and nests of cells with hyperchromatic nuclei and abundant clear to eosinophilic cytoplasm. Cellular pleomorphism and cytologic atypia are present to varying degrees and are much more prevalent than in sebaceous adenomas. Squamous differentiation is common. There may be areas of basaloïd differentiation, particularly at the periphery of cellular nests. Areas of necrosis and fibrosis are common. Perineural invasion is seen in greater than 20% of tumours; vascular invasion is infrequent. Rare oncocyes and foreign body giant cells with histiocytes may be observed, but lymphoid tissue with follicles or subcapsular sinuses is not seen.

**Prognosis and predictive factors**
The treatment of choice is wide surgical excision for low stage carcinomas. Adjunctive radiation therapy is recommended for higher-stage and grade tumours. The overall 5-year survival rate is 62% [669,896], slightly less than the survival for similar tumours arising in the skin and orbit (84.5%) [234].

**Sebaceous lymphadenocarcinoma**

**Definition**
Sebaceous lymphadenocarcinoma is the malignant counterpart of sebaceous lymphadenoma. It is a carcinoma arising in a sebaceous lymphadenoma.

**ICD-O code** 8410/3

**Synonym**
Carcinoma ex sebaceous lymphadenoma.

**Epidemiology**
It is the rarest salivary gland sebaceous tumour. To date, only three have been reported [901,1525]. All three patients were in their seventh decade; two patients were male and one female.

**Localization**
The tumours arose within the parotid gland or in periparotid lymph nodes.

**Clinical features**
Patients had histories of a mass, two of which were present for more than 20 years.

**Macroscopy**
Tumour colour varies from yellow-tan to grey.

**Histopathology**
These carcinomas are partially encapsulated and locally invasive with foci of sebaceous lymphadenoma intermixed with or adjacent to regions of pleomorphic carcinoma cells exhibiting varying degrees of invasiveness. The malignant portion has ranged from sebaceous carcinoma to sheets of poorly differentiated carcinoma, with areas of ductal differentiation, adenoid cystic carcinoma-like areas or foci of epithelial-myoepithelial carcinoma. Perineural invasion, collections of histiocytes and a foreign body giant cell reaction may occur. Cellular atypia is not observed in the sebaceous lymphadenoma portion of the tumour.

---

Fig. 5.18 A Sebaceous carcinoma. Solid growth of pleomorphic sebaceous tumour cells. Inset: Tumour cells are positive for fat stain (Sudan-III). B Sebaceous lymphadenocarcinoma composed of poorly differentiated carcinoma cells with areas of ductal differentiation.
Cystadenocarcinoma

Definition
Cystadenocarcinoma is a rare malignant tumour characterized by predominantly cystic growth that often exhibits intraluminal papillary growth. It lacks any additional specific histopathologic features that characterize the other types of salivary carcinomas showing cystic growth. It is conceptually the malignant counterpart of the benign cystadenoma.

ICD-O code
8440/3

Synonyms
Papillary cystadenocarcinoma, mucus-producing adenopapillary (non-epidermoid) carcinoma, malignant papillary cystadenoma, and low-grade papillary adenocarcinoma of the palate.

Epidemiology
There is no sex predilection. The average age of patients is 59 years; more than 70% are over 50 years of age.

Localization
About 65% occur in the major salivary glands and most of these arise in the parotid. Involvement of the sublingual gland is proportionately greater than of other benign or malignant tumours. The buccal mucosa, lips, and palate are the most frequently involved minor gland sites.

Clinical features
Cystadenocarcinomas usually manifest as a slowly growing, compressible asymptomatic mass. Tumours of the palate may erode bone.

Macroscopy
The tumours have multiple cystic spaces that are variable in size and often filled with mucin. They are grossly at least partially circumscribed and have ranged in size from 0.4-6 cm.

Histopathology
The tumours are usually well circumscribed but not encapsulated. Numerous haphazardly arranged cysts are evident that are partially filled with mucin, vary in shape and size, and have limited intervening fibrous connective tissue. Small solid neoplastic islands or duct-like structures may occur between the cysts or at the advancing front of the tumour. In about 75% of the cases the lumens of the cysts exhibit varying degrees of papillary proliferation. In either case, cell types that comprise the lining epithelium include, most often, small and large cuboidal, and columnar cells, but mucous, clear and oncocytic cells are occasionally noted. The columnar-rich tumours often predominate in the intraluminal papillary areas and account for their "gastrointestinal" appearance, but the cells usually fail to stain for neutral mucin. Although nucleoli are evident, the nuclei typically are uniformly bland and mitoses rare. However, a prerequisite for the diagnosis is that the cysts and smaller duct-like structures at least focally infiltrate the salivary parenchyma and surrounding connective tissue. The presence of ruptured cysts with haemorrhage and granulation tissue is common.

Differential diagnosis
Distinction from cystadenoma may be difficult and relies largely on identification of infiltrative growth into salivary parenchyma or surrounding tissues. Review of multiple sections is often helpful. Low-grade mucoepidermoid carcinoma is typically cystic but, unlike cystadenocarcinoma, usually has a wide variety of cell types and areas that are more solid than cystic. The papillary cystic variant of acinic cell carcinoma has focal acinar differentiation and a greater degree of epithelial proliferation. Epidermoid differentiation in cystadenocarcinomas is rare.

Prognosis and predictive factors
Cystadenocarcinoma is a low-grade adenocarcinoma treated by superficial parotidectomy, glandectomy of submandibular and sublingual tumours, and wide excision of minor gland tumours. Bone resection is performed only when it is directly involved by tumour. In a study of 40 patients with follow-up data, all were alive or had died of other causes, four suffered metastasis to regional lymph nodes, one at the time of diagnosis and one after 55 months, and three experienced a recurrence at a mean interval of 76 months.

Fig. 5.19 Cystadenocarcinoma. A Focal collections of lymphoid tissue are present. No significant papillary luminal growth. B Cystic spaces are lined by morphologically bland low cuboidal epithelium, and are separated by loosely arranged fibrous stroma. C Papillary cystadenocarcinoma.
Low-grade cribriform cystadenocarcinoma

Definition
A rare, cystic, proliferative carcinoma that resembles the spectrum of breast lesions from atypical ductal hyperplasia to micropapillary and cribriform low-grade ductal carcinoma in-situ.

Synonym
Low-grade salivary duct carcinoma

Epidemiology
To date, all but one tumour have been diagnosed in the parotid gland and one in the palate (259,578,899,2562). There is a female predominance of 2:1.

Clinical features
Patients are usually elderly and all but one patient presented with cystic parotid tumours.

Histopathology
Low-grade cribriform cystadenocarcinomas (LGCCC) are unencapsulated, consisting of single or multiple cysts, accompanied by adjacent intraductal proliferation. The cysts are lined by small, multilayered, proliferating, bland ductal cells with finely dispersed chromatin and small nucleoli. Within the cystic areas, they typically are arranged in a cribriform pattern and frequently have anastomosing, intracycstic micropapillae lining the cavity, which may contain fibrovascular cores. Separate, smaller ductal structures are variably filled by proliferating ductal epithelium with cribriform, micropapillary and solid areas. The overall appearance is very similar to breast atypical ductal hyperplasia and low-grade ductal carcinoma in-situ. Many superficial cells contain cytoplasmic apocrine-type microvacuoles (PAS-positive/diastase-resistant) and/or fine yellow to brown pigment resembling lipofuscin. Focal invasion into the surrounding tissue can be seen, characterized by small solid islands and reactive inflammation and desmoplasia. Perineural or vascular invasion typically is not present. Cellular pleomorphism and mitotic figures are usually absent and necrosis is extremely uncommon. Occasional tumours may demonstrate transition from low to intermediate or high-grade cytology, with scattered mitotic figures and focal necrosis.

Immunoprofile
These tumours demonstrate strong, diffuse S100 positivity. Myoepithelial markers (calponin or smooth muscle actin) highlight cells rimming the cystic spaces, confirming the intraductal nature of most, or all, of each tumour. No myoepithelial cells are admixed within the proliferative cellular component. Those tumours studied for HER2-neu antigen are uniformly negative.

Variants
Originally, this tumour was reported as a low-grade variant of salivary duct carcinoma. However, as no data have accumulated definitely relating this entity to ductal carcinoma and since there frequently is a prominent cystic component, for the purposes of this WHO classification, the tumour is listed as a variant of cystadenocarcinoma.

Differential diagnosis
The following tumours require exclusion: papillary cystic variant of acinic cell carcinoma, (PCVACC) and other variants of cystadenocarcinoma. PCVACC contains vacuolated cells similar to the microvacuolated cells of LGCCC. However, the vacuoles of the latter are smaller, refractile, and associated with a yellow to brown pigment, while areas with PAS positive diastase resistant fine cytoplasmic granules will be found in the former. Conventional cystadenocarcinoma differs from LGCCC by the lack of intraductal proliferation, golden brown pigment, solid cellular foci, and overall resemblance to atypical hyperplasia or carcinoma-in-situ of the breast. Cystadenocarcinoma tends to be an invasive tumour, whereas LGCCC is usually contained within cysts (790).

Prognosis and predictive factors
Treatment is complete surgical excision. Although the number of cases with follow-up is small, none of the cases, to date, have recurred. Greater experience and longer follow-up periods are necessary to substantiate the excellent prognosis.
Mucinous adenocarcinoma

Definition
Mucinous adenocarcinoma is a rare malignant tumour composed of epithelial clusters within large pools of extracellular mucin. The mucin component usually occupies the bulk of the tumour mass.

ICD-O code 8480/3

Epidemiology
It usually arises in patients over 50 years of age. Males are affected more frequently than females (859,1374,1909, 1957,2551).

Localization
The most frequently affected sites are the palate and the sublingual gland, followed by the submandibular gland and the upper lip. Occurrence in the parotid gland is rare (859).

Clinical features
The patients usually present with a slow-growing, painless swelling. However, local dull pain may be encountered in some cases. The tumour is firm and usually elevated.

Macroscopy
The tumour is nodular and ill defined. The cut surface is greyish-white, containing many cystic cavities with gelatinous contents.

Histopathology
The tumour is composed of round and irregular-shaped neoplastic epithelial cell nests or clusters floating in mucus-filled cystic cavities separated by connective fibrous strands. The tumour cells are cuboidal, columnar or irregular in shape, usually possess clear cytoplasm and darkly-stained, centrically placed nuclei. The tumour cells may have atypical nuclei, but mitotic figures are sparse. The tumour cells are arranged in solid clusters and tend to form secondary lumens or incomplete duct-like structures. Mucus-producing cells may arrange in a papillary pattern projecting into the mucous pools. Mucous acinus-like tumour islands may also be present. Both intracellular and extracellular mucin components show positive staining for periodic acid Schiff, Alcian blue and mucicarmine.

Immunoprofile
Immunocytochemically, the tumour cells express pankeratin AE1/AE3 as well as cytokeratins 7, 8, 18 and 19 that are usually found in simple epithelia (859,1374). Expression of cytokeratins 4 and 13 is seen in about 10-20%. Negative staining is noted for cytokeratins 5/6, 10, 14, 17 and for smooth muscle actin (SMA).

Electron microscopy
The cytoplasm of the tumour cells is densely packed with numerous low-electron-density mucous droplets, and seromucous droplets containing electrondense dots are also seen. Tumour cells possessing mucous or seromucous droplets form a luminal structure, and they have irregularly arranged microvilli on the luminal side.

Differential diagnosis
Mucoepidermoid carcinoma, mucin-rich variant of salivary duct carcinoma and cystadenocarcinoma should be differentiated from mucinous adenocarcinoma. Mucoepidermoid carcinoma also shows extravasated mucin, but it consists of intermediate and epidermoid cells. Cystadenocarcinoma shows cystic spaces lined by epithelium. Extracellular mucin pools are not evident in acinic cell carcinoma.

Prognosis and predictive factors
Mucinous adenocarcinoma is insensitive to radiotherapy and has a propensity for local recurrence and regional lymph node metastases.
Oncocytic carcinoma

Definition
Oncocytic carcinoma is a proliferation of cytologically malignant oncocytic and adenocarcinomatous architectural phenotypes, including infiltrative qualities. These may arise de novo, but are usually seen in association with a pre-existing oncocytoma (1833). Rarely, a benign appearing oncocytic tumour metastasizes following local recurrence (2498) and is designated carcinoma, despite the absence of malignant cellular morphology.

ICD-O code 8290/3

Epidemiology
Men are affected in two-thirds of cases. A wide age range from 25-91 years has been reported with a mean age of 62.5 years (71). This neoplasm represents only 5% of oncocytic salivary gland tumours and less than 1% of all salivary gland tumours (922).

Localization
Nearly 80% involve the parotid gland, 8% the submandibular gland, with all others in minor salivary glands.

Clinical features
Typically there is a painless, nondescript mass in the parotid or submandibular gland. In cases of malignant transformation of a benign oncocytoma a rapid increase in size is noted after a period of slow growth. Facial nerve involvement may cause pain, paresis or neuropathy (922).

Macroscopy
They are firm, unencapsulated, tan to grey, unilocular or multilocular masses, occasionally with necrotic areas.

Histopathology
Sheets, islands and nests are composed of large, round to polyhedral cells with fine, granular, eosinophilic cytoplasm and central, round vesicular nuclei, often with prominent nucleoli (257). Occasionally there are multinucleated cells. In some tumours there are duct-like structures of variable calibre. They are unencapsulated and often invade muscle, lymphatics and nerves. They are characterised cytologically by cellular atypia and pleomorphism. Histochemically, phosphotungstic acid-haematoxylin (PTAH) staining reveals fine, blue, cytoplasmic granules. Other methods to demonstrate mitochondria such as the Novelli technique, cresylecht violet V, Klüver-Barrera Luxol fast blue stains (2601) and antimitochondrial antibodies can also be used (2343).

Immunoprofile
Ki-67 immunostaining has been suggested in separating benign from malignant oncocytoma (1188). In addition, alpha-1-antitrypsin staining has been helpful (476).

Electron microscopy
There are large numbers of mitochondria which are often abnormal in shape and size. Intracytoplasmic lumina lined with microvilli and lipid droplets have also been reported. A nearly continuous basal lamina, evenly spaced desmosomes and rearrangement of mitochondrial cristae have been demonstrated (218).

Prognosis and predictive factors
These high-grade tumours are characterised by multiple local recurrences and regional or distant metastases (922,940). In one series, 7 of 11 patients studied ultimately developed metastatic disease (1227). It appears that the most important prognostic indicator is the presence or absence of distant metastases (1833).

Fig. 5.23 Oncocytic carcinoma. A Invasion into the parotid gland. B Atypical tumour cells have prominent nucleoli and eosinophilic, granular cytoplasm. C Perineural invasion.
Salivary duct carcinoma

Definition
An aggressive adenocarcinoma which resembles high-grade breast ductal carcinoma.

ICD-O code 8500/3

Synonyms
Cribriform salivary carcinoma of excretory ducts, high-grade salivary duct carcinoma

Epidemiology
Salivary duct carcinoma (SDC) is an uncommon, but not a rare form of salivary malignancy. De novo and/or expleomorphic adenoma, SDC represents 9% of salivary malignancies. The male:female ratio is at least 4:1. Most patients present after age 50 [135,259,1488]. The parotid is most commonly involved, but submandibular, sublingual, minor salivary gland, maxillary and laryngeal tumours have been reported [682,745,1383,2021,2583,2862,2909].

Etiology
A unique case of SDC arising in a long-standing chronic obstructive sialadenitis has been reported [1113].

Clinical features
Patients with SDC typically present with recent onset of a rapidly growing tumour that may fluctuate in size. Occasional patients have longer clinical histories. Pain and facial paresis may be present.

Macroscopy
SDC are usually firm, solid, tan, white or grey, with a cystic component. Infiltration of the adjacent parenchyma is usually obvious, but occasional tumours may appear to be circumscribed. SDC may also arise as the malignant component of a carcinoma ex pleomorphic adenoma, so that the macroscopic features of pleomorphic adenoma may also be present.

Tumour spread and staging
For SDC, perineural spread (60%) and intravascular tumour emboli (31%) are common. Most patients present with Stage III or IV disease, as lymph nodes are positive in 59% of patients [135].

Histopathology
SDC resembles intraductal and infiltrating mammary duct carcinoma, both architecturally and cytologically. The diagnostic "ductal lesion" comprises pleomorphic, epithelioid tumour cells with a cribriform growth pattern, "Roman bridge" formation, and intraductal comedonecrosis. The tumour infiltrates and metastasizes with a cribriform pattern, or it totally recapitulates the intrasialodochal "ductal lesion". Solid and papillary areas may be seen, with psammoma bodies, as well as evidence of squamous differentiation. Cytologically, these cells have abundant, pink cytoplasm and large pleomorphic nuclei with prominent nucleoli and coarse chromatin. The cytoplasm may also be densely eosinophilic, granular, or oncocytic. Mitotic figures are usually abundant. Goblet cells are not seen. Rare tumours may have a prominent spindle cell or sarcomatoid growth pattern similar to the metaplastic ductal carcinomas of the breast [1064,1819]. The mucin-rich SDC is a recently described variant of SDC [2371]. The tumour is composed of areas of typical SDC, but in addition, contains mucin lakes with islands of carcinoma cells. Another variant showing an invasive micropapillary component has also been reported [1820].

Immunoprofile
SDC is immunoreactive for low- and high-molecular-weight cytokeratin, and markers such as carcinoembryonic antigen (CEA), LeuM1, and epithelial membrane antigen (EMA) [579,1488]. Strong nuclear reactivity for androgen receptors (AR) is reported in all SDC [1265,1488,2371]. SDC cells are focally positive for...
apocrine marker GCDFP-15 and mitochondrial antigen (MIA), and typically negative for S-100 protein, myoepithelial markers, estrogen and progesterone receptors. Variable expression of prostatic markers (prostate specific antigen, prostatic acid phosphatase) is seen (555). The MIB1 proliferative index is high, with an average value of 43% (range 25-80%). Most SDC show positive distinct membrane staining for HER-2/neu protein (1644,2392,2393).

**Differential diagnosis**
Other diagnoses to consider for SDC include metastatic breast and squamous carcinomas, oncocytic carcinoma and mucoepidermoid carcinoma. Despite a superficial resemblance to squamous carcinoma, this diagnosis can be discarded as soon as the infiltrating cribriform pattern is recognized. Identification of sialodochodysplasia supports a primary parotid origin. Goblet cells are not seen with SDC (aside from intraductal goblet cell metaplasia), thus ruling out mucoepidermoid carcinoma.

**Genetics**
Only two studies of these tumours have been published. Seven of eight tumours had LOH in at least one marker on chromosome 9p21 (351) in one study. In the other study, a high incidence of LOH was found at 6q,16q, 17p and 17q regions (1110). Amplification of HER-2/neu gene and gene product overexpression are reported in SDC (725,1644,1803,2392,2393). Mutations and overexpression of the TP53 gene and protein are frequent (1110,1803,1823). Loss of heterozygosity at microsatellite loci, TP53 point mutations and frequent alterations of certain loci on chromosome arm 6q have been reported (1110). The chromosomal locus 9q21 contains the CDKN2A/p16 tumour suppressor gene that has been implicated in a variety of tumour types, including SDC (351). More polymorphic genetic markers located at this particular region suggest that inactivation of CDKN2A/p16 gene is associated with progression of SDC (351).

**Prognosis and predictive factors**
SDC is one of the most aggressive salivary malignancies. A review of 104 cases concluded that 33% of patients developed local recurrence and 46% developed distant metastasis (135). Sites for distant metastasis include lungs, bones, liver, brain and skin. Sixty-five percent of patients died of disease, between 5 months to 10 years, usually within 4 years of diagnosis. The clinical course is characterized by early distant metastases. Tumour size, distant metastasis, and HER-2/neu overexpression are putative prognostic parameters for SDC, while expression of p53 protein, DNA aneuploidy, and proliferative activity do not correlate with outcome (2393). The clinical outcome for the mucin-rich variant of SDC is similar to that of conventional SDC (2371). The invasive micropapillary variant appears to be particularly aggressive (1820).
**Adenocarcinoma, not otherwise specified**

**Definition**
Adenocarcinoma, not otherwise specified, is a malignant salivary gland tumour that exhibits ductal differentiation but lacks any of the histomorphologic features that characterize the other defined types of salivary carcinoma. The modifying term “not otherwise specified” should be included because most other epithelial salivary gland malignancies are also adenocarcinomas.

**ICD-O code** 8140/3

**Synonyms**
These tumours have often been reported as miscellaneous or unclassified adenocarcinomas or, simply, as adenocarcinoma [1662,1815,2447]. It appears that many reports include cases that should be classified as one of the more specific carcinoma types [668]. They should not be grouped together with tumours that arise from the seromucous glands of the nasal cavity, paranasal sinuses or larynx because in these sites they appear to have a more aggressive biologic behaviour [2447].

**Epidemiology**
The inconsistent reporting of these tumours limits our understanding of them. In one report they are second in frequency only to mucoepidermoid carcinomas among malignant salivary gland tumours and account for about 17% of the carcinomas [668]. Women outnumber men slightly and the average patient age is 58 years. They are extremely rare in children.

**Localization**
About 60% and 40%, respectively, occur in the major and minor glands. The vast majority that involve the major glands occur in the parotid, and the minor gland tumours most often arise from the glands in the hard palate, buccal mucosa, and lips.

**Clinical features**
Most patients with tumours of major glands present with solitary, asymptomatic masses, but about 20% have pain or facial weakness [2447]. Pain is more often associated with tumours of the submandibular glands. Minor gland tumours may be ulcerated and about 25% of palatal tumours involve the underlying bone. Tumour duration ranges from one to 10 years [2447].

**Macroscopy**
Adenocarcinoma, NOS, is often partially circumscribed but in many areas the periphery is irregular and ill defined. Areas of necrosis or haemorrhage may contrast with the white or yellowish cut surface.

**Histopathology**
Shared by all tumours in this group are the presence of glandular or duct-like structures, infiltrative growth into parenchyma or surrounding tissues, and lack of features that characterize other salivary adenocarcinomas. There is considerable variability in the architectural structure. Some have small confluent nests or cords of tumour cells, others large discrete islands with intervening trabeculae of fibrous connective tissue, and still others large solid, densely cellular sheets. This latter group reveals very limited stromal connective tissue.

Ductal differentiation is widespread in low and intermediate grade tumours but usually much more subtle in high-grade tumours. Small cysts are occasionally present in those with numerous ducts. Cuboidal or ovoid cells predominate in most tumours but scattered clear and oncocyctic cells are occasionally evident. Small deposits of eosinophilic acellular material and extracellular mucin may be present. Unlike most other salivary adenocarcinomas, the cytologic variability is useful for grading these tumours [2447]. Low-grade
Adenocarcinoma, not otherwise specified

Tumours demonstrate minimal variability of nuclear size, shape, or staining density, and rare mitoses. In some, the bland nuclear morphology suggests benignity and determination of their malignant nature is based largely on the identification of invasive growth. Intermediate grade tumours show nuclear variability and more frequent mitoses. High-grade tumours have enlarged, pleomorphic, hyperchromatic nuclei, focal necrosis, and frequent and atypical mitoses. The presence of ductal differentiation helps in the distinction from undifferentiated carcinoma.

**Differential diagnosis**

Because these tumours do not have pathognomonic histopathologic features, the possibility of metastatic adenocarcinoma should be considered. While immunohistochemical studies may be useful in this evaluation [2370] it should be remembered that immunoreactivity with prostate-specific antigen has been reported [2571, 2574].

**Prognosis and predictive factors**

Limited data suggest that the clinical stage, site of involvement and grade of tumour influence prognosis [1662, 2447, 2708]. Minor gland tumours have a better prognosis than those of the major glands. Distant metastases may occur despite regional control and recurrence is more frequent with high-grade tumours [2447]. In one study, the 15-year survival for low, intermediate and high-grade tumours was 54, 31, and 3%, respectively, and the cure rate of the low-grade tumours was similar to that of acinic cell adenocarcinoma [2447].

---

**Fig. 5.28** Adenocarcinoma, not otherwise specified. A This example demonstrates an organoid arrangement of cells that have abundant eosinophilic and clear cytoplasm. B Low-grade tumours are characterized by distinct ductal differentiation, cells with limited nuclear variability and uniform nuclei that have small nucleoli, and rare mitoses. C Intermediate grade. Greater variability in the size, shape and staining of the nuclei is typically present. Nucleoli are often more prominent and scattered mitoses are often present. D Large, hyperchromatic, pleomorphic nuclei and frequent mitoses characterize high-grade tumours. Although ductal differentiation is present in these infiltrating tumour islands, other areas had large solid sheets of similar cells with rare to no ductal differentiation.
Definition
Myoepithelial carcinoma of the salivary glands is a neoplasm composed almost exclusively of tumour cells with myoepithelial differentiation, characterized by infiltrative growth and potential for metastasis. This tumour represents the malignant counterpart of benign myoepithelioma.

ICD-O code
8982/3

Synonym
Malignant myoepithelioma

Epidemiology
The mean age of patients at presentation is 55 years with a wide age distribution (range 14-86). Males and females are affected equally. In large series, myoepithelial carcinomas comprise less than two percent of all salivary gland carcinomas, but they may not be as rare as has been suggested before [2251,2304]. The very low historic incidence is probably due to their recent recognition as a separate tumour entity.

Etiology
No etiological factors are known.

Localization
Most cases (75%) arise in the parotid, but they also occur in the submandibular and minor glands.

Clinical features
The tumours are locally destructive. The majority of patients present with the complaint of a painless mass.

Macrosopy
Myoepithelial carcinomas are unencapsulated but may be well-defined with nodular surfaces. Tumour size varies considerably (2-10 cm). The cut surface is grey-white and can be glassy. Some tumours show areas of necrosis and cystic degeneration.

Tumour spread and staging
They can involve adjacent bone. Perineural and vascular invasion may occur. Regional and distant metastases are uncommon at presentation, but may occur late in the course of disease.

Histopathology
Myoepithelial carcinoma characteristically has a multilobulated architecture. The range of cell types in myoepithelial carcinoma reflects that seen in its benign counterpart. The tumour cells often are spindled, stellate, epithelioid, plasmacytoid (hyaline), or, occasionally, vacuolated with signet ring like appearance. Other tumours tend to be more cellular composed of spindle-shaped cells, and they can resemble sarcoma. Rarely, myoepithelial carcinoma is composed of a monomorphic population of clear cells with myoepithelial features [1719]. The tumour cells may form solid and sheet-like formations, trabecular or reticular patterns, but they can also be dissociated, often within plentiful myxoid or hyaline stroma. The neoplastic nodules frequently have necrotic centres. Pseudocystic or true cystic degeneration can occur. Sparse areas with squamous differentiation may be found. Rarely, myoepithelial carcinoma contains duct-like lumina usually with non-luminal cell differentiation of the lining cells. A tumour containing more than the occasional true luminal cell should not be included in the category of purely myoepithelial neoplasia. Different cell types and architectural patterns may be found within the same tumour. In fact, most myoepithelial carcinomas are less monomorphic than benign myoepithelioma. They also may demonstrate high mitotic activity with considerable variation [595,1154,1827,2251]. Cellular pleomorphism can be marked, and necrosis may occur [1827, 2251]. However, unequivocal evidence of infiltrative, destructive growth is the major requirement for diagnosis, and it is this property that distinguishes myoepithelial carcinoma from benign myoepithelial tumours.

Immunoprofile
Reactivity for cytokeratin and at least one
of the other myoepithelial markers, including smooth muscle actin, GFAP, CD10, calponin and smooth muscle myosin heavy chain, is required for diagnosis (595,1827).

Electron microscopy
Ultrastructural criteria for the diagnosis of myoepithelial carcinoma include longitudinally oriented 6-8 nm fine cytoplasmic microfilaments with focal dense bodies, pinocytic vesicles, desmosomes and hemidesmosomes, basal lamina and intermediate filaments (41,640).

Precursor lesions
Myoepithelial carcinomas may arise de novo, but it is important to note that about half of cases develop in pre-existing pleomorphic adenomas, or from benign myoepitheliomas, particularly in recurrences (595,1827,2251).

Genetics
Comparative genomic hybridization has revealed infrequent abnormalities in these lesions with only three of 12 myoepitheliomas manifesting various chromosomal losses. Of myoepithelial carcinomas, five have manifested chromosome 8 alterations (1154).

Prognosis and predictive factors
Myoepithelial carcinomas are locally aggressive salivary gland neoplasms that exhibit diverse clinical outcomes. Approximately one third of patients die of disease, another third have recurrences, mostly multiple, and the remaining third are disease free. Marked cellular pleomorphism and high proliferative activity correlate with a poor clinical outcome (1827,2251). There is no difference in clinical behaviour of "de novo" myoepithelial carcinomas and of those arising in pleomorphic adenomas and benign myoepitheliomas (595,2251).

Fig. 5.30 Myoepithelial carcinoma. A Clear cell myoepithelial carcinoma composed of solid nodules separated by thin fibrous septa. B Epithelioid pleomorphic myoepithelial cells. C Hyaline (plasmacytoid) myoepithelial cells with prominent mitotic activity and abundant eosinophilic cytoplasm. D Spindle-shaped myoepithelial cells with abundant eosinophilic cytoplasm.

Fig. 5.31 Myoepithelial carcinoma. A Gland-like growths of myoepithelial tumour cells within plentiful myxoid or hyaline stroma. B Focal squamous metaplasia. C High mitotic activity and nuclear polymorphism. Focally, the tumour undergoes necrosis (right upper corner). D Positive staining for smooth muscle actin (SMA).
Carcinoma ex pleomorphic adenoma

Definition
Carcinoma ex pleomorphic adenoma is defined as a pleomorphic adenoma from which an epithelial malignancy is derived.

ICD-O code
8941/3

Synonyms
Carcinoma arising in a benign mixed tumour, carcinoma ex benign mixed tumour, carcinoma arising in a pleomorphic adenoma, malignant mixed tumour.

Epidemiology
Many large series of carcinoma ex pleomorphic adenoma (Ca-ex-PA) have been reported and recently summarized: they comprise approximately 3.6% of all salivary tumours (range 0.9-14%), 12% of all salivary malignancies (range 2.8-42.4%), and 6.2% of all pleomorphic adenomas (range 1.9-23.3%) [898]. Ca-ex-PA usually presents in the 6th or 7th decades, approximately one decade later than patients with pleomorphic adenoma.

Etiology
Many Ca-ex-PA probably result from the accumulation of genetic instabilities in long-standing pleomorphic adenomas.

Localization
Ca-ex-PA most frequently arises in the parotid gland; but may also originate from the submandibular gland and minor salivary sites, most commonly the palate, occasionally with involvement of the nasopharynx [838].

Clinical features
The typical history is that of a long-standing mass present much longer than 3 years with rapid growth over the previous few months; however, a significant proportion of patients present with a clinical history of less than three years [898,1533]. Patients frequently complain of a painless mass; but pain, facial nerve palsy, and skin fixation may also occur.

Macrosopy
The average size of Ca-ex-PA is more than twice that of its benign counterpart, ranging from 1.5-25 cm in greatest diameter [786,2624]. Grossly, Ca-ex-PAs are usually poorly circumscribed and many are extensively infiltrative. Occasionally, tumours are well circumscribed, scar-like or appear completely encapsulated [252,2624].

Histopathology
The proportion of benign versus malignant components can be quite variable. Occasionally, extensive sampling is necessary to find the benign component and in rare cases, a benign remnant might not be found. But if there is clinicopathologic documentation of a previously excised pleomorphic adenoma in the same site, then the malignancy can also be classified as a Ca-ex-PA. The malignant component is most frequently a poorly differentiated adenocarcinoma (salivary duct type or not otherwise specified) or an undifferentiated carcinoma; however, virtually any form of carcinoma may be found [898,1338,1491]. An infiltrative, destructive growth pattern is the most reliable diagnostic criterion. Nuclear hyperchromasia and pleomorphism are frequent, although occasional tumours may demonstrate minimal atypia. This latter feature (tumour grade) directly correlates with prognosis. Necrosis is often present and mitoses are usually easy to find. Ca-ex-PAs should be subclassified into non invasive, minimally invasive (≤1.5 mm penetration of the malignant component into extra capsular tissue) and invasive (>1.5 mm of invasion from the tumour capsule into adjacent tissues), as the first two groups usually have an excellent prognosis while the latter has a more guarded prognosis. The distinction between noninvasive and invasive tumours is based on destructive invasion through the capsule into peritumoral tissues. Non-invasive Ca-ex-PAs are also referred to as carcinoma in-situ arising in a pleomorphic adenoma, intracapsular carcinoma ex pleomorphic adenoma or pleomorphic adenoma with severe dysplastic changes. Atypical changes within these tumours range from focal to diffuse often...
with multifocal areas containing carcinoma, which frequently overgrows and replaces many of the benign elements. The earliest changes typically consist of tumour cells replacing the normal inner duct epithelial layer leaving the normal peripherally located myoepithelial layer intact.

**Differential diagnosis**
The most important differential diagnosis is between minimally invasive Ca-ex-PA and the more typical invasive Ca-ex-PA. This differential has prognostic significance, and affects decisions regarding the need for lymph node dissection and adjuvant radiotherapy. Also carcinomas may rarely arise in a histologically benign “adenoma” (“monomorphic” adenoma); they appear to have a more favourable prognosis [1576].

**Genetics**

**Cytogenetics**
Deletions of chromosome 5(q22-23, q32-33) and t(10;12) (p15;q14-15) with 12q breakpoint at the 5’ of the HMGIC and translocation of the entire gene to the 10 marker chromosome followed by deletion/amplification of the segment containing HMGIC and MDM2 genes have been reported [653,1220,2193]. Rearrangements of 8q12 are a frequent finding. Alterations at 12q13-15 with amplification of HMGIC and MDM2 genes have also been reported [2125]. Cytogenetic evidence of amplification (homogeneously stained region and double minute) was found in 40% of these tumours. Both genes may contribute to the malignant transformation of pleomorphic adenoma. Alterations at chromosomes 6q deletion and 8q rearrangements have been reported.

**Molecular genetics**
Microsatellite analysis of these tumours has shown LOH at chromosome 8q and 17p. Concurrent analysis of the benign and malignant components of these tumours showed 8q and/or 12q in both components and additional alterations in 17p only in the carcinoma [651]. In another study homozygous deletion of the p16 gene on chromosome 9p21 was found in carcinoma of one case and microsatellite instability was noted in both the adenoma and carcinoma components in two tumours [2510]. A single case report of a carcinosarcoma, in which the carcinoma and the sarcoma components were concurrently analyzed, showed lack of p53 alterations and concomitant LOH at different loci on chromosome 17 and 18 supporting monoclonality [932].

**Prognosis and predictive factors**
In general, the recommended therapy is wide local excision with contiguous lymph node dissection. Adjuvant radiation therapy is recommended for widely invasive tumours. If the carcinomatous component is low-grade and/or minimally invasive and if the tumour is adequately excised, then adjuvant radiation therapy may not be necessary.

Patients with non-invasive or minimally invasive Ca-ex-PA typically have an excellent prognosis, similar to benign pleomorphic adenoma. Metastatic spread is exceptional [726]. Invasive Ca-ex-PAs, as a group, are extremely aggressive malignancies with approximately 23-50% of patients developing one or more recurrences [786, 898,1491,1533]. The metastatic rate varies with each series; up to 70% of patients develop local or distant metastasis [877,898,1491]. Metastatic sites in order of frequency are lung, bone (especially spine), abdomen and central nervous system [786,2592]. Ca-ex-PA with capsular penetration of more than 1.5 mm is associated with a poor prognosis; survival rates at 5, 10, 15, and 20 years range from 25-65%, 18-50%, 10-35%, and 0-38%, respectively [786,877,1491,1533,2592,2624]. Therefore, it is important to designate those Ca-ex-PA that are confined within the capsule and those invading through the capsule as non-invasive or invasive, respectively, and to differentiate within the latter group between widely invasive and minimally invasive tumours.

One study showed that no patient with less than 8 mm invasion from the capsule died from the tumour, whereas all patients with invasion greater than 8 mm beyond the capsule ultimately died of disease [2624]. The local recurrence rate (LRR) in this latter series also correlated with extent of invasion; a LRR of 70.5% was found for tumours with invasion beyond 6 mm from the capsule, as compared to a LRR of 16.6% for tumours with invasion of less than 6 mm. In another study consisting of four patients with 5 mm of invasion beyond the tumour capsule, two died of disease and two were alive and well [1491]. The two patients with less than 5 mm of invasion (2 and 3 mm) were alive and well with no evidence of disease. Also, all four patients with intracapsular carcinoma were alive and well without evidence of disease progression. The improved prognosis for minimally invasive tumours has been confirmed by Brandwein et al who observed recurrence free for periods ranging from 1-4 years (mean 2.5 years) [252].

Tumour size and grade are also significant prognosticators in the more widely invasive Ca-ex-PAs. The five-year survival rates have been correlated with histologic subtype of the carcinoma component: there was a 30% survival rate for undifferentiated carcinomas, 50% for myoepithelial carcinomas, 62% for ductal carcinomas and 96% survival rate for terminal duct carcinomas [2624]. In addition, 63% of patients with high-grade carcinomatous components died of the disease, while patients with lower grade carcinomatous elements did not [1491].

Fig. 5.33 Carcinoma ex pleomorphic adenoma. A Detail of adenocarcinoma with back-to-back glands composed of pleomorphic tumour cells with focal necrosis. B Many tumour cells are positive for MIB-1 in the carcinoma component (right), whereas only a few positive cells are observed in the pleomorphic adenoma component (left).
Carcinosarcoma

Definition
Carcinosarcoma is a malignant tumour composed of a mixture of both carcinomatous and sarcomatous elements.

ICD-O code 8980/3

Synonym
True malignant mixed tumour

Epidemiology
Carcinosarcoma is extremely rare; approximately 50-60 cases have been reported to date [47, 898, 911, 932, 1010, 1320, 2377, 2466]. The mean age at presentation was 58 years with a range of 14-87 years [899]. A number of patients have had a history of recurrent pleomorphic adenoma [2466] and several cases have arisen in a pleomorphic adenoma (carcinosarcoma ex pleomorphic adenoma) [899, 1010, 1320, 1400].

Localization
Two-thirds have arisen in the parotid gland, approximately 19% in the submandibular glands, and 14% in the palate [899]. One case has been reported in the tongue and one in the supraglottic region [691].

Clinical features
Patients typically present with a mass, which may be painful.

Macroscopy
Tumours are well to poorly circumscribed.

Histopathology
The tumour is composed of mixtures of carcinomatous and sarcomatous elements in varying proportions [225]. Chondrosarcoma and osteosarcoma are the most common sarcomatous elements and moderate to poorly differentiated ductal carcinoma or undifferentiated carcinoma are the most common carcinomatous components. Local tissue infiltration and destruction are characteristic of this neoplasm.

Genetics
LOH at 17p13.1, 17q21.3 and 18q21.3 has been found in one carcinosarcoma. Sequencing studies excluded TP53 mutations, suggesting inactivation of another tumour suppressor gene at 17p13 [932].

Prognosis and predictive factors
Treatment is wide surgical excision combined with radiotherapy. Almost 60% of patients die of local recurrence and/or metastatic disease (lungs, bones, central nervous system), usually within a thirty month period [47, 899, 2466].

Fig. 5.34 Carcinosarcoma. Low power. The majority of this tumour is composed of poorly differentiated sarcoma with focal areas of poorly differentiated adenocarcinoma at the periphery.

Fig. 5.35 Carcinosarcoma A Tumour composed of mixtures of adenocarcinomatous and osteosarcomatous components. B Midportion of tumour. Note areas with chondrosarcomatous differentiation (right side) and a small focus with osteosarcomatous differentiation (upper left).
Metastasizing pleomorphic adenoma

Definition
A histologically benign pleomorphic adenoma that inexplicably manifests local or distant metastasis.

ICD-O code
8940/1

Synonyms
Metastasizing benign mixed tumour, malignant mixed tumour.

Epidemiology
To date, approximately 40 cases have been described [406,2768].

Etiology
It has been postulated that multiple recurrences and surgical procedures allow some tumours to gain venous access and metastasize.

Localization
Greater than three-quarters arise in the parotid gland, 13% in the submandibular gland and 9% in the palate.

Macroscopy
Tumours are well-circumscribed in primary and metastatic sites.

Histopathology
Characteristically, the primary salivary gland tumour and metastases are composed of the typical mixture of benign-appearing epithelial and mesenchymal components of a pleomorphic adenoma. The histology is not predictive regarding its ability to metastasize. Mitotic figures and nuclear pleomorphism may be seen, but the tumour is not overtly histologically malignant.

Prognosis and predictive factors
The treatment of choice is surgical excision. Metastasizing pleomorphic adenomas are characterized by multiple local recurrences and a long interval (1.5-55 years) between development of the primary tumour and its metastasis. Half of the tumours metastasize to bone, 30% to lung and 30% to lymph nodes; rarely tumours spread to other body sites. Forty percent of patients died with disease; 47% were alive and well, and 13% were alive with disease [899].

Squamous cell carcinoma

Definition
A primary malignant epithelial tumour composed of epidermoid cells, which produce keratin and/or demonstrate intercellular bridges by light microscopy. It is essential to exclude the possibility of metastatic disease. By convention, the diagnosis of salivary squamous cell carcinoma is restricted to the major salivary glands, since minor salivary squamous carcinomas cannot be reliably distinguished from tumours of mucosal origin.

ICD-O code
8070/3

Synonym
Epidermoid carcinoma

Epidemiology
Primary squamous cell carcinoma (PSCC) probably represents less than 1% of salivary gland tumours. PSCC occurs in patents over a wide age range, but the majority present in the 6th through 8th decades, with a mean of 60-65 years. They are unusual in patients younger than 20 years, although several cases have been described in children [669]. There is a male to female ratio of approximately 2:1.

Etiology
In several studies, PSCC has been associated with a history of prior radiotherapy, with a latent period of 15-30 years [2329].

Localization
Roughly 80% of PSCC arise in the parotid gland and 20% in the submandibular gland. PSCC of the sublingual gland is quite unusual. Occasionally, cases arise from the mucosa lining Stensen’s duct.

Clinical features
Patients with PSCC present with a rapidly enlarging mass, which is frequently painful. Tumours are firm and fixed and may be associated with facial nerve weakness. PSCC is typically high stage at the time of diagnosis [2329,2468].

Macroscopy
PSCC is an invasive neoplasm with ill-defined margins. Most tumours are greater than 3 cm in size. The cut surface is typically solid, firm, and light grey or tan to white, sometimes with focal necrosis.
Histopathology
The histology of PSCC of salivary origin is similar to that of well- to moderately-differentiated squamous cell carcinoma originating elsewhere in the head and neck. The tumour infiltrates the salivary parenchyma in irregular nests and trabeculae, accompanied by a fibrous to desmoplastic stromal response. Squamous metaplasia and dysplasia of salivary ducts are occasionally identified in association with PSCC. Perineural invasion and extension into adjacent soft tissue are common findings. There is a significant incidence of cervical nodal metastases (both clinically apparent and occult) at the time of initial surgery (779, 869,1456,2329).

Differential diagnosis
The most critical distinction in the differential diagnosis of PSCC is ruling out the possibility of metastatic squamous cell carcinoma, whose incidence is greater than true PSCC. PSCC must also be distinguished from mucoepidermoid carcinoma (MEC). MEC is typically composed of a variable cell population, including mucocytes, basaloid, and intermediate cells, in addition to epidermoid cells. However, prominent keratinization is not characteristic of MEC. MEC may exhibit cystic areas and focal clear cell differentiation, features not observed in PSCC. Histochemical stains for intracellular mucin to rule out high-grade MEC are recommended before making a definitive diagnosis of PSCC (669). Squamous metaplasia in infarcted or surgically manipulated tumours can be misinterpreted as PSCC.

Keratocystoma is a recently described, rare lesion of salivary glands that may be confused with squamous cell carcinoma (1822). It is characterized by multicytic spaces lined by stratified squamous cells containing keratotic lamellae and focal solid epithelial nests. The consistent absence of metastasis, necrosis or invasion, as well as the lack of cytological atypia and minimal cellular proliferative activity in keratocystoma is essential in distinguishing this lesion from PSCC.

Genetics
Cytogenetic studies in several cases of PSCC have yielded somewhat variable results, although it appears that various 6q deletions may be common, similar to the findings in other salivary carcinomas (1222). Interestingly, this karyotype is unusual in squamous cell carcinoma of other head and neck sites (1222).

Prognosis and predictive factors
PSCC is considered a relatively high-grade, aggressive salivary carcinoma. Five-year disease specific survival is approximately 25-30%. Local-regional recurrence develops in at least half of patients and distant metastases are found in 20-30% (2329). Overall, 75% die of their disease, usually within 5 years (1456,2329). In the largest published specific analysis of PSCC (2329), tumour stage was the most important prognostic factor. Age greater than 60 years, ulceration, and fixation also had a significant negative impact on survival. Two additional series, which only considered parotid tumours, reported that age, facial nerve paralysis, deep fixation, and type of treatment were of statistical significance (869,1456).

Fig. 5.37 A Squamous cell carcinoma. Moderately differentiated, keratinizing primary squamous cell carcinoma of the parotid gland. B Squamous cell carcinoma. Poorly differentiated, nonkeratinizing primary squamous cell carcinoma of the parotid gland.

Fig. 5.38 Keratocystoma A Cut surface of the parotid tumour, showing multiple cystic formations filled with keratin material. B Low-power view showing multilocular cystic lesions filled with lamellar keratin material. C Portion of the cyst wall consists of stratified squamous epithelium with keratinization through parakeratotic cells. Note the lack of a granular cell layer. Tumour cells exhibit uniform, bland nuclei and abundant eosinophilic cytoplasm.
Small cell carcinoma

Definition
Small cell carcinomas of the salivary glands are rare, malignant epithelial tumours characterized by a proliferation of small anaplastic cells with scant cytoplasm, fine nuclear chromatin, and inconspicuous nucleoli.

ICD-O code 8041/3

Synonyms
Small cell undifferentiated carcinoma, small cell anaplastic carcinoma, oat cell carcinoma, neuroendocrine carcinoma.

Epidemiology
They account for less than 1% of all salivary gland tumours and approximately 2% of salivary gland malignancies [668]. Most patients are older than 50 years at the time of initial diagnosis; however, these tumours have been described in younger patients [668,902]. The tumour has a slight predilection for males.

Localization
The tumours can involve major and intraoral minor salivary glands, and are most common in the parotid gland.

Clinical features
Patients typically present with a painless, rapidly growing mass of several months duration. Cervical lymphadenopathy and facial nerve palsy are common findings. Paraneoplastic syndromes accompanied by the production of ectopic hormones are unusual [1746].

Macroscopy
It is a firm, poorly circumscribed tumour that often infiltrates the surrounding salivary gland parenchyma and adjacent soft tissues. The tumour is usually grey to white and commonly accompanied by necrosis and haemorrhage.

Histopathology
Small cell carcinoma is characterized by sheets, cords, or irregular nests of anaplastic cells and a variable amount of fibrous stroma. The tumour cell nests may exhibit a peripheral palisading pattern. Rosette-like structures are occasionally seen. Tumour cells are usually 2-3 times larger than mature small lymphocytes and have round to oval nuclei with scant cytoplasm. Fusiform or polygonal cells as well as occasional larger cells are sometimes observed. Nuclear chromatin is finely granular, and nucleoli are absent or inconspicuous. Cell borders are ill defined, and nuclear moulding is common. Mitotic figures are numerous. A tumour may have small foci of ductal differentiation [902]. Focal areas of squamous differentiation also have been described [1030,2196]. Extensive necrosis and vascular and perineural invasion are common.

Immunoprofile
In most small cell carcinomas, the tumour cells express at least one neuroendocrine marker such as chromogranin A, synaptophysin, CD57 (Leu-7), CD56 (neural cell adhesion molecule) and neurofilament [907,1818]. However,
immunoreactivity for neuron-specific enolase alone is insufficient evidence for confirming the neuroendocrine differentiation of the tumour. Most small cell carcinomas are positive for cytokeratins, which often have a characteristic paranuclear dotlike pattern of reactivity (372,1818). The majority of the tumours are also positive for epithelial membrane antigen (907,1818). Similar to Merkel cell carcinoma, but unlike pulmonary small cell carcinoma, three out of four salivary small cell carcinomas are cytokeratin 20 positive (1818). Also, small cell carcinomas are negative for S-100 protein and HMB-45.

**Electron microscopy**

Electron microscopic examination shows membrane-bound neuroendocrine granules in about one-third of small cell carcinomas (907). The tumour cells contain sparse cytoplasmic organelles, and either poorly or well-formed desmosomes interconnect the cells. Multidirectional differentiation with the presence of myofilament-like microfilaments and tonofilaments has been reported (1030,2628,2836).

**Prognosis and predictive factors**

Local recurrence and distant metastases develop in more than 50% of patients after the initial diagnosis. Cervical lymph node involvement is less common than haematogenous metastasis. The 5-year survival rate for patients with small cell carcinomas arising in the major salivary glands ranges from 13 to 46% (902, 1818,2042). Overall survival is reduced for patients with a primary tumour larger than 3 cm, negative immunostaining for cytokeratin 20 and decreased immunoreactivity for neuroendocrine markers (1818).
Large cell carcinoma

Definition
Large cell carcinomas are rare, high-grade malignant salivary gland epithelial tumours composed of pleomorphic cells with abundant cytoplasm and absence of features of other specific tumour types.

ICD-O code 8012/3

Synonym
Large cell undifferentiated carcinoma.

Epidemiology
Large cell carcinomas are exceptionally rare [1151,1816]. In the majority of cases, the patients were older than 60 years. Males and females are affected equally.

Localization
The majority of large cell carcinomas arise in the major salivary glands, especially the parotid gland [1151,1432,1768,1816,1828,2836]. A few tumours of minor salivary gland origin have been reported [1768].

Clinical features
Many patients present with a rapidly growing firm mass that often is fixed to adjacent tissue. Facial nerve paralysis and cervical lymph node enlargement are common findings.

Macroscopy
A large cell carcinoma is usually a poorly circumscribed, solid tumour with greyish white or tan cut surface. Necrosis and haemorrhage are easily found. Invasion into the adipose and muscular tissue adjacent to the salivary gland is common.

Histopathology
The tumour is composed of large, pleomorphic cells (>30µm) with an abundance of eosinophilic or occasionally clear, cytoplasm. In some tumours there is striking dyscohesive architecture resembling lymphoma. The tumour cell nuclei have a polygonal or fusiform shape, prominent nucleoli, and coarse chromatin with a vesicular distribution. Cell borders are usually well-defined. Bizarre giant tumour cells may be present. Mitotic figures are readily identified. The tumour growth pattern consists of sheets and trabeculae, with a conspicuous tendency for necrosis. Organoid, rosette-like, and peripheral palisading patterns characterize some of the large cell carcinomas [1828]. Rare foci of ductal or squamous differentiation can be present in large cell carcinomas. Lymphoid cell infiltration is usually focal and patchy. Perineural and vascular involvement is prominent.

Immunoprofile
Some cases of large cell carcinoma may be positive for one of the neuroendocrine markers, including chromogranin A, synaptophysin, CD57 (Leu-7), PGP9.5, or CD56 (neural cell-adhesion molecule). No immunoreactivity for cytokeratin 20 was found. The Ki-67 (MIB-1) labeling index is high and often greater than 50%. In two reported cases, the tumour cells showed diffuse immunexpression of bcl-2 protein, epidermal growth factor receptor, and cyclin D1 and reduced immunexpression of p21/waf1 and p27/kip1 [1828]. Diffuse TP53 nuclear immunexpression has been found in 4 of 5 cases [1803,1828,2421].

Fig. 5.42 Large cell carcinoma. A Sheet-like growth pattern of large pleomorphic cells with abundant eosinophilic cytoplasm and prominent nucleoli. B Strong immunoreactivity for cytokeratin.
Electron microscopy
Ultrastructurally, tumour cells occasionally have a squamous or glandular differentiation not apparent on conventional light microscopic examination (1816, 2836). Neuroendocrine differentiation is rare; neurosecretory granules have been described in 3 cases (1151, 1432, 1828). Prominent desmosome-like junctions connect the tumour cells.

Genetics
Genetic studies of salivary gland large cell carcinoma are scant. TP53 mutation has been detected in two of three cases, and 1 case demonstrated loss of heterozygosity (LOH) at chromosome 17p (1803, 1828). Two cases of large cell neuroendocrine carcinoma exhibited LOH at chromosome 9p21 (1828).

Prognosis and predictive factors
Large cell carcinoma is an aggressive tumour with a propensity for local recurrence, cervical lymph node metastases, and distant spread. However, one study has shown that cell size (small vs large type of carcinoma) has no influence on prognosis (1151). Tumour size has been found to be a prognostic indicator; all patients with tumours larger than 4 cm died of disease with distant metastases (1151).

Fig. 5.43 Large cell carcinoma. A Organoid growth pattern. B Solid growth with peripheral palisading and rosette-like structures. Tumour cells have large and polygonal nuclei with vesicular chromatin and prominent nucleoli.
Lymphoepithelial carcinoma

Definition
Lymphoepithelial carcinoma (LEC) is an undifferentiated carcinoma accompanied by a prominent non-neoplastic lymphoplasmacytic infiltrate.

ICD-O code 8082/3

Synonyms
Lymphoepithelioma-like carcinoma (LEC) {1173,1387}; malignant lymphoepithelial lesion {236,2253}; undifferentiated carcinoma with lymphoid stroma {459,2304}; undifferentiated carcinoma {986,1359}; carcinoma ex lymphoepithelial lesion {152}.

Epidemiology
LEC of the salivary gland is rare, accounting for less than 1% of all salivary gland tumours. It shows a striking racial predilection for Inuits (Eskimo) in the Arctic regions (Greenland, Canada, Alaska), South-eastern Chinese, and Japanese {32,236,986,1479,2253,2326}. The Inuit populations have the highest worldwide incidence of malignant salivary gland tumours, with the majority represented by LEC {32,236,1708}. Slight female predominance, higher frequency of parotid gland involvement, more frequent high stage disease and apparently more aggressive clinical course have been reported in Inuits [236,1428,1479,1708,2253,2326,2636]. Patients affected by LEC span a wide age range from the first to the ninth decades, with most cases occurring in the fifth decade. There is a slight male predominance {236}.

Clinical features
LEC presents as a parotid or submandibular swelling (which may be longstanding with recent rapid increase in size), with or without pain {236,857,2253}. Advanced tumours may become fixed to the underlying tissues or the skin, although facial nerve palsy occurs in only about 20% of cases. Cervical lymph node involvement, which may be extensive, is seen in 10-40% of cases at presentation {236,1000,1387,1479,2253,2636}. There is no clinical or serologic evidence of an underlying Sjögren syndrome {1373,1479,2253}. Since LEC of salivary gland is morphologically indistinguishable from nasopharyngeal carcinoma (which is much more common), it is important to examine and biopsy the nasopharynx thoroughly before accepting the salivary gland tumour as primary LEC {377,2252}.

Macroscopy
The tumours can be circumscribed or show frank invasion into the surrounding...

**Fig. 5.44** Lymphoepithelial carcinoma of parotid gland. In this example, irregular islands of carcinoma (purple-staining) are intermingled with abundant lymphoid tissues which include lymphoid follicles (blue-staining).
Tumours of the salivary glands

gland and extraglandular soft tissues. They are fleshy and firm, and range from 1-10 cm in size (mean 2-3 cm) [2252].

**Tumour spread and staging**
LEC has a propensity to spread to regional cervical lymph nodes [236, 1479,2636]. Distant metastasis, which can be found in up to 20% of cases at presentation, tends to occur in the lung, liver, bone and brain. In metastatic deposits, the prominent lymphoplasmacytic infiltrate characteristic of the primary lesion may or may not be present.

**Histopathology**
The tumour grows in infiltrative sheets, islands and cords separated by a lymphoid stroma. The tumour cells possess indistinct cell borders, lightly eosinophilic cytoplasm, oval vesicular nuclei with open chromatin, and conspicuous nucleoli. The nuclei usually show moderate variation in size, although rare cases exhibit fairly uniform-appearing nuclei. Necrosis and mitotic figures are usually easily found. Sometimes the tumour cells can be plump and spindly, with formation of fascicles [445]. Focal squamous differentiation in the form of increased amount of eosinophilic cytoplasm and vague intracellular bridges is occasionally present.
The tumour is by definition richly infiltrated by lymphocytes and plasma cells, often accompanied by reactive lymphoid follicles. The lymphoid component can sometimes be so heavy that the epithelial nature of the tumour may not evident. Histiocytes are abundant in the tumour islands in some cases, imparting a “starry sky” appearance [2253]. Other inconsistent findings are non-caseating granulomas with or without multinucleated giant cells, amyloid deposition [1387], cyst formation in some tumour islands, perineural and lymphovascular invasion. Tumour cells are immunoreactive for pan-cytokeratin and epithelial membrane antigen. The lymphoid cells include a mixture of B cells and T cells. Electron microscopy shows features of squamous differentiation, with desmosomes and tonofilaments.

In endemic cases, EBV-encoded RNA (EBER) and EBV-DNA can be detected in the tumour cells by in-situ hybridization. Immunohistochemical expression of EBV latent membrane protein 1 is more variable [377,857,986,1316,1479,2326].

**Differential diagnosis**
Important differential diagnoses include metastatic undifferentiated carcinoma, malignant lymphoma, lymphoepithelial sialadenitis (no definite cytological atypia, presence of basement membrane-like material, no desmoplastic stroma, no EBV association), lymphadenoma (definite or subtle gland formation, no definite cytological atypia, no desmoplastic stroma, and no EBV association), and large cell undifferentiated carcinoma.

**Precursor lesions**
Most LEC arise de novo but rarely they may develop within lymphoepithelial sialadenitis (formerly myoepithelial sialadenitis) [938].

**Genetic susceptibility**
Clustering of salivary gland LEC in family members has been reported [31,91, 1708]. One such family also showed dominantly inherited trichoepitheliomas, suggesting hereditary predisposition related to tumour suppressor genes [1708].

**Prognosis and predictive factors**
Five-year survival rate of 75-86% has been reported in patients treated by combined surgery (including neck dissection) and radiation therapy, although local recurrence can occur [236,1387, 1479,2252,2636]. The prognosis is significantly related to tumour stage. There have been attempts to grade LEC based on nuclear pleomorphism and mitotic activity [459,1373], with suggestion that high-grade tumours are more aggressive, but there are currently no widely accepted or well-validated grading systems.
Definition
This is a rare, potentially aggressive, parotid or submandibular tumour that is usually present at birth and recapitulates the primitive salivary anlage.

ICD-O code
8974/1

Synonyms
Congenital basal cell adenoma, basal cell adenoma, basaloid adenocarcinoma, congenital hybrid basal cell adenoma-adenoid cystic carcinoma, embryoma (2570,2685).

Epidemiology
Most tumours are identified at birth or shortly thereafter; occasional children may be diagnosed after the age of two years. The male to female ratio is 2:1. Sialoblastomas are extremely rare; 23 such cases have been reported (48,156, 251,867,945,1016,1574,1688,1786,1952,2353,2570,2685).

Localization
The ratio of parotid to submandibular gland involvement is approximately 3:1.

Clinical features
Most babies present with a mass of the cheek or submandibular region. Occasional tumours may reach massive proportions and ulcerate skin. One baby presented with a concomitant hepatoblastoma (2353), and two other children both had congenital nevi associated with their tumours (251,945). Some babies have been diagnosed by prenatal sonography. Radiographically, these tumours appear as expansile, lobulated masses. True-cut preoperative biopsy can be diagnostic, and is useful in ruling out neoplasia that require neoadjuvant chemotherapy, such as rhabdomyosarcoma.

Histopathology
Sialoblastomas are composed of basaloid epithelial cells, with scanty cytoplasm, round to oval nuclei, single or few nucleoli, and relatively fine chromatin pattern. More mature cuboidal epithelial cells with pink cytoplasm can also be seen. These cells form ductules, bud-like structures and solid organoid nests, and may demonstrate peripheral palisading. The intervening stroma may appear loose and immature. Myoepithelial cells can be identified, and have been confirmed by ultrastructural study. More familiar salivary patterns such as adenoid cystic-like cribriform areas can be seen. The mitotic rate within sialoblastomas is highly variable, and may increase with subsequent recurrences (251), as may necrosis, nuclear pleomorphism and MIB1 proliferative index.

It has been suggested that these tumours be separated into benign and malignant based on the absence or presence of invasion of nerves or vascular spaces, necrosis and cytologic anaplasia (251,1574).

Immunoprofile
These tumours express S-100 and vimentin diffusely. Cytokeratin accentuates the ductal structures.

Histogenesis
It has been suggested that these tumours originate from retained blastemal cells rather than basal reserve cells (2570). Dysembryogenic parotid changes have been described adjacent to the tumour, with proliferation of the terminal ductal epithelial bulbs (1952).

Prognosis and predictive factors
Sialoblastomas have the potential to recur (22%), and can occasionally metastasize regionally (9%), and one fatality has been reported (251,1688). Most of these children are cured by primary surgical resection.

![Fig. 5.47 Sialoblastoma. A Solid nests composed of basaloid cells. B Brisk mitotic rate within this sialoblastoma.](image)
Pleomorphic adenoma

**Definition**
Pleomorphic adenoma is a tumour of variable capsulation characterized microscopically by architectural rather than cellular pleomorphism. Epithelial and modified myoepithelial elements intermingle most commonly with tissue of mucoid, myxoid or chondroid appearance.

**Synonym**
Mixed tumour

**ICD-O code** 8940/0

**Epidemiology**
Pleomorphic adenoma is the most common salivary gland tumour and accounts for about 60% of all salivary neoplasms (2439). The reported annual incidence is 2.4-3.05 per 100,000 population (244, 2053). The mean age at presentation is 46 years but the age ranges from the first to the tenth decades (703). There is a slight female predominance (703,2711).

**Localization**
About 80% of pleomorphic adenomas arise in the parotid, 10% in the submandibular gland and 10% in the minor salivary glands of the oral cavity, nasal cavity and paranasal sinuses and the upper respiratory and alimentary tracts (703). The lower pole of the parotid gland is the most common location but deep lobe tumours can present as a parapharyngeal mass. The accessory parotid is occasionally involved.

**Clinical features**
Pleomorphic adenomas usually are slow growing painless masses. Small tumours typically form smooth, mobile, firm lumps but larger tumours tend to become bossellated and may attenuate the overlying skin or mucosa. Multifocal, recurrent tumours may form a fixed mass. Pleomorphic adenomas are usually solitary but they may show synchronous or metachronous association with other tumours, particularly Warthin tumour, in the same or other glands (2298). Pain or facial palsy are uncommon but are occasionally seen, usually in relation to infarcted tumours. The size of most tumours varies from about 2-5 cm but some reported cases have been massive (388). In the palate, tumours are usually seen at the junction of the hard and soft palate unilaterally. In the hard palate they feel fixed due to the proximity of the underlying mucoperiosteum.

**Macroscopy**
Pleomorphic adenomas tend to form well-defined, ovoid or round tumours. They are often encapsulated but the capsule varies in thickness and may be partially or completely absent, particularly in predominantly mucoid tumours. Those developing in the minor glands usually have a poorly developed or absent capsule. In major gland pleomorphic adenomas there is a distinct tendency for the tumour to separate from the capsule when handling the specimen. The outer surface of larger tumours is frequently bossellated. The cut surface is typically homogeneous and white or tan. It may have a glistening appearance where there are cartilaginous or myxochondroid areas. There may be areas of haemorrhage or necrosis. Recurrent tumours are usually multifocal and may be widely dispersed.

**Histopathology**
Pleomorphic adenoma shows a remarkable degree of morphological diversity. The essential components are the capsule, epithelial and myoepithelial cells, and mesenchymal or stromal elements. The capsule varies in thickness and presence. A quantitative study showed the thickness ranged from 15-1750 mm (2732). When tumours were serially sectioned areas of capsular deficiency were seen in all cases (1418). In predominantly mucoid pleomorphic adenomas, the capsule may be virtually absent and the tumour abuts onto the adjacent salivary gland. Most tumours show areas where finger-like processes extend into the capsule. In addition, the tumour sometimes bulges through the capsule and forms what appear to be separate satellite nodules. These satellites are invariably attached to the main tumour by an isthmus (1418,1986). There is a tenden-
Pleomorphic adenoma

For clefts to form close to and parallel with the capsule. These clefts are within the tumour itself and leave tumour cells attached to the capsular wall. The epithelial component shows a wide variety of cell types including cuboidal, basaloid, squamous, spindle cell, plasmacytoid and clear cells. Rarely, mucous, sebaceous and serous acinar cells are seen. These cells are cytologically bland and typically have vacuolated nuclei, without prominent nucleoli, and a low mitotic frequency. The epithelium usually forms sheets or duct-like structures. There is a wide range of epithelial cellularity; sometimes, the epithelial component forms the bulk of the tumour (cellular pleomorphic adenoma). This phenomenon has no prognostic significance. The ducts show cuboidal luminal cells and there may be an abluminal layer of myoepithelial cells. These may be morphologically similar to the luminal cells or have clear cytoplasm and somewhat angulated nuclei. In limited material tumours showing these features could easily be confused with adenoid cystic carcinoma and epithelial-myoeipithelial carcinoma. The ducts often contain eosinophilic secretory material and are usually small but may be distended to form microcysts. Squamous metaplasia, sometimes with the formation of keratin pearls, can be seen in both ducts and sheets and occasionally there is mucous metaplasia or conspicuous clear cell change. These appearances can be confused with mucoepidermoid carcinoma. More rarely, sebaceous cells or serous cells with zymogen granules are seen. Another rare feature is the presence of multinucleated epithelial cells. Myoepithelial cells may form a fine reticular pattern or sheets of spindle-shaped cells. These may be palisaded forming a Schwannoma-like appearance. A very distinctive appearance is seen when the myoepithelial cells are plasmacytoid or hyaline (1552). Focal oncocyctic change is not uncommon but occasionally the entire tumour is affected and may be mis-diagnosed as an oncocytoma (1973). Crystalloid material in the form of collagenous crystalloids, tyrosine and oxalate crystals are occasionally present (324). The mesenchymal-like component is mucoid/myxoid, cartilaginous or hyalinised and sometimes this tissue forms the bulk of the tumour. Cells within the mucoid material are myoepithelial in origin and their cellular periphery tends to blend into the surrounding stroma. The cartilage-like material appears to be true cartilage and is positive for type II collagen and keratan sulphate. Occasionally it is the major component of the tumour. Bone may form within this cartilage or form directly by osseous metaplasia of the stroma. Deposition of homogeneous, eosinophilic, hyaline material between tumour cells and within the stroma can be a striking feature of some tumours. It forms globular masses or sheets and

**Fig. 5.50 Pleomorphic adenoma.** A Epithelial component with ductal structures (left) and a mesenchymal myxoid component (right). B Ducts showing luminal cells and several layers of abluminal cells, the latter being merged into myxoid stroma. C Cellular type. D Plasmacytoid cells.
typically is positive with stains for elastin. This material can push apart epithelial elements to give a cylindromatous or cribiform appearance that is readily mistaken for adenoid cystic carcinoma. Some long-standing tumours show increasing hyalinisation and the epithelial component is progressively effaced. It is important, however, to scrutinise the residual epithelial elements of such old, scarred pleomorphic adenomas as there is a significant risk of malignant progression in such tumours [85]. Tumours that have a lipomatous stromal component of 90% or more have been called lipomatous pleomorphic adenomas [1881, 2299]. More extensive inflammation and necrosis can be seen following spontaneous infarction or fine needle aspiration. In such tumours there may be an increase in mitotic figures and some cellular atypia [361,1495]. In addition, squamous metaplasia may be present and these changes can be mistaken for malignancy. Some tumours show cystic degeneration with the neoplastic elements forming a rim around a central cavity. Occasionally tumour cells can be seen within vascular spaces [475]. These are usually within the body of the tumour or at the periphery and this is assumed to be a peroperative phenomenon. Sometimes this is seen in vessels distant from the main tumour mass. However, this finding does not appear to have any significance in terms of tumour behaviour and, in particular, the risk of metastasis.

**Immunoprofile**

The inner ductal cells in the tubulo-glandular structures are positive for cytokeratin 3, 6, 10, 11, 13, and 16, whereas the neoplastic myoepithelial cells are irregularly positive for cytokeratin 13, 16, and 14 [311]. The neoplastic myoepithelial cells co-express vimentin and pan-cytokeratin and are variably positive for S-100 protein, α-smooth muscle actin, GFAP, calponin, CD10 and muscle-specific actin (HHF-35) [545]. Modified myoepithelial cells in these tumours are also reactive for p63 [214]. The non-lacunar cells in the chondroid areas are positive for both vimentin and pan-cytokeratin, whereas the lacunar cells are positive only for vimentin [1776]. The spindle-shaped neoplastic myoepithelial cells around the chondroid areas express bone morphogenetic protein (BMP) [1083] whereas the inner ductal cells in the tubulo-glandular structures and the lacunar cell in the chondroid areas express BMP-6 [1397]. Type II collagen and chondromodulin-I is present in the chondroid matrix [1396]. Aggrecan is present not only in the chondroid matrix but also in the myxoid stroma and in the inter-cellular spaces of the tubulo-glandular structures [2898].

**Genetics**

**Cytogenetics**

Extensive cytogenetic studies of pleomorphic adenomas have shown that approximately 70% of the tumours are...
karyotypically abnormal [306,1639, 2239]. Four major cytogenetic subgroups may be discerned:
> Tumours with rearrangements involving 8q12 (39%)
> Tumours with rearrangements of 12q13-15 (8%)
> Tumours with sporadic, clonal changes not involving 8q12 or 12q13-15 (23%)
> Tumours with an apparently normal karyotype (30%).
Whereas t(3;8)(p21;q12) and t(5;8)(p13;q12) are the most frequently observed translocations in the first subgroup, a t(9;12)(p24;q14-15) or an ins(9;12)(p24;q12q15) are the most frequent rearrangements seen in the second subgroup. In addition, many variant translocations have been identified in which a number of other chromosome segments are found as translocation partners of both 8q12 and 12q13-15. Secondary chromosome changes, including trisomies, dicentrics, rings and double minutes, are found in about one-third of the cases with abnormal karyotypes. Previous studies have also indicated that patients with karyotypically normal adenomas are significantly older than those with rearrangements of 8q12 (51.1 years versus 39.3 years, p < 0.001) and that adenomas with normal karyotypes are often more stroma rich than tumours with 8q12 abnormalities [306].

Molecular genetics
The target gene in pleomorphic adenomas with 8q12 abnormalities is PLAG1, a developmentally regulated zinc finger gene [82,1279,2701]. Translocations involving 8q12 commonly result in promoter swapping/substitution between PLAG1 and a ubiquitously expressed translocation partner gene, leading to activation of PLAG1 expression. The breakpoints invariably occur in the 5'-noncoding regions of both the target gene and the promoter donor genes. The most commonly observed fusions are CTNNB1-PLAG1 and LIFR-PLAG1, resulting from t(3;8)(p21;q12) and t(5;8)(p13;q12) translocations, respectively [1279,2701]. Recently, cryptic gene fusions involving CTNNB1-PLAG1 and SII-PLAG1 were also found in karyotypically normal adenomas [82]. The PLAG1 protein is a nuclear oncoprotein that functions as a DNA-binding transcription factor. Deregulation of PLAG1 target genes, including IGF2, is likely to
play a major role in the genesis of pleomorphic adenomas [2700]. The target gene in adenomas with rearrangements of 12q14-15 is the high mobility group protein gene, HMGA2 (a.k.a. HMGIC) [878,879,2269]. HMGA2 encodes an architectural transcription factor that promotes activation of gene expression by modulating the conformation of DNA. The protein contains three DNA-binding domains that bind to the minor groove of AT-rich DNA. The majority of breakpoints in HMGA2 occur within the third large intron, resulting in separation of the DNA-binding domains from the highly acidic, carboxy-terminal domain. Two fusion genes, HMGA2-NFIB and HMGA2-FHIT, have been identified in adenomas with ins(9;12) and t(3;12), respectively [878,879]. Since no common functional domain has been found among the translocation partners, the critical event seems to be the separation of the DNA-binding domains from potential mRNA destabilizing motifs in the 3’-UTR, leading to deregulation of HMGA2 oncprotein expression. High-level expression of HMGA2 resulting from gene amplification was recently suggested to be of importance for malignant transformation of pleomorphic adenomas [2194].

The five PLAG1- and HMGA2-containing fusion genes so far identified are all tumour specific and may therefore be used as diagnostic markers for pleomorphic adenomas [2194]. The fusions may be detected either by RT-PCR or by interphase fluorescence in-situ hybridization [878,879,1279,2701]. Molecular studies of the RAS and ERBB2 oncogenes have shown that mutation and activation of RAS frequently occur in pleomorphic adenomas, particularly in tumours with PLAG1 activation [1727, 2198,2464,2465], whereas amplification and/or overexpression of ERBB2 seem to be rare [2198,2465]. Similarly, TP53 alterations are infrequent in adenomas [1907, 2198,2734]. In contrast, mutation and overexpression of TP53 are found in a relatively high proportion of carcinoma ex pleomorphic adenomas [1491,1907,2169]. In addition, recent studies have shown that the TP53-related genes TP63 and TP73, which are novel myoepithelial markers, are overexpressed in basal and myoepithelial cells in pleomorphic adenomas [214,2734]. The pathogenetic relevance of the latter observations is uncertain. Studies using the human androgen receptor gene assay have demonstrated that the stromal and epithelial cells in pleomorphic adenomas are clonal and derived from the same progenitor cell [1455].

Finally, it was recently demonstrated that pleomorphic adenomas contain Simian virus 40 (SV40) DNA sequences and express the SV40 large T antigen, suggesting that this oncogenic virus may be involved in the genesis and/or progression of this tumour [1643].

**Prognosis and predictive factors**

Although pleomorphic adenoma is a benign tumour it can cause problems in clinical management due to its tendency to recur and the risk of malignant transformation. Recurrences are rare in the minor glands but in a meta-analysis of parotid tumours 3.4% of tumours recurred after 5 years and 6.8% after 10 years with a range of 1-50% [1083]. The variation of frequency of recurrence in this survey probably reflected the inclusion of cases reported before superficial parotidectomy became a widely used treatment and the variability of long-term follow-up. Some single centre, long-term surveys however, have shown recurrence rates as low as 1.6% [2169]. Recurrences appear to be much more likely in younger patients [1436,1681]. The possible reasons for recurrences or persistence in pleomorphic adenoma include:

- The diluent nature of predominantly mucoid tumours [2157].
- The variability of the thickness of the capsule, together with the tendency of the tumour to invade the capsule [1065].
- Tumour nodules bulging through the capsule.
- Intratumoural splitting beneath the capsule.
- It is probable that the tumour cells have low biological requirements and this enables them to survive when split into the operative site.

Many recurrent pleomorphic adenomas are multifocal and some are so widely distributed that surgical control becomes impossible.
Myoepithelioma

**Definition**
Myoepithelioma is a benign salivary gland tumour composed almost exclusively of sheets, islands or cords of cells with myoepithelial differentiation that may exhibit spindle, plasmacytoid, epithelioid or clear cytoplasmic features.

**ICD-O code**
8982/0

**Synonyms**
Myoepithelial adenoma, benign myoepithelial tumour.

**Epidemiology**
Myoepitheliomas account for 1.5% of all tumours in the major and minor salivary glands and represent 2.2% and 5.7%, respectively of all benign major and minor salivary gland tumours [668]. Both sexes are affected with equal frequency [41,128,546,668,1647,2282,2367]. Most tumours occur in adults, but rare examples have been recorded in children [1527]. The age of patients with myoepithelioma ranges from 9-85, with an average of 44 years and the peak age of occurrence in the third decade [668].

**Localization**
Myoepitheliomas develop preferentially in the parotid gland (40%) [668]. Minor salivary glands follow in frequency, especially in hard and soft palates [546,668,2282,2367]. Other minor salivary gland sites can also be affected [41,1647].

**Clinical features**
Myoepitheliomas usually present as slow growing painless masses [41,2282,2367].

**Macroscopy**
Myoepitheliomas are well-circumscribed, solid tumours that usually measure less than 3 cm in diameter [41,541,2367]. Myoepitheliomas have a solid, tan or yellow-tan, glistening cut surface [668].

**Histopathology**
A variety of cell morphologies has been recognized, including spindle, plasmacytoid or hyaline, epithelioid, and clear [546]. Most are composed of a single cell type but combinations may occur. Spindle cells are arranged in interlacing fascicles with stroma-like appearance [1579]. Plasmacytoid cells are polygonal cells with eccentric nuclei and dense, nongranular or hyaline, abundant eosinophilic cytoplasm. Plasmacytoid cells are found more often in tumours arising in the minor salivary glands than in the parotid gland. These hyaline cells may simulate neoplastic plasma cells, skeletal muscle or “rhabdoid” cells [1575]. Epithelioid cells are arranged in nests or cords of round to polygonal cells, with centrally located nuclei and a variable amount of eosinophilic cytoplasm. The surrounding stroma may be either collagenous or mucoid. Some myoepitheliomas are composed predominantly of clear polygonal cells with abundant and optically clear cytoplasm, containing large amounts of glycogen but devoid of mucin or fat. These tumours may show intercellular micr ecstatic spaces. In other myoepitheliomas, occasional duct-like structures and intercellular microcystic spaces may be present. An unusual reticular variant of myoepithelioma characterized by netlike arrangements of interconnected cell cords, extending through a loose, vascularized stroma, has been reported [546].

**Immunoprofile**
The cells of myoepithelioma are usually positive for cytokeratins, especially for CK7 and 14. The reactivity of the spindle cells is variable for α-smooth muscle actin, muscle specific actin (MSA), calponin, S-100, GFAP and smooth muscle myosin heavy chain. There is considerable variation of tumour expression of MSA. The spindle cells react strongly for MSA, the epithelioid cells react sporadically, and the plasmacytoid and clear cells are often nonreactive [805].

**Electron microscopy**
Ultrastructural studies confirmed the epithelial and myoepithelial differentiation of myoepithelioma [538,541].

**Differential diagnoses**
Distinction from pleomorphic adenoma is based on the relative lack of ducts and the absence of myxochondroid or chondroid areas. Myoepitheliomas with clear cells, or mixed epithelioid and clear cells have to be separated from other salivary gland tumours with clear cells, such as: mucoepidermoid carcinoma, acinic cell carcinoma, epithelial-myoepithelial carcinoma, oncocytoma and clear cell carcinoma. All these tumours lack the characteristic immunoprofile of the myoepithelial cells. In contrast to carcinomas, myoepitheliomas have a non-infiltrative, well-circumscribed periphery.

---

Table 5.03 Classification of clear cell tumours of the salivary glands.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benign</strong></td>
<td>Pleomorphic adenoma, myoepithelioma, sebaceous adenoma, oncocytoma and oncocytic hyperplasia</td>
</tr>
<tr>
<td><strong>Malignant, primary</strong></td>
<td>a. Carcinomas not usually characterized by clear cells, but with clear cell predominant areas; e.g. mucoepidermoid and acinic cell carcinomas.</td>
</tr>
<tr>
<td></td>
<td>b. Carcinomas usually characterized by clear cells;</td>
</tr>
<tr>
<td></td>
<td>i. Dimorphic epithelial-myoepithelial carcinoma.</td>
</tr>
<tr>
<td></td>
<td>ii. Monomophic clear cell carcinoma.</td>
</tr>
<tr>
<td></td>
<td>iii. Sebaceous carcinoma.</td>
</tr>
<tr>
<td><strong>Malignant, metastatic</strong></td>
<td>Carcinomas, especially kidney, thyroid, melanoma.</td>
</tr>
</tbody>
</table>

---

A. Cardesa  
L. Alos
Predominantly spindle cell myoepitheliomas must be distinguished from benign and malignant mesenchymal tumours.

**Genetics**
Cytogenetic studies have demonstrated structural alterations of chromosomes 1, 9, 12, and 13: t(1;12)(q25;q12), del(9) (q22.1q22.3), del(13)(q12q22) in a parotid myoepithelioma [654]. Mutations of TP53 have been observed in 3 of 12 (25%) myoepitheliomas [2734].

**Prognosis and predictive factors**
According to well-documented series myoepitheliomas are less prone to recur than pleomorphic adenomas [2282]. However, higher recurrence rates have been reported by others [41,646]. Recurrence is correlated with positive margins at the first excision [646]. The recommended treatment is complete surgical excision. Benign myoepitheliomas can undergo malignant transformation, especially in long standing tumours or in tumours with multiple recurrences [41].

---

Fig. 5.56 Myoepithelioma. A Spindle cell type. B Epithelioid cell type. C Plasmacytoid cell type. D Clear cell type.

Fig. 5.57 Myoepithelioma. A α-SMA stain. B Spindle cell type: cytokeratin 7 stain.
Basal cell adenoma

Definition
Basal cell adenoma (BCA) is a rare benign neoplasm characterized by the basaloid appearance of the tumour cells and absence of the myxochondroid stromal component present in pleomorphic adenoma.

ICD-O code
8147/0

Epidemiology
Accurate epidemiological data are hard to obtain since in the past BCA was included within non-pleomorphic tumours. The BCAs are rare, accounting for 1-3% of all salivary gland tumours. They are typically seen in adults in the 7th decade with a 2:1 female predilection (2303), except for the membranous type that has an equal female: male distribution (668).

Localization
The majority arise in the major glands, and the parotid is the most frequent site of occurrence (~75%), followed by the submandibular gland (~5%) (162, 2881). It is extremely rare in minor salivary glands, the upper lip being the most common site, followed by the buccal mucosa (704, 2711).

Clinical features
Most tumours are solitary, well-defined, movable nodules. They are usually firm but occasionally cystic. The membranous type (dermal analogue tumour) (153) may be multiple and co-exist with dermal cylindromas or trichoepitheliomas (1033, 1582, 2867).

Macroscopy
Most of the tumours present as small, well-circumscribed, encapsulated nodules measuring between 1-3 cm, except for the membranous type that may be multinodular or multifocal. On cut section they are solid and homogeneous or cystic, with a greyish-white to brown colour.

Histopathology
Microscopically, BCAs are composed of basaloid cells with eosinophilic cytoplasm, indistinct cell borders and round to oval nuclei, distributed in solid, trabecular, tubular, and membranous patterns. However, tumours may present with more than one of these patterns, usually with the predominance of one. The solid type is composed of sheets or islands of variable shapes and sizes, usually with peripheral palisading of cuboidal to columnar cells. The islands are separated by strands of dense collagenous tissue. The trabecular type is characterized by narrow strands, trabeculae or cords of basaloid cells separated by cellular and vascular stroma. A rare but distinctive feature is the presence of a richly cellular stroma composed of modified myoepithelial cells (542). Ductal lumina are often observed among the basaloid cells and these cases are considered as tubulo-trabecular type. The membranous type of BCA has thick bands of hyaline material at the periphery of basaloid cells and as intercellular coalescing droplets. In the tubular type, ductal structures are a prominent feature. All variants may demonstrate cystic change, squamous differentiation in the form of whorls or ‘eddies’, or rare cribriform patterns. Occasional tumours, particularly of the tubular type, are largely oncocytic.

Immunoprofile
Immunopositivity for keratin, myogenic markers, vimentin and p63 indicate ductal and myoepithelial differentiation (214, 553, 1598, 2883). Also the palisading cells of the solid type can stain for vimentin and myogenic markers. The pattern of expression reflects the different differentiation stages of the tumour cells, varying from the solid type, the less differentiated, to the tubular type, the most differentiated.

Genetics
Genetic aberration has been described in three cases of BCA. Two cases presented trisomy 8 and one case the 7;13 translocation and/or inv(13) (1136, 2385).

Prognostic and predictive factors
BCA is usually a non-recurrent tumour, except for the membranous type, that has a recurrence rate of approximately 25% (1582). Although exceedingly rare, malignant transformation of BCA has been reported (1825).

Fig. 5.58 Basal cell adenoma. A Solid type - Varied size nests of cuboidal cells. Note the palisading of nuclei in peripheral cells. B Trabecular type, with anastomosing cords of basaloid cells.
Fig. 5.59 Histological types of basal cell adenoma. **A** Tubular type, with small duct lumens lined by cuboidal eosinophilic cells. **B** Membranous type, with prominent hyaline material around and inside epithelial islands. **C** Occasional features found in basal cell adenoma include variable sized cystic spaces. **D** High cellularity of the stroma represented by spindle-shape cells.

Fig. 5.60 Immunohistochemical profile of basal cell adenoma. Tubulo-trabecular type. **A** CK7 positivity in ductal cells. **B** Smooth muscle actin expression in myoepithelial cells.
Warthin tumour

Definition
A tumour composed of glandular and often cystic structures, sometimes with a papillary cystic arrangement, lined by characteristic bilayered epithelium, comprising inner columnar eosinophilic or oncocytic cells surrounded by smaller basal cells. The stroma contains a variable amount of lymphoid tissue with germinal centres.

ICD-O code 8561/0

Synonyms
Adenolymphoma, cystadenolymphoma, papillary cystadenoma lymphomatosum. Warthin tumour is preferred to avoid any possible confusion with a lymphoid malignancy, and with the separate entity, lymphadenoma {1591}.

Epidemiology
In most countries, Warthin tumour is the second commonest tumour of the salivary glands. In the United States (US) it comprised about 3.5% of all primary epithelial tumours (5.3% in the parotid) {668}. Other studies revealed higher percentages, such as 14.4% of primary epithelial tumours of the parotid gland in the United Kingdom (UK) {703}, 27% in Denmark {2075}, and 30% in Pennsylvania, USA {1765}. Warthin tumour occurs in Caucasians and Asians {451}, but has a lower incidence in African-Americans {668} (although this may now be increasing {2856}) and in Black Africans {2590}. The mean age at diagnosis is 62 years, (range 12-92) {668}, and it is rare before 40. The relative sex incidence has changed during the last half-century: In 1953 the male to female ratio was 10:1 {786}, whereas in 1996 it was 1.2:1 {668}, and in 1992 it was equal {1765}. In the UK in 1986 the ratio was 1.6:1 {705}.

Localization
Warthin tumour is almost exclusively restricted to the parotid glands and the periparotid lymph nodes. Most cases involve the lower pole although 10% are in the deep lobe. Occasional tumours (2.7% in one series) arise within adjacent lymph nodes {664}. Very rare examples have been reported in other glands {2669}, but some tumours thought initially to be within the submandibular gland have usually arisen from the anterior tail of the parotid or from lymph nodes {668}. Warthin tumour is clinically multicentric in 12-20% of patients (either synchronous or metachronous), and is bilateral in 5-14% {899,1610}. In addition, serial sectioning revealed additional sub-clinical lesions in 50% of cases {1417}.

Etiology
There is a strong link between Warthin tumour and cigarette smoking {633,2052} – the incidence is eight times that of non-smokers {1360}. In addition, the increased numbers of female smokers during the second half of the 20th century closely parallels the increase in Warthin tumour in women, and largely explains the change in sex incidence during this period {1421,2856}. The mechanisms are not clear but in has been speculated that irritants in tobacco smoke cause metaplasia in the parotid {2866}. Radiation exposure may be relevant as there is an increase in Warthin tumour among atomic bomb survivors {2229}. There is also said to be a higher frequency of autoimmune disorders in patients with Warthin tumour than in those with pleomorphic adenomas or healthy subjects {899}. At present, the balance of probabilities is that EBV does not play a significant role in the etiology of Warthin tumour {2733}. The metaplastic (infarcted) variant can follow trauma, particularly from FNA biopsy {596,706}.

Clinical features
Most patients present with a painless mass, on average, 2-4 cm, although

Fig. 5.61 A Warthin tumour. Low power showing lymphoid stroma, cystic change and intraluminal papillary epithelial projections. B Intermediate power showing oncocytic epithelium and characteristic lymphoid stroma with germinal centres.
occasional cases have reached 12 cm [2783]. The mean duration of symptoms is 21 months, but in 41% of patients it is less than six months [705]. Many patients notice fluctuation in size of the tumour, especially when eating [1711]. Pain has been reported in 9% [705], particularly those with the metaplastic variant [2866]. Facial paralysis is very rare, and is the result of secondary inflammation and fibrosis, and likewise can be seen in the metaplastic variant [706,1876].

Warthin tumour is able to concentrate Technetium (99mTc), appearing as a “hot” lesion. It is usually well-circumscribed, but secondary inflammation can cause the edges to become indistinct.

**Macroscopy**
Most Warthin tumours are well-circumscribed, spherical to ovoid masses, and partly cystic. The cysts vary from small slits to spaces up to several centimetres, and contain clear, mucoid, creamy white or brown fluid. Solid areas are tan to white, and often firm and fibrous in the metaplastic variant. In all cases of Warthin tumour, the parotidectomy specimen should be examined for other lesions.

**Histopathology**
The tumour is sharply demarcated with a thin capsule. There are cystic and solid areas, composed of epithelial and lymphoid components. The cysts and slit-like spaces vary in size and shape, and papillary structures project into the lumen. The papillae have fibrovascular cores often with lymphoid stroma. The epithelium comprises two layers of cells: the oncocytic luminal cells are tall and columnar, and show palisading of their bland single ovoid nuclei. The surface often shows apocrine blebbing and cilia are occasionally identified [705]. Deep to this layer lie smaller flattened or cuboidal basal cells. Their cytoplasm is similar, but less abundant. No significant nuclear atypia or mitotic activity is identified. Small foci of squamous metaplasia, scanty goblet cells and very occasional sebaceous cells are seen.

The stroma comprises lymphoid tissue displaying varying degrees of reactivity, and germinal centres are usual. Increased numbers of mast cells and plasma cells may also be seen. The cystic spaces contain eosinophilic secretions with occasional crystal formation and laminated bodies resembling corpora amylacea.

Some tumours, variously termed, infarcted, infected or metaplastic, account for 6-7% of Warthin tumours [706,2295]. They are likely to be encountered more frequently in the future with the increasing use of pre-operative FNA. There is extensive necrosis, in which a ghost architecture of papillary structures is often identified – this can be highlighted with a reticulin stain. Non-keratinizing squamous metaplasia is prominent, consisting of tongues and cords of often spongiotic squamous cells extending into surrounding tissues in a pseudo-infiltrative pattern. Cytological atypia can be prominent, and mitotic figures numerous, but none is abnormal. Goblet cells can also be seen, but should not be numerous. At the periphery of the lesions, there is extensive fibrosis, with dense hypocellular collagen and myofibroblastic spindle cell proliferation. There is a heavy mixed inflammatory infiltrate, comprising neutrophils, chronic inflammatory cells, as well as sheets of macrophages, some with foamy cytoplasm. Lipogranulomas, with or without cholesterol crystals, are not uncommon. Areas of residual undamaged Warthin tumour can be found, but not in every case, and there may thus be few clues to the nature of the original lesion [596,706].

**Immunoprofile**
Lymphoid marker studies have shown B (CD20), NK (CD56) and T (CD3) cells, including helper (CD4) and suppressor (CD8) subtypes. This profile of lymphocyte subsets is similar to that in normal or reactive lymph nodes [432]. Special stains and immunohistochemistry have little to offer in the diagnosis of Warthin tumour, although there may be a role in diagnosing the metaplastic variant with epithelial markers, particularly when no residual viable Warthin tumour can be identified [596,2279].
Cytopathology
The cytopathological findings reflect the histopathological appearance, except that mast cells are more noticeable. The other cellular elements are oncocytic epithelial cells and lymphocytes, with a background of cell debris and proteinaceous material [776]. Uncommon findings include ciliated cells [2899], squamous cells, mucous cells, siderophages, giant cells, calcifications and crystalloids [776]. The diagnostic sensitivity of FNA cytology is moderately accurate [1984], but the error rate is clinically significant, as for example, the findings in lymphocyte-rich acinic cell carcinoma are almost identical [2135].

Differential diagnosis
Of all salivary gland tumours, the typical type of Warthin tumour is usually unmistakable. Papillary cystadenoma is similar and possibly related, but any lymphoid tissue is scanty. There is some resemblance to other lymphoepithelial cystic lesions such as simple benign lymphoepithelial cyst (unrelated to AIDS), lymphoepithelial sialadenitis (LESA) with cystically dilated ducts, cystic lymphoid hyperplasia of AIDS and MALT lymphoma with cystically dilated ducts [2372]. An important differential is from cystic metastases in intra and periparotid lymph nodes – the malignant nature of most should be obvious, but a recently-reported variant of papillary thyroid carcinoma has been described as “Warthin-like” [113,1572]. It is characterised by a heavy lymphoid stroma and oncocytic metaplasia of the epithelium. The best guide to its true nature is that the nuclei display typical chromatin clearing, inclusions and groove-formation, and the epithelial cells show immunohistochemical expression of thyroglobulin. If there is marked cytological atypia and mitotic activity, the metaplastic variant can be mistaken for squamous or mucoepidermoid carcinoma, either primary or metastatic [596]. The resemblance is particularly close if there has been total infarction of the original Warthin tumour. Clues to the true nature of the lesion include any ghost papillary architecture in the necrotic zones. Also, the squamous metaplasia lacks keratinization (seen in most squamous carcinomas), and mucinous goblet cells are usually much less numerous than in low-grade cystic mucoepidermoid carcinoma.

Histogenesis
There are two principal theories of the histogenesis [668]: one is an origin from intercalated and basal cells of heterotopic salivary ductal inclusions in intra- or peri-parotid lymph nodes. In particular, this explains the distribution of Warthin tumour and its absence from other salivary tissue lacking incorporated lymph nodes. The alternative theory is that Warthin tumour is a benign epithelial neoplasm or proliferation that attracts a heavy lymphoid reaction, similar to that seen in certain other salivary neoplasms [83,1717,2372]. More recently, it has been suggested that Warthin tumour initially develops in a parotid lymph node as an adenomatous epithelial proliferation responding to as yet unidentified stimuli (probably including tobacco either as a direct stimulus or a promoter), followed by lymphocytic infiltration. The stage of this process seen at the time of surgery determines the proportions of epithelial and lymphoid elements [20].

Genetics
Cytogenetic studies have shown Warthin tumour to have three main stemline groups, one with a normal karyotype, a second with numerical changes only (loss of Y chromosome or trisomy or monosomy 5) and a third group involving structural changes with one or two reciprocal translocations [1711]. Damage to the mitochondrial DNA may account for the ultrastructural changes seen in the mitochondria, as well as the oncocytic change seen morphologically [1494]. Analysis of the X chromosome-linked human androgen receptor gene showed that Warthin tumour is non-clonal, and thus likely to be non-neoplastic [1118]. This finding supports morphological observations that suggested Warthin tumour (as well as various thymic and head and neck cysts) resulted from the induction of cystic changes in branchial cleft epithelium by an inflammatory infiltrate, accompanied by oncocytic change in the epithelium [2199,2509]. A study of 13 cystadenolymphomas (Warthin tumours) showed minimal chromosomal alterations in these tumours [1905]. Interestingly, at least two tumours with cytogenetic analysis have been reported to have t(11;19) (q21;p13) translocation, suggesting a link to mucoepidermoid carcinoma [305,1638]. It is interesting, that the rearrangements on 8q and 12q have, so far, been found to be mutually exclusive [306,2239].

Prognosis and predictive factors
Primary treatment is surgical, either superficial parotidectomy or enucleation. After this, most studies show low recurrence rates of about 2-5.5% [668,705], presumably the result of multifocality. Malignant change is rare, at about 1% [669,2295], and may involve the epithelial or lymphoid components. Some patients give a history of radiation [1984,2229,2295]. Several types of carcinoma have been described, including squamous [2390], adenocarcinoma [2295], mucoepidermoid [1826,2294], oncocytic [2585], Merkel cell [788] and undifferentiated. The differential diagnosis includes squamous or mucous metaplasia, and metastases of extra-salivary malignancies to a pre-existing Warthin tumour. Lymphomas include nodal types [115,1694,2338], and one report of lymphoepithelial lesions suggesting a MALT-type neoplasm [113]. Warthin tumour is sometimes seen in association with other benign salivary tumours, particularly pleomorphic adenoma [664,905,1458,2338,2395], although it is not clear if this is greater than would be expected by chance with what is after all not an uncommon tumour. Another study found an increased incidence of extra-salivary neoplasms. A common etiology of cigarette smoking explains the carcinomas of the lung, larynx and possibly the bladder, whilst the others (lymphoma, kidney and breast cancers) could just be a coincidence [1610].
Oncocytoma

Definition
Benign tumour of salivary gland origin composed exclusively of large epithelial cells with characteristic bright eosinophilic granular cytoplasm (oncocytic cells).

ICD-O code 8290/0

Synonym
Oncocytic adenoma, oxyphilic adenoma

Epidemiology
Oncocytoma accounts for about 1% of all salivary gland neoplasms and occurs most commonly in the 6-8th decades (257). The mean age of the patients is 58 years. There is no sex predilection.

Etiology
Approximately 20% of all the patients will have a history of radiation therapy to the face or upper torso or long-term occupational radiation exposure five or more years prior to tumour discovery [257]. Patients with previous radiation exposure are on the average 20 years younger at tumour discovery than those without a documented history of irradiation.

Localization
Among oncocytic major salivary gland tumours, 84% occur in the parotid (male to female ratio of 1:1), and the remainder arise in the submandibular gland (2601). Minor salivary gland sites include the lower lip, palate, pharynx, and buccal mucosa.

Clinical features
Symptoms vary according to the site of occurrence and most commonly present as a painless mass, less frequently nasal or airway obstruction.

Imaging
CT scan: Well-defined area of increased density in the host salivary gland. Radiouclide imaging shows increased uptake of technetium-99m that does not disappear following sialogogue administration. This finding plays an important role in the diagnosis and is related to the presence of oncocytes and their increased mitochondrial content.

Macroscopy
On gross examination, oncocytomas are usually 3-4 cm in size and possess a well-defined capsule. The cut surface is light brown and lobular.

Histopathology
Histologically, the oncocytic cells are arranged in a solid or trabecular pattern. Microcyst formation can rarely be observed. The oncocytes display ample granular acidophilic cytoplasm. Typically the predominant cells have abundant oncocytic cytoplasm and an oval, vesicular nucleus (light cells). In addition, there are cells with very brightly eosinophilic cytoplasm and pyknotic nuclei (dark cells). The cells are arranged in uniform sheets and they may aggregate into clusters, and sometimes they form duct-like structures. Rarely, oncocytomas present with large polyhedral clear cells in an organoid distribution. A thin fibrovascular stroma is also present. An intimate mixture of typical eosinophilic and clear cell oncocytes may be encountered within the same tumour. Tumours with a predominantly clear cell component are referred to as clear cell oncocytoma (665). The opticaly clear cell appearance is due to fixation artefact and/or intracytoplasmic glycoegen deposition (551,2291). The tumour cells typically stain with phosphotungstic acid haematoxylin (PTAH). Electron microscopy shows elongated cristae and a partial lamellar internal structure (1227). The nuclei of the oncocytes are irregular and contain inclusions and glycogen granules.

Differential diagnosis
The most important differential diagnosis of oncocytoma includes acinic cell carcinoma and clear cell carcinoma. Mucoepidermoid carcinoma with prominent clear cell alteration and metastatic renal cell carcinoma may also be practical considerations. Also, stroma-poor Warthin tumour, oncocytic carcinoma, and metastatic thyroid carcinoma should be included.

The clear-cut separation of an oncocytic adenomatous (nodular) hyperplasia of the parotid gland from a multinodular oncocytoma (a true neoplasm) is not always possible since the two entities overlap histologically (223,882,2427).

Prognosis and predictive factors
Complete surgical excision is the treatment of choice. Radiotherapy is not indicated especially since oncocytes are radioresistant. Local recurrence of an oncocytoma is extremely rare, but when it occurs, it may be multiple and bilateral. The incidence of bilateral oncocytomas is 7%. It seems there is an association between bilateral disease, tumour recurrence, and marked clear cell change (clear cell oncocytosis).

A G Huvos

Fig. 5.64 Oncocytoma  A Tumour cells having eosinophilic, granular cytoplasm and showing both light and dark cells.  B Clear cell variant.
Canalicular adenoma

Definition
The tumour is composed of columnar epithelial cells arranged in thin, anastomosing cords often with a beaded pattern. The stroma is characteristically paucicellular and highly vascular.

ICD-O code 8149/0

Synonyms
Basal cell adenoma, canalicular type, monomorphic adenoma, canalicular type, adenomatosis of minor salivary glands

Epidemiology
There is a peak incidence in the seventh decade (mean 65 years). The age range is 33-87 years. It is uncommon before the age of 50 [529,668,1864] and the female-to-male ratio is 1.8:1 [529,668]. It comprised 1% of all salivary gland neoplasms and 4% of minor salivary gland neoplasms in a major series [668].

Localization
Canalicular adenoma has a peculiar predilection to involve the upper lip (about 80% of tumours) [529,1864]. The next most common location is the buccal mucosa (9.5% of tumours) [1864]. Rarely, canalicular adenoma can involve the major salivary glands [529].

Clinical features
These tumours present as enlarging nodules with no accompanying symptoms such as pain or paralysis. The overlying mucosa shows typical coloration but in some cases may appear bluish. A peculiar presentation of canalicular adenoma is that of multiple/multifocal canalicular adenomas [1308,1866,2206]. When this occurs, the upper lip and buccal mucosa are typically involved but other sites can be affected.

Macroscopy
Canalicular adenomas range in size from 0.5-2.0 cm in diameter and are grossly well circumscribed. The colour is light yellow to tan [668].

Histopathology
The microscopic appearance at low magnification likewise shows circumcision. Some canalicular adenomas have a fibrous capsule while smaller tumours often do not. It is not uncommon to see multifocal microscopic canalicular adenomas adjacent to a larger canalicular adenoma. In addition, very small foci of adenomatous tissue can be seen which may represent the earliest recognizable microscopic manifestation of canalicular adenoma. Superimposed necrosis can occur in some cases [36]. The epithelial component manifests as two rows of columnar cells which alternately are situated opposed to each other and alternately widely separated. This leads to the characteristic appearance of these tumours - canalici - where the epithelial cells are widely separated. The alternating arrangement of closely opposed and widely separated epithelial cells also leads to the characteristic beaded appearance of these tumours. The epithelial cells forming the cords are typically columnar but can be cuboidal. Nuclei are regular and show no pleomorphism. Nucleoli are inconspicuous and mitotic figures are rare. The stroma is characteristic and a useful clue to the diagnosis. It is paucicellular but shows a prominent vascular pattern. The capillaries often have an eosinophilic cuff of connective tissue.

Immunoprofile
Canalicular adenomas stain with anti-keratin, anti-vimentin and anti S-100 antibodies [758]. Rare focal GFAP positivity is seen [758]. Canalicular adenomas are devoid of staining when more sensitive markers of myogenous differentiation such as smooth muscle actin, smooth muscle myosin heavy chain and calponin are used [2883].

Differential diagnosis
The most important are adenoid cystic carcinoma and basal cell adenoma. Multifocality and cribriform pattern should not be misinterpreted as carcinoma. Hybrid tumours composed of canalicular adenoma and basal cell adenoma have been reported [2297].

Prognosis and predictive factors
The prognosis is excellent and recurrences are rare even if the tumours are treated with just a local excision or lumpectomy. Whether new tumours are true recurrences or are a manifestation of the multicentric growth pattern is difficult to ascertain.

Fig. 5.65 Canalicular adenoma, showing thin, beaded anastomosing cords, paucicellular stroma and prominent vascularity.
Sebaceous adenoma

Definition
It is a rare, usually well-circumscribed tumour composed of irregularly sized and shaped nests of sebaceous cells without cytologic atypia, often with areas of squamous differentiation and cystic change.

ICD-O code 8410/0

Epidemiology
They account for 0.1% of all salivary gland neoplasms and slightly less than 0.5% of all salivary adenomas. The mean age is 58 years (22-90 years) and the male:female ratio is 1.6:1. Unlike cutaneous sebaceous neoplasms, there is no increased risk of developing a visceral carcinoma.

Localization
Approximately 50% of tumours arise in the parotid gland, 17% in the buccal mucosa, 13% in the retromolar region or area of the lower molars and 8% in the submandibular region.

Clinical features
Patients typically present with a painless mass.

Macroscopy
These adenomas range in size from 0.4-3.0 cm in greatest dimension, are commonly well circumscribed to encapsulated and are greyish-white to yellow.

Histopathology
They are composed of sebaceous cell nests often with areas of squamous differentiation with minimal atypia and pleomorphism with no tendency to invade local structures. Many tumours are microcystic or composed predominantly of ectatic ductal structures. The sebaceous glands frequently vary markedly in size and tortuosity and are often embedded in a fibrous stroma. Occasional tumours demonstrate marked oncocytic metaplasia. Histiocytes and/or foreign body giant cells can be seen focally. Lymphoid follicles, cytologic atypia, cellular necrosis, and mitoses are usually not observed. Infrequently, these tumours may be part of a hybrid neoplasm.

Treatment and prognosis
Treatment consists of complete surgical excision. They do not recur.
Lymphadenomas: sebaceous and non-sebaceous

Definition
Sebaceous lymphadenoma is a rare, well-circumscribed to encapsulated tumour composed of variably sized and shaped nests of sebaceous glands without atypia often intermixed with different proportions of variably sized ducts, within a background of lymphocytes and lymphoid follicles. Lymphadenoma is a similar tumour lacking sebaceous differentiation.

ICD-O code
Sebaceous lymphadenoma 8410/0

Epidemiology
Approximately 75% of sebaceous lymphadenomas are first diagnosed in the 6-8th decades of life (25-89 years). There is no sex predominance. Lymphadenoma is a rare tumour, with only 5 cases having been reported in the literature [83,1399,1591]. From the limited available data, all patients are male ranging in age from 17-57 years.

Localization
Well over 90% of sebaceous lymphadenomas occurred in or around the parotid gland with one tumour arising in the anterior midline of the neck [896], and two tumours occurring in the oral region [1393,1654]. All cases of lymphadenomas reported so far have occurred in the parotid gland [83,1591].

Clinical features
Patients typically present with a painless mass.

Macroscopy
Tumours have ranged from 1.3-6.0 cm in greatest dimension. They are usually encapsulated, solid, multicystic, or unilocular masses that range from yellow to grey. Sebum is commonly found in many of the cysts.

Histopathology
Sebaceous lymphadenoma.
The majority of sebaceous lymphadenomas are composed of variably sized sebaceous glands admixed with salivary ducts in a diffuse lymphoid background. Others consist mainly of lymphocytes and lymphoid follicles surrounding ductal structures with only occasional sebaceous glands. All tumours have a lymphoid background, and about one half have well-developed lymphoid follicles. In addition, tumours may contain small areas of identifiable residual lymph node and focal necrosis has rarely been observed. Occasional tumours may also contain or be intermixed with components of a Warthin tumour or membranous basal cell adenoma [896,901]. Histiocytes and foreign body giant cell inflammatory reactions secondary to extravasated sebum are commonly observed. This foreign body reaction can be helpful in differentiating these tumours from mucoepidermoid carcinoma (MEC). Unlike MEC, which contains a variety of cell types; mucin positivity is never found in the clear sebaceous cells. However, intracellular and extracellular mucin may be occasionally found within ducts adjacent to sebaceous cells.

Lymphadenoma
It can take the form of anastomosing trabeculae or solid tubules surrounded by basement membrane-like material, or cystically-dilated glands filled with proteinaceous materials. Papillary structures can be found in some cases. The lining cells are cuboidal to columnar and show no significant cytologic atypia or mitotic activity. Basal cells can be identified in some areas. However, the epithelial component can be obscured by abundant admixed and intraepithelial lymphocytes; the diastase-peroxidase acid Schiff stain can help in highlighting the basement membrane around the epithelial nests. The lymphoid stroma comprises dense populations of lymphoid cells with lymphoid follicle formation. The lymphoid component is generally considered to represent tumour-associated lymphoid proliferation [83,604], hence conventional salivary gland adenomas occurring within intraparotid or cervical lymph node are excluded.

Differential diagnosis
The most important differential diagnosis of lymphadenoma is lymphoepithelial carcinoma; distinguishing features of lymphadenoma are lack of mitotic activity, lack of invasive growth with desmoplastic stroma, presence of subtle or overt ductal differentiation, and absence of EBV association. Metastatic adenocarcinoma in lymph node is characterized by recognizable nodal structures, definite nuclear atypia and invasive growth. Lymphadenoma can be distinguished from lymphoepithelial sialadenitis by the circumscribed borders as well as a more proliferative epithelial component.

Treatment and prognosis
Treatment consists of complete surgical excision. These tumours rarely recur.
Ductal papillomas are a group of relatively rare, benign, papillary salivary gland tumours known as inverted ductal papilloma, intraductal papilloma, and sialadenoma papilliferum. They represent adenomas with unique papillary features with a common relationship to the excretory salivary duct system, a non-aggressive biologic behaviour, and a predilection for the minor salivary glands. They tend to occur in the middle-aged and elderly and rarely in children. The three types of ductal papillomas possess distinct clinical and histologic features allowing differentiation from each other and other adenomas with a papillary pattern.

**Inverted ductal papilloma**

**Definition**
Inverted ductal papilloma is a luminal papillary proliferation arising at the junction of a salivary gland duct and the oral mucosal surface epithelium and exhibits an endophytic growth pattern that forms a nodular mass.

**ICD-O code** 8503/0

**Synonym**
Epidermoid papillary adenoma

**Epidemiology**
The true incidence of inverted ductal papilloma (IDP) is unknown, but it is thought to be relatively rare based on the sparse number of reported cases. Lesions have arisen in adults with an age range of 28-77 years and a male predilection [264].

**Localization**
All of the reported sites have been in the minor salivary glands—the most common location is the lower lip followed by the buccal mucosa/mandibular vestibule. Other reported sites have been the palate and the floor of mouth [264].

**Clinical features**
IDP typically presents as a painless nodular submucosal swelling, often with a dilated pore or punctum surfacing the swelling [1046]. Lesions have been described as being present from months to several years.

**Macroscopy**
Lesions have ranged from 0.5-1.5 cm. They are nodular masses that are often papillary and occasionally cystic.

**Histopathology**
The neoplasms are unencapsulated.

Well demarcated endophytic epithelial masses that are typically continuous with the mucosal epithelium. The mucosal epithelium has a central pore-like opening in the mucosal surface. The peripheral borders of the epithelial mass show a broad, smooth “pushing” interface juxtaposed to the connective tissue stroma. The epithelium proliferates in broad papillary projections that extend into the luminal cavity and are composed predominantly of epidermoid and basal cells that show columnar epithelium on the surface of the papillae. Acinar aggregates or individual mucocytes can be found in the columnar epithelial layer and/or in the subjacent epidermoid component. The epithelial cells are cytologically bland with little or no pleomorphism. Mitotic figures are rare.

**Differential diagnosis**
IDP must be differentiated from mucoepidermoid carcinoma since both have epidermoid and mucous cells. Inverted ductal papilloma does not have the multicystic, multinodular, and infiltrative growth pattern of mucoepidermoid carcinoma. Papillary features are rarely found in mucoepidermoid carcinomas.

**Prognosis and predictive factors**
There have been no reported recur-
references following conservative surgical excision based on 12 cases with adequate follow-up time [264].

**Intraductal papilloma**

**Definition**
Intraductal papilloma is a luminal papillary proliferation of duct epithelium that arises from a segment of the interlobular or excretory duct and causes unicystic dilatation.

**ICD-O code** 8503/0

**Epidemiology**
The intraductal papilloma is very rare. Age range is 8-77 years with most cases occurring in the 6th and 7th decade of life [264,1375]. Sex distribution is essentially even.

**Localization**
The minor salivary glands are more frequently involved than the major glands. Intraductal papillomas are most commonly found in the lips and buccal mucosa. Tumours have been reported in the palate and tongue as well. Of the major glands the parotid is most frequently involved, but cases in the submandibular and sublingual glands have also been cited [264,1008,1749].

**Clinical features**
Intraductal papillomas of major and minor salivary glands present as painless, well-defined solitary masses or swellings. Duration can range from weeks to years.

**Macroscopy**
Grossly, intraductal papillomas are well-circumscribed, unicystic nodules that range in size from 0.5-2.0 cm. The lumina contain finely granular, often friable tissue and mucinous material.

**Histopathology**
The tumour is entirely confined within a circumscribed or encapsulated unicystic cavity. The lumen is partially or completely filled with many branching papillary elements consisting of fibrovascular cores surfaced by columnar to cuboidal cells of one to two layers that originate from a focal point in the wall. Mucocytes, often goblet-like, are interspersed throughout the epithelium lining the papillary elements. These mucous-containing cells can be few to many in number. The epithelium that lines the cyst-like cavity is composed of the same type of epithelium as the papillary fronds. In many instances, the cystic structure has a dense fibrous connective tissue wall surrounding it. Cytologic atypia and mitotic figures are virtually absent [264].

**Differential diagnosis**
In contrast to intraductal papillomas, papillary cystadenomas are morphologically multicystic with numerous small to medium-sized cystic spaces. In the papillary cystadenoma the intraluminal growth is often characterized by multiple papillary projections with a variety of epithelial cell types, but usually the papillary growth occupies the lumen to a limited degree.

**Prognosis and predictive factors**
Excision appears to be curative based on five cases with an adequate follow-up of 2-5 years [1186,1302,1375,1829,2039].

**Sialadenoma papilliferum**

**Definition**
Sialadenoma papilliferum is an exophytic papillary and endophytic proliferation of mucosal surface and salivary duct epithelium.

**ICD-O code** 8406/0

**Epidemiology**
Sialadenoma papilliferum is a rare neoplasm [2711]. The age range is 31-87 years (mean age 59) with a male to female ratio of 1.5:1 [264].

**Localization**
The vast majority of cases have occurred in the minor salivary glands. Major salivary gland involvement is very rare with the parotid gland being the most frequently involved. Over 80% of the neo-
Tumours of the salivary glands

Plasms occur on the hard and/or soft palate. Buccal mucosa is the second most common site. Other intraoral sites are the upper lip, the retromolar pad, and the faucial pillar.

Clinical features
The sialadenoma papilliferum typically manifests as a painless, exophytic papillary growth that is often interpreted clinically as a squamous papilloma. Duration ranges from months to several years.

Macroscopy
Gross findings usually show a well-demarcated papillary or verrucoid, sessile to pedunculated surface morphology. Overall, the tumours generally range from 0.5-1.5 cm in size.

Histopathology
The neoplasm consists of a biphasic pattern with a glandular component consisting of collections of cysts and duct-like spaces underlying a papillary or verrucous type proliferation of squamous epithelium. These papillary extensions of squamous epithelium are supported by fibrovascular cores and extend above the level of the adjacent mucosa. At or near the base of the fronds there is a transition from squamous epithelium to columnar ductal epithelium, which lines the proliferating ductal elements. These ductal elements consist of small and ectatic ducts, some of which show cystic enlargement. The ducts and their papillary folds are lined by a double row of cells showing a basal layer composed of cuboidal cells and a luminal lining of low columnar cells. Mucocytes can be interspersed throughout the lining of ductal cells as well as in the squamous component. Columnar oncocytic cells may also be present. The lack of encapsulation of the ductal structures can at times give the false impression of an invasive growth pattern.

Differential diagnosis
The differential diagnosis typically centres around three lesions: squamous papilloma, inverted ductal papilloma, and mucoepidermoid carcinoma. Squamous papilloma is composed entirely of squamous epithelium and lacks the endophytic growth pattern and glandular differentiation of sialadenoma papilliferum. Inverted ductal papilloma in contrast to the sialadenoma papilliferum, lacks the glandular complexity, and is a well-circumscribed tumour with blunted, pushing non-infiltrative margins. The invasive pattern and variable mixture of epidermoid, intermediate, mucous, and clear cells found in mucoepidermoid carcinoma set it apart from sialadenoma papilliferum.

Prognosis and predictive factors
The recurrence rate for sialadenoma papilliferum is in the 10-15% range based on 20 reported cases with adequate follow-up. Therefore, it is characterized by a higher risk of recurrence than the other types of ductal papillomas of the salivary gland. Complete surgical excision is the treatment of choice.

Fig. 5.72 Sialadenoma papilliferum. Surface growth is exophytic and papillary to verrucous in nature with clusters of underlying minor salivary gland tissue deep to the surface.

Fig. 5.73 Sialadenoma papilliferum. A Ductal ectasia of varying caliber with lining cells forming short luminal projections or nodular thickenings. B Ductal structures are lined by cuboidal cells with large, uniform and centrally placed nuclei as well as a tall columnar cell population.

272 Tumours of the salivary glands
Definition
Cystadenoma is a rare benign epithelial tumour characterized by predominantly multicystic growth in which the epithelium demonstrates adenomatous proliferation. The epithelial lining is frequently papillary and rarely mucinous.

ICD-O code 8440/0

Synonyms
Monomorphic adenoma, cystic duct adenoma (2301), Warthin tumour without lymphoid stroma (668), intraductal papillary hyperplasia (401), oncocytic cystadenoma.

Epidemiology
The frequency of cystadenoma is between 4.2-4.7% of benign tumours (668,2711). There is a female predominance and the average age of patients with cystadenoma is about 57 years (range 12-89).

Localization
About 45% of all cases of cystadenoma arise in the parotid; the majority of tumours are located in minor salivary glands, particularly in the lips and buccal mucosa (668,2711).

Clinical features
Cystadenomas of the major glands typically present as slowly enlarging painless masses. In oral mucosa, these tumours produce smooth-surfaced nodules that resemble mucoceles.

Macroscopy
Cut section reveals multiple small cystic spaces or a single large cyst surrounded by lobules of salivary gland or by connective tissue.

Histopathology
Cystadenomas are often well circumscribed and surrounded by complete or incomplete fibrous capsules. The tumours are composed of cystic spaces, the number and size of which is variable. Twenty percent of cystadenomas are unilocular (2711). Most cases are multilocular with individual cystic spaces separated by limited amounts of intervening stroma. The lumens often contain eosinophilic material with scattered epithelial, inflammatory or foamy cells. Rarely, psammoma bodies or crystalloids have been described within the luminal secretion (2389). The lining epithelium of these cystic structures is mostly columnar and cuboidal. Oncocytic, mucous, epidermoid and apocrine cells are sometimes present focally or may even predominate. An oncocytic variant of cystadenoma is composed predominantly of oncocytes in unilayered or bilayered papillary structures thus resembling the epithelium of Warthin tumour without lymphoid stroma. Cystadenomas often show a mixture of cell types in the epithelial lining. An unusual case of oncocytic cystadenoma with apocrine, mucinous, sebaceous and signet ring cell appearance has been described (1715). Squamous epithelium may be present focally but rarely predominates. Cystadenomas of the salivary glands are usually devoid of foci of solid growth, cytologic atypia, fibrosis and apposed lymphoid tissue (790). Cystadenoma occurs in two major variants, as papillary and mucinous cystadenoma. Papillary cystadenoma is composed of large multilocular or unilocular cysts with multiple papillary projections. The lining epithelium is, in some cases, composed of oncocytic cells. Mucinous cystadenoma is composed of multiple cysts lined by mucous tall columnar epithelium with small basally situated nuclei and eosinophilic to clear cytoplasm. The lumens contain PAS and mucicarmine positive abundant mucus. The columnar epithelial lining has a uniform thickness with limited papillary growth.

Prognosis and predictive factors
Cystadenomas are benign tumours, and conservative but complete surgical removal is recommended. The tumours are unlikely to recur but rare cases of mucinous cystadenoma with malignant transformation have been described (1716).

Fig. 5.74 Cystadenoma, composed of cystic spaces, the number and size of which is variable.
Fig. 5.75 Cystadenoma. A The lumen contains eosinophilic material. Cystic spaces are lined by columnar epithelium with focal apocrine metaplasia. B Scattered foamy cells within the secretion. C Oncocytic variant of cystadenoma is composed of prevailing oncocyes present in unilayered or bilayered papillary structures thus resembling Warthin tumour without lymphoid stroma. D Oncocytic cystadenoma with apocrine, mucinous, sebaceous and signet ring cell appearance.

Fig. 5.76 Cystadenoma. A Cystic spaces are lined by columnar epithelium with multiple papillary projections. B Prominent intracystic papillary growth pattern.
Excluding haematopoietic neoplasms, pure mesenchymal tumours account for 1.9-4.7% of salivary gland tumours [347, 669,678,2301] with benign soft tissue lesions being more common than sarcomas. The ratio of benign to malignant mesenchymal tumours varies from series to series, ranging from 18.1-2.4:1 [669,2301]. Over 85% of soft tissue tumours arise in the parotid gland, over 10% involve the submandibular gland and, rarely, a tumour arises in the sublingual gland. Vascular tumours are the most common benign mesenchymal neoplasm, accounting for almost 40% of the benign tumours [669,2301]. Seventy-five to 80% of the vascular neoplasms are haemangiomas, typically the juvenile or cellular variant, with the greatest incidence occurring in the first decade of life [430]. Most other vascular tumours are lymphangiomas. Other major salivary gland benign soft tissue neoplasms include neural tumours, most frequently neurofibroma or schwannoma [669] and fibroblast/myofibroblastic tumours, most frequently nodular fasciitis, and fibromatoses with an infrequent myofibromatosis, fibroma, haemangiopericytoma, solitary fibrous tumour [953,2248] or inflammatory pseudotumour (inflammatory myofibroblastic tumour [775]) [2794] being reported. Lipomas, including the pleomorphic variety [934] and miscellaneous other tumours including granular cell tumour [2222], angiomyoma, glomangioma, myxoma, fibrous histiocytoma, giant cell tumour, osteochondroma and rarely a metastatic sarcoma may be also seen. Several cases of lipomas entrapping salivary glandular tissue have been recently described and termed sialolipomas [810,1824], including a congenital case [1129]. Salivary gland sarcomas arise in an older population than their benign soft tissue counterparts. They are rare tumours, accounting for only 0.3% of salivary gland neoplasms [347]. Almost any type of sarcoma can arise primarily in the salivary gland [87,669,1583]. In the largest published series, haemangiopericytoma, malignant schwannoma, fibrosarcoma and malignant fibrous histiocytoma were the most common neoplasms, accounting for 16, 15, 14, and 11% of reported sarcomas, respectively [87]. These are aggressive neoplasms: 40-64% of patients develop recurrences, 38-64% develop metastases (usually haematogenous), and the mortality rate ranges from 36-64% with death occurring frequently within 3 years of diagnosis [87,1583]. The most successful treatments are wide surgical excision or surgery combined with radiation. For more specific information about each type of tumour, refer to the other texts [775,2745].

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Armed Forces Institute of Pathology Registry (87)</th>
<th>MD Anderson Medical Center (1583)</th>
<th>University of Hamburg Registry (2301)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemangiopericytoma</td>
<td>14</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Malignant schwannoma</td>
<td>13</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>12</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Malignant fibrous histiocytoma</td>
<td>9</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>7</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>3</td>
<td>3**</td>
<td></td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alveolar soft part sarcoma</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epithelioid sarcoma</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extraskeletal chondrosarcoma</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant haemangioendothelioma</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Sarcoma, poorly differentiated</td>
<td></td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>**TOTAL</td>
<td>**85</td>
<td><strong>14</strong></td>
<td><strong>9</strong></td>
</tr>
</tbody>
</table>

*Excluding lymphomas

**Arose in intraparotid lymph nodes

![Fig. 5.77 Sialolipoma. A A well-circumscribed, encapsulated, yellow mass of the parotid gland. B Low-power view of a palatal tumour showing a mass clearly demarcated from the adjacent salivary gland tissue. The tumour consists of salivary gland tissue and adipose element, in approximately equal amounts in this case.](image-url)
Haemangioma

Definition
This is characterized by a proliferation of endothelial cells and pericytes.

ICD-O code 9120/0

Synonyms
Benign or infantile haemangioendothelioma, infantile haemangioma, cellular haemangioma, immature capillary haemangioma, juvenile haemangioma

Epidemiology
Haemangiomas of the salivary glands account for approximately 0.4% of salivary tumours (668). Lesions may present at any age but two thirds of cases are diagnosed in the first two decades (668,2301). They are twice as common in females as males.

Localization
The haemangioma occurs almost exclusively in the parotid gland.

Clinical features
Lesions are asymptomatic soft swellings. They usually appear during the first 6 months of life and grow slowly. Most eventually involute by the age of 5-6 years (914,1413). A bluish colour may be visible through skin but the overlying skin is not usually involved. Lesions are usually limited to the parotid gland but some are part of an angiomatosis that extends to involve the parapharyngeal space, infratemporal fossa or base of skull (1625). Diagnosis may be aided by imaging (312,624).

Macroscopy
Lesions cause diffuse enlargement of the gland.

Histopathology
The lesion is composed of varying sized and shaped vascular spaces. The juvenile variant comprises small round densely packed endothelial cells and pericytes clustered within sheets that extend diffusely through the gland but divided into lobules by the gland septa. Lesional cells replace acinar cells, enlarging the lobules but leaving ducts scattered through the lesion. Mitoses are sparse or moderate in the juvenile form. In the early stages no vascular lumens are present but these develop with time to be the dominant feature (668,2301,2745). Mature lesions are typical capillary haemangiomas with thin endothelial cell linings and no atypia. Thrombi and phleboliths may be present and foci of normal salivary tissue may persist in the mature lesion (668,914,1814,1817,2301).

Prognosis and predictive factors
Neonatal and infantile lesions grow rapidly initially but the majority involute before age 7 years and often much earlier (668,874,1413,1625,2301,2626,2632,2745,2790). No treatment may be required and any intervention should be delayed. Steroids reduce growth and are the main treatment; pressure therapy (2626) or embolisation (265) may be considered if large. Occasional cases show progressive growth (2185).

Fig. 5.78 Juvenile haemangioma. A Immature appearance with little lumen formation from a patient under 1 year in age. B More mature area with well-organised vessels. C Highly vascularized haemangioma.
Haematolymphoid tumours

Hodgkin lymphoma

Involvement of the salivary glands by Hodgkin lymphoma is very rare. Combining data from four large series on primary lymphomas of the salivary glands, Hodgkin lymphoma only accounts for 4% of all cases \( \{473,893,1164,2267\} \). Both classical Hodgkin lymphoma and nodular lymphocyte predominant Hodgkin lymphoma have been reported \( \{101,391,893\} \), and all have involved the parotid gland only. Some of these tumours have originated from intraparotid lymph nodes, and thus are strictly-speaking not genuine primary extranodal lymphomas of the salivary glands. Rarely, Hodgkin lymphoma can arise within a Warthin tumour \( \{1702\} \). Please refer to the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues \( \{1197\} \).

Non-Hodgkin lymphoma

Overview
Primary salivary gland non-Hodgkin lymphomas (NHL) are uncommon, accounting for only 5% of all primary extranodal NHL \( \{809\} \) and 2% of all salivary gland tumours \( \{893\} \). For a case to be considered as primary in the salivary gland, the bulk of disease should occur in this site, and the glandular parenchyma should be involved. A major problem in definition is caused by the normal presence of intraglandular lymph nodes in the parotid gland. Strictly speaking, cases of NHL limited to these lymph nodes without glandular parenchymal involvement should be considered as nodal NHL instead. However, the distinction is not always easy because cases with extensive parenchymal and nodal involvement can still have originated from intraglandular lymph nodes.

The most commonly affected gland is the parotid gland (75% of all cases), followed by the submandibular gland (20%) \( \{473,893,1164\} \). Most patients are in the sixth decade, and multiple glands (especially bilateral) are involved in about 10% of cases \( \{473\} \). The patients present with a palpable mass, and pain and tenderness are observed in a minority of cases.

Histologic types of NHL affecting the salivary glands
Most NHL occurring in salivary glands are B-cell lymphomas. In some older series, follicular lymphoma is the most common, accounting for about half of all cases \( \{473,893,1164\} \). However, many of these tumours are probably nodal lymphomas arising from intraglandular lymph nodes with subsequent infiltration of the glandular parenchyma, or represent extranodal marginal zone B-cell lymphoma of MALT type with prominent follicular colonization. In follicular lymphoma, lymphoepithelial lesions may be present in occasional cases \( \{1017\} \). Extranodal marginal zone B-cell lymphoma of MALT type is probably the most common type of lymphoma truly of salivary gland origin. It is frequently associated with Sjögren syndrome. Mantle cell lymphoma can also present as salivary gland involvement, but staging often reveals additional sites of disease. It is important not to misdiagnose mantle cell lymphoma for extranodal marginal zone B-cell lymphoma, because of the worse prognosis of the former.

Diffuse large B-cell lymphoma accounts for about 15% of all NHL of the salivary glands \( \{473,893,1164\} \). The tumour is infiltrative, with destruction of the salivary gland parenchyma and interstitial infiltration among residual salivary acini. The tumour comprises large lymphoid cells that may resemble centroblasts or immunoblasts, and express pan-B markers. Some cases represent transforma-
tion from an underlying extranodal marginal zone B-cell lymphoma of MALT type (2103). Anaplastic large cell lymphoma (ALCL), peripheral T-cell lymphoma unspecified, and extranodal NK/T cell lymphoma of nasal-type can also rarely affect the salivary glands (373,1081,1203). Please refer to the section of ‘non-Hodgkin lymphoma’ in ‘Tumours of the nasal cavity and paranasal sinuses’ for details.

Rare cases of NHL can arise in the lymphoid stroma of Warthin tumour, with follicular lymphoma being the most frequent type (307,1694). The lymphoma discovered in the Warthin tumour may be the presenting feature of more generalized disease.

Differential diagnosis

Some benign conditions can mimic NHL histologically. Lymphoepithelial sialadenitis (LESA), a condition associated with Sjögren syndrome, is a precursor lesion for extranodal marginal zone B-cell lymphoma of MALT type, and will be discussed in details in the next section. Kimura disease is a benign lesion of unknown etiology, commonly affecting the soft tissues in the head and neck region of young adults. It shows a predilection for Asian populations. Involvement of the major salivary glands is frequent (369,1385,1497,2581). It is characterized by reactive lymphoid follicles, vascularization of germinal centres, heavy eosinophilic infiltration, proliferation of high endothelial venules and prominent sclerosis. See Chapter 7 for details. Chronic sclerosing sialadenitis (Küttner tumour) is a chronic inflammatory disorder affecting the submandibular gland (366). It can be bilateral. Since the gland is enlarged and hard, it usually imparts a clinical suspicion for malignancy. Histologically, there is a heavy lymphoplasmacytic infiltrate, accompanied by reactive lymphoid follicles, atrophy of salivary acini, periductal fibrosis and interlobular sclerosis. In the early phases, the striking lymphoid infiltrate can lead to a misdiagnosis of lymphoma. In contrast to lymphoma, the follicles are obviously reactive, the interfollicular lymphoid cells lack atypia, a permissive infiltrative pattern is lacking, there is a mixture of B and T cells, and the B cells are polymorphic.

Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy) can also affect the major salivary glands (791,2760).

Prognosis and predictive factors

The prognosis of salivary gland lymphomas depends on the histologic type and clinical stage. T cell lymphomas and extranodal NK/T cell lymphomas are generally associated with a poorer outcome. A study reports that cases of probable nodal origin have a worse prognosis compared to those of probable extranodal-parenchymal origin (1193).

Extranodal marginal zone B-cell lymphoma (EMZBCL)

Definition

A low-grade B-cell lymphoma arising in mucosa-associated lymphoid tissue (MALT).

ICD-O code 9699/3

Epidemiology

Primary EMZBCL of the salivary gland is an uncommon neoplasm that usually develops in the setting of lymphoepithelial sialadenitis (LESA) in patients with Sjögren syndrome (59,98,710,2210,2266,2915). It is characterized by reactive lymphoid follicles, vascularization of germinal centres, heavy eosinophilic infiltration, proliferation of high endothelial venules and prominent sclerosis. See Chapter 7 for details.

Chronic sclerosing sialadenitis (Küttner tumour) is a chronic inflammatory disorder affecting the submandibular gland (366). It can be bilateral. Since the gland is enlarged and hard, it usually imparts a clinical suspicion for malignancy. Histologically, there is a heavy lymphoplasmacytic infiltrate, accompanied by reactive lymphoid follicles, atrophy of salivary acini, periductal fibrosis and interlobular sclerosis. In the early phases, the striking lymphoid infiltrate can lead to a misdiagnosis of lymphoma. In contrast to lymphoma, the follicles are obviously reactive, the interfollicular lymphoid cells lack atypia, a permissive infiltrative pattern is lacking, there is a mixture of B and T cells, and the B cells are polymorphic.

Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy) can also affect the major salivary glands (791,2760).

Prognosis and predictive factors

The prognosis of salivary gland lymphomas depends on the histologic type and clinical stage. T cell lymphomas and extranodal NK/T cell lymphomas are generally associated with a poorer outcome. A study reports that cases of probable nodal origin have a worse prognosis compared to those of probable extranodal-parenchymal origin (1193).

Extranodal marginal zone B-cell lymphoma (EMZBCL)

Definition

A low-grade B-cell lymphoma arising in mucosa-associated lymphoid tissue (MALT).

ICD-O code 9699/3

Epidemiology

Primary EMZBCL of the salivary gland is an uncommon neoplasm that usually develops in the setting of lymphoepithelial sialadenitis (LESA) in patients with Sjögren syndrome (59,98,710,2210,2266,2915). It is characterized by reactive lymphoid follicles, vascularization of germinal centres, heavy eosinophilic infiltration, proliferation of high endothelial venules and prominent sclerosis. See Chapter 7 for details.

Chronic sclerosing sialadenitis (Küttner tumour) is a chronic inflammatory disorder affecting the submandibular gland (366). It can be bilateral. Since the gland is enlarged and hard, it usually imparts a clinical suspicion for malignancy. Histologically, there is a heavy lymphoplasmacytic infiltrate, accompanied by reactive lymphoid follicles, atrophy of salivary acini, periductal fibrosis and interlobular sclerosis. In the early phases, the striking lymphoid infiltrate can lead to a misdiagnosis of lymphoma. In contrast to lymphoma, the follicles are obviously reactive, the interfollicular lymphoid cells lack atypia, a permissive infiltrative pattern is lacking, there is a mixture of B and T cells, and the B cells are polymorphic.

Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy) can also affect the major salivary glands (791,2760).

Prognosis and predictive factors

The prognosis of salivary gland lymphomas depends on the histologic type and clinical stage. T cell lymphomas and extranodal NK/T cell lymphomas are generally associated with a poorer outcome. A study reports that cases of probable nodal origin have a worse prognosis compared to those of probable extranodal-parenchymal origin (1193).
setting of LESA in association with Sjögren syndrome, it is postulated that this low-grade B cell lymphoma develops subsequent to the accumulation of mucosa-associated lymphoid tissue (MALT) that is acquired as a result of the autoimmune process.

**Localization**

EMZBCL usually presents as a persistent unilateral or bilateral mass in the parotid gland region, although any major or minor salivary gland may be involved (1181). The regional lymph nodes may also be enlarged due to involvement by the tumour.

**Clinical features**

EMZBCL may occur in the salivary gland as a manifestation of either primary or disseminated disease (473,813). Presenting signs include persistent enlargement of the involved salivary gland(s), sometimes in association with regional lymphadenopathy or monoclonal gammopathy (56). The patient may also show signs of other autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus or Hashimoto thyroiditis (1181). Occasionally, EMZBCL may present in a cervical lymph node with subsequent development in the salivary gland. There is a variable period of time between the documented occurrence of LESA and the development of malignant lymphoma, which has been reported to range from 6 months to 29 years (630,710,2266). When EMZBCL of the parotid gland develops, there is a tendency for it to remain localized for long periods of time, as is the case with EMZBCL at other anatomic sites, including the stomach (468).

**Macroscopy**

The cut surface of EMZBCL of salivary gland is yellowish-tan in colour and has a “fish-flesh” appearance. Microcysts may be present.

**Tumour spread and staging**

The majority of patients with EMZBCL of salivary gland present with Stage IE (extranodal) or IIE disease. Dissemination most often occurs to cervical lymph nodes and other mucosal sites such as lung, conjunctiva and stomach (710,1003).

---

Fig. 5.81 Extranodal marginal-zone B-cell lymphoma (EMZBCL). **A** Lymphoepithelial lesion (left) highlighted by antibody to cytokeratin (right). **B** EMZBCL. Immunoglobulin light chain restriction for kappa (left) compared to lambda (right). **C** Follicular lymphoma of salivary gland with monotonous, neoplastic follicles extending into periglandular fat (left) and demonstrating reactivity for bcl-2 (right).
Tumours of the salivary glands

**Histopathology**
EMZBCL of the parotid gland occurs in a background of lymphoepithelial sialadenitis (LESA) in almost all cases. The histologic features include a vaguely nodular to diffuse heterogeneous B-cell infiltrate that totally or subtotally effaces the normal glandular architecture. It is variably comprised of atypical small lymphocytes, centrocyte-like (cleaved) cells, monocytoïd B-cells, immunoblasts, lymphoplasmacytic cells and plasma cells. Plasma cell differentiation may be striking, causing confusion with a plasmacytoma. Intranuclear inclusions (Dutch bodies) may be seen in the plasma or lymphoplasmacytic cells. Reactive germinal centres, often colonized by neoplastic B cells, are often present (1182). Lymphoepithelial lesions, representing infiltration of the ductal and epithelial structures by neoplastic B cells, are seen in both LESA and EMZBCL. Ductal dilatation occasionally imparts a multicystic appearance to the gland. An important early change that occurs in EMZBCL of parotid gland, developing in the setting of LESA, is the formation of ”halos”, comprised of monocytoïd and centrocyte-like B cells surrounding epithelial islands (lymphoepithelial lesion) (1162). These cells may coalesce into broad, interconnecting sheets. Clusters of epithelioid histiocytes and prominent fibrosis may also be noted. There may be single or multifocal foci of large cell transformation adjacent to the low-grade component.

**Immunoprofile**
The B cell immunophenotype is confirmed by immunoreactivity for CD20 or CD79a. The lymphocytes and monocytoïd B cells express surface immunoglobulin. The neoplastic B cells are negative for CD5, CD10, CD23 and bcl-1 (Cyclin D1). Bcl-2 reactivity in the neoplastic, colonizing B cells (but not in the residual, reactive germinal centre cells) is also characteristic. An antibody to cytokeratin may be useful to highlight the epithelial remnants in the lymphoepithelial lesions.

**Differential diagnosis**
The distinction between EMZBCL and LESA may be extremely difficult. Although histologic evaluation remains the gold standard for diagnosis, immunohistochemical, flow cytometric or molecular genetic analyses may be required. In both reactive follicular hyperplasia and EMZBCL, benign germinal centres are present but in the latter entity, the follicles may be colonized by neoplastic B-cells that express bcl-2. A dense diffuse B cell infiltrate, intranuclear inclusions (Dutch bodies) and cytologic atypia are characteristically seen in EMZBCL. Lymphoepithelial lesions may be seen in both LESA and EMZBCL. The demonstration of light chain restriction by immunohistochemistry or flow cytometry supports the monoclonality of the B cell lymphoma. Extranodal marginal zone lymphoma with prominent nodularity may simulate a follicular lymphoma (FL). It is necessary, therefore, to distinguish the reactive, colonized germinal centres in EMZBCL from the neoplastic germinal centres in FL. The majority of cases of FL will show immunoreactivity for bcl-2 and will express the germinal centre cell markers CD10 and bcl-6.

**Somatic genetics**
There are clonal rearrangements of the immunoglobulin genes [2,104,608,630,2103,2524]. The significance of this finding, however, is somewhat unclear and controversial since gene rearrangements have also been found in histologically benign cases of LESA [105,770,2103] and in the salivary gland lesions of Sjögren syndrome patients who subsequently developed overt lymphoma [1238]. The cell of origin of EMZBCL lymphoma has not been definitively identified and has been postulated to be of post germinal centre origin. In some cases, however, the variable regions of the immunoglobulin genes have been shown to undergo somatic hypermutation, suggesting that this tumour may arise from germinal centre B cells [104]. Although no specific oncogene has been described in association with MALT lymphoma, numerical chromosomal abnormalities, especially Trisomy 3 [293,2823,2824], and the chromosomal translocation, t (11;18) (q21;q21) [1961] have been reported in EMZBCL in various anatomic sites.

**Prognosis and predictive factors**
The prognosis of salivary gland EMZBCL lymphoma is usually very favourable. Tumours that are localized (Stage IE) at the time of presentation and demonstrate purely low-grade histology have an excellent prognosis. With lymph node involvement (Stage IIE), the prognosis is usually similar to primary nodal low-grade B cell lymphomas. Although EMZBCL of salivary gland may show histologic transformation to a higher grade, similar to what has been reported in the stomach, the clinical significance of this finding remains unclear. There is no conclusive evidence that treatment of EMZBCL prevents transformation to a higher grade. With or without treatment, EMZBCL of the salivary gland is usually an indolent neoplasm that does not result in significant morbidity or mortality. There are reports, however, of patients with EMZBCL associated with LESA subsequently developing extensive extra salivary gland lymphoma or nodal large B-cell lymphoma.

**Salivary gland extramedullary plasmacytoma**
Please refer to Chapter 1 for details.
Secondary tumours

Definition
A metastatic tumour involving salivary glands that originates in a distant site.

Epidemiology
Secondary tumours comprise about 5% of all malignant tumours of salivary glands (669,2293,2300), but this incidence is considerably higher in some countries (199). The peak incidence is in the 7-8th decade. Almost 70% of cases occur in males. The majority of cases are squamous cell carcinoma and melanoma is second in frequency.

Localization
The large majority of metastases are located in the parotid, while fewer are seen in the submandibular gland. Metastases occur within the interstitial tissue and the intra-/periglandular lymph nodes with a slight predominance of extranodal infiltrates (2300).

Clinical features
Eighty percent of secondary tumours of the parotid are metastases from head and neck neoplasms. On the other hand, 85% of metastatic tumours in the submandibular glands are from distant sites (899). Primary sites frequently are the upper and middle parts of the facial region (including skin, mucous membranes, deep soft tissues as well as eyes and ears) (443,692,1917,1987). A further 10% originate from distant tumours among which lung carcinoma (especially the small cell carcinoma type), kidney and breast carcinomas are the most common (669,806,1585,2219,2293,2300). However, almost 10% of the secondary tumours remain undefined as to their origin.

Histopathology
Generally, metastases retain to some extent the histological pattern and cytological characteristics of the respective primary tumour.

Fig. 5.82 Small cell carcinoma diffusely infiltrating the salivary gland tissue. Tumour cells are marked by immunoreactivity to synaptophysin (right).

Fig. 5.83 Metastatic renal cell carcinoma in the parotid gland. Low magnification.