

The Pathology and Surgery of the Salivary Glands

R. A. Cawson, M. J. Gleeson, J. W. Eveson

Chapter 7: Carcinoma of salivary glands

Introduction

In terms of registration in England and Wales, cancers of salivary glands (ICD 142) form a little under 0.3% of all cancers. They were also estimated to form 0.3% of all malignant tumours in Sweden.

Internationally, there appear to be wider variations, some of which may depend on criteria for defining malignancy. In Norway, for example, the incidence appears to be half that of other European countries. Nevertheless, this lower recorded morbidity is associated with a considerably higher relative mortality. There are also other differences even within Scandinavia; the incidence and mortality ratio in Denmark is similar to that in the rest of Europe while in Sweden they are intermediate between those of Norway and Denmark. The incidence is even lower in Japan, particularly in women in whom the incidence is reported to be only 0.3 per 100 000 as compared with 1.4 per 100 000 in England and Wales.

It should perhaps be noted that though it is reasonable to assume that cancers of salivary glands, as registered in England and Wales, are carcinomas, this may not be entirely true. Not merely are a few malignant non-epithelial tumours included, but it has certainly happened in the past if not now, that in some centres, pleomorphic adenomas have been included because of obsolete ideas that these tumours were 'semi-malignant'. We have even known cases where Warthin's tumours (adenolymphomas) have been registered as malignant lymphomas. However, such mistakes are probably on a small scale and do not bias the incidence data to a significant degree.

Table 7.1 Percentages of benign and malignant, epithelial salivary gland tumours in different series

Sources	Adenomas	Carcinomas	No. of cases
Thackray & Lucas (1974)	83.4%	15.6%	651 (parotid glands only)
Seifert <i>et al</i> (1986)	74.3%	25.7%	2579
British Salivary	78.9%	23.1%	3254

Gland Tumour Panel (1991 unpublished data).

The relative frequency of malignant compared with benign salivary gland tumours in different series is shown in Table 7.1 and the site to site variation in Table 7.2. Our data suggest that 23% of salivary gland tumours are malignant whilst in Germany, the figure is almost 26% (Seifert *et al*, 1986). However, most series agree that the lowest *relative* frequency of malignant salivary gland tumours compared with benign is in the parotid (15%) and the highest in the sublingual glands (86%), though the overall numbers there were minute. Of the moderate numbers of salivary gland tumours in the minor glands, 46% are likely to

be malignant.

Classification

The main classifications have been shown in Chapter 6. There it will be noted that mucoepidermoid and acinic cell tumours were placed in a separate category in the first (1972) WHO classification, from carcinomas. However, they are not (justifiably) termed mucoepidermoid and acinic cell carcinomas and will be discussed with other carcinomas here.

Table 7.3 Site distribution of different types of 3195 epithelial salivary gland tumours (BSGTP) material

Tumour	Parotid	Submandibular	Sublingual	Minor glands
All types	78.0%	11.0%	0.005%	11.0%
<i>Adenomas</i>				
Pleomorphic adenoma	61.7%	61.0%	11.1%	42.5%
Warthin's tumour	14.2%	1.3%	0.0%	0.0%
Oncocytoma	0.8%	0.3%	0.0%	0.0%
Other monomorphic adenomas	7.1%	1.9%	11.1%	10.3%
<i>Carcinomas</i>				
Mucoepidermoid	1.9%	1.3%	0.0%	8.8%
Acinic cell	2.7%	0.3%	0.0%	1.9%
Adenoid cystic	1.9%	15.2%	22.2%	12.2%
Adenocarcinomas (various)	3.2%	4.8%	11.1%	13.3%
Epidermoid	1.1%	2.2%	0.0%	1.1%
Undifferentiated	1.6%	4.1%	11.1%	1.7%
Carcinoma in pleomorphic adenoma	3.5%	7.6%	33.3%	6.9%

General clinical features

Malignant salivary gland tumours usually grow more rapidly and, in addition to swelling, frequently cause pain at some stage. Typical features, in the later stages particularly, include fixation, ulceration and involvement of regional lymph nodes. In the parotid gland, facial palsy is a highly significant sign and is likely to imply a poor prognosis. In the series of Seifert *et al* (1986), well-differentiated mucoepidermoid and acinic cell carcinomas never caused facial palsy, but it was present in 40-67% of the more malignant tumours and, in particular, in squamous cell, undifferentiated and solid adenoid cystic carcinomas.

In practice, most malignant salivary gland tumours, unless seen at an unusually late stage, cannot be distinguished from benign tumours.

General management considerations

Overall, only a minority of malignant salivary gland tumours betray their nature clinically and are not recognized until after histology has been carried out. Indeed, many salivary gland cancers present as secondary or tertiary referrals following open biopsy, attempts at enucleation or superficial parotidectomy.

There is usually, therefore, preoperative uncertainty about the best method of management for each individual patient, because of the impossibility of predicting behaviour preoperatively and the absence of any guide that a conventional biopsy might provide. Preoperative fine-needle aspiration cytology followed by frozen-section confirmation during operation may therefore be valuable in suggesting a need for more radical procedures which may lead to the decision to sacrifice the facial nerve and carry out neck dissection. However, where facilities are limited, it may not be possible even to obtain a preoperative frozen section. In such circumstances, as conservative an approach as possible, but consistent with the clinical picture, is appropriate. Alternatively, it may be better for all concerned to refer any patients where the clinical presentation arouses suspicion, to a specialist centre. The literature, in fact, suggests that the number of reoperations and complication rates are less in centres which have specialized in, and have the best facilities for salivary gland surgery.

With regard to the preservation of the facial nerve in patients with malignant tumours but normal facial nerve function preoperatively, it is impossible to lay down hard-and-fast rules. On the one hand, sacrifice of the facial nerve may allow more complete resection and the term 'radical resection' may be interpreted to mean obligatory resection of the facial nerve. However, sacrifice of the facial nerve may not improve the ultimate prognosis. In any case, a patient with a highly malignant tumour may have such a short expectation of life that it becomes difficult to decide whether it is justifiable to add to their disabilities in the time remaining to them.

In recent years, the groundswell of surgical opinion appears to be that a functional facial nerve should be preserved unless found to be involved by tumour. In the cases of tumours merely abutting the facial nerve, it is probably justifiable, despite general oncological principles of surgical clearance, to preserve it and rely on postoperative radiotherapy to control microscopic residual disease.

There is also considerable variation in the interpretation of what constitutes a thorough superficial parotidectomy. The need for reoperation or completion surgery has inevitably to be judged in each individual case from the operative description and the tumour type and margins, as indicated by the histological findings.

Another consideration affecting management is that of the patient's age. Malignant tumours more frequently affect elderly persons and there is often a natural reluctance to operate on someone > 80 years. This reluctance may be justified after clinical investigations and fine-needle aspiration biopsy have shown that the tumour is benign or of low-grade malignancy. In such cases, the tumour may progress so slowly that the patient's expectation and quality of life may be better without any operative interference. By contrast, some patients may not be able to tolerate the idea of having to live with a tumour and their request for surgery should be respected. If this is agreed and the patient is fit for the operation,

surgery should be definitive, not palliative.

Despite such considerations, the behaviour of tumours in some individuals can be so unpredictable that an overenthusiastic surgeon can soon regret having performed a mutilating operation if the patient lives only a few weeks in acute discomfort.

The role of radiotherapy is discussed in relation to individual tumour types below. However, there is no firm evidence that radiotherapy is satisfactory as primary treatment of salivary gland tumours, apart from lymphomas, and for many other types of tumour there is little hard evidence of its value as adjunctive treatment. High success rates have been claimed for neutron beam (cyclotron) therapy, but the numbers of individual types of salivary gland tumours that have been treated have been insignificant and the period of follow-up so short that results are of no statistical value. There is also considerable concern about the severity of the complications and insufficient evidence to indicate that neutron beam therapy offers a better risk:benefit ratio than conventional forms of treatment.

In the end, therefore, we can do no more than suggest guidelines, which are in no way dogmatic, for the management of salivary gland tumours based on our own experience and on a broad survey of the world literature.

Histogenesis

All carcinomas arising from salivary glands must broadly be regarded as adenocarcinomas. However, few of them resemble typical adenocarcinomas, like those originating from the gastrointestinal tract, and those categorized as 'adenocarcinoma, not otherwise specified' are rare, as noted by Batsakis *et al* (1992). Their number has diminished greatly as other entities formerly categorized as adenocarcinomas have been recognized. These workers firmly tie the origin and behaviour of salivary gland carcinomas to different parts of the duct system. Thus they believe that duct carcinomas, papillary and non-papillary adenocarcinomas, high-grade mucoepidermoid carcinomas, squamous carcinomas, oncocytic carcinomas and high-grade carcinoma ex-pleomorphic adenoma are of excretory duct origin. Warthin's tumour, oncocytoma and oncocytic carcinoma, they suggest, arise from striated ducts. The remainder, pleomorphic adenomas, monomorphic adenomas (*sic*), acinic cell carcinomas, adenoid cystic carcinomas, epithelial-myoepithelial carcinomas, terminal duct (polymorphous low grade) adenocarcinomas, low-grade carcinomas ex-pleomorphic adenoma and carcinomas ex monomorphic adenomas, they suggest, arise from intercalated ducts. It is not clear why these workers suggest that oncocytic carcinomas arise from either excretory or striated ducts and hence may fall into the high-grade or benign categories. In any case, little is known of the behaviour of these rare tumours.

Mucoepidermoid Carcinoma

Mucoepidermoid carcinomas form 4.8% of all salivary gland tumours in the series of Seifert *et al* (1986) but only 2.8% in our material. This represents 19.5% and 12%, respectively, of malignant epithelial tumours in these two series. Moreover, the relative frequency of mucoepidermoid carcinomas appears to be considerably greater in the USA and in the series by Foote and Frazell (1954), for example, they formed 11% of all salivary gland tumours and 33% of the malignant tumours. Mucoepidermoid carcinomas have a high relative

frequency in the minor glands where they form between 10 and 15% of all tumours there. The sex incidence is almost equal and the peak age incidence is in the fifth decade.

Mucoepidermoid carcinoma is one of the most common types of post-irradiation salivary gland tumours and in a review of previous reports (including those relating to the survivors of the atomic bombing of Hiroshima and Nagasaki), Watkin and Hobsley (1986) noted that of 70 malignant salivary gland tumours that resulted, 33 (47%) were mucoepidermoid carcinomas which formed the single largest group. Mucoepidermoid carcinomas are also the most frequent type of intraosseous salivary gland tumours as discussed in Chapter 8. Mucoepidermoid carcinoma has also been, apparently uniquely, reported as a second malignant neoplasm by Loy *et al* (1989), in two children who had had multidrug chemotherapy and cranial irradiation for leukaemia.

Clinical features

Well-differentiated mucoepidermoid carcinomas are likely only to give rise to painless swelling and cannot be distinguished from adenomas. As mentioned earlier, they did not cause facial palsy in the series of either Foote and Frazell (1953) or of Seifert *et al* (1986), but the latter record that 20% of high-grade tumours caused facial palsy and other signs or symptoms typical of carcinomas.

Macroscopic and microscopic features

The gross appearances are likely to vary with the grade by in general, mucoepidermoid carcinomas form irregular, poorly circumscribed masses. Unlike most other salivary gland tumours, cyst formation is common, usually as several small cysts, but occasionally as a single large cyst. The cyst contents are typically clear or mucoid unless there has been bleeding.

The distinctive microscopic feature of mucoepidermoid carcinomas is, as the name implies, the juxtaposition of both mucous and epidermoid cells and usually, multiple microcysts (Fig. 7.1).

The mucous cells are large and pale, with a cytoplasm having a frosted-glass appearance. They have a well-defined cell membrane and vary in shape from rounded polygonal to columnar, and form small solid masses or line cysts (Fig. 7.2). Their numbers vary widely but in predominantly solid tumours, are heavily outnumbered by epidermoid cells. Their mucin content is confirmed by using such stains as mucicarmine, which are useful when mucous cells, which contain only minute droplets of mucin, are not otherwise recognizable (Fig. 7.3). This particularly applies to solid or poorly differentiated tumours.

Mucin also fills the cysts, which may burst to release mucin into the surrounding tissues. The released mucin excites an inflammatory and sometimes, a granulomatous reaction. These cysts vary in size from microscopic to gross and occasionally the tumour forms only a mural thickening in a single large cyst.

The epidermoid cells can usually be seen to have intercellular bridges and are mostly in solid masses (Fig. 7.4). Occasionally there may also be keratin and, rarely, cell nest formation. However, Batsakis and Luna (1990) consider that these latter features, if prominent, cast doubt on the diagnosis as they consider that the epidermoid cells are not true squamous cells.

Other cells sometimes present, usually in small numbers, are small, dark, intermediate cells which can form a basal layer to the cyst-lining epithelium. Oncocyte-like cells may also be seen (Fig. 7.5) and these may undergo change into clear cells (Figs 7.6 and 7.7). Clear cells may then form a major part of the tumour, as discussed later with other clear-cell tumours. Aufdemorte *et al* (1985) have also noted melanin pigmentation in a mucoepidermoid carcinomas of a minor gland but this appears to be an exceptionally unusual finding.

Poorly differentiated mucoepidermoid carcinomas, as mentioned earlier, are frequently solid and may appear to be purely epidermoid unless small droplets of mucin can be demonstrated in some of the cells by appropriate stains (Fig. 7.8). Also, gross nuclear pleomorphism, with giant hyperchromatic nuclei (Fig. 7.9), is common and mitotic activity is more frequent (Fig. 7.10). These tumour cells form broad strands, clearly demarcated from the fibrous stroma in which inflammatory infiltrate is usually scanty. Perineural (Fig. 7.11) or intravascular invasion may be seen and suggests a poor prognosis. High-grade tumours may also show areas of necrosis (Fig. 7.12); this was present in 13% of 89 tumours analyzed by us, and all either recurred or caused the death of the patient.

An intermediate grade can sometimes be distinguished and is characterized by predominance of epidermoid or intermediate cells, a solid pattern of growth with relatively little mucin production, and slight-to-moderate pleomorphism with few mitoses.

The stroma consists of fibrous connective tissue and lack myxochondroid differentiation. Focal inflammatory infiltrates, or foreign-body reactions round cholesterol clefts or extravasated mucus may be seen (Fig. 7.13). Rarely, fibrosis and hyalinization are so extensive that the tumour becomes sclerotic (Fig. 7.14). Chan and Saw (1987), in their report of a sclerotic mucoepidermoid carcinoma, were unable to find any earlier recorded examples. However, Batsakis and Luna (1990) mention stromal desmoplasia as a feature of high-grade mucoepidermoid carcinomas.

Behaviour, grading and prognosis

Spread through the gland is more diffuse than that of pleomorphic adenomas and may be aided, as Thackray and Lucas (1974) have suggested, by extravasation of mucus carrying tumour cells with it (Fig. 7.15). As with other salivary gland tumours, enucleation or inadequate local resection is likely to lead to recurrence and should not be considered as appropriate treatment.

Several attempts have been made to correlate grades of malignancy with behaviour. In general, low-grade (cytologically benign) mucoepidermoid carcinomas, with abundant mucous cells and mucin production, are less aggressive (as suggested by their failure to damage the facial nerve mentioned earlier) but, nevertheless, can sometimes show invasive activity microscopically and can occasionally metastasize. Microscopic invasive activity

should therefore be looked for and reported, as it is the only feature that may suggest a potential for metastasis in a cytologically benign tumours. Even when tumours show neither invasion nor any other adverse microscopic feature, they can occasionally disseminate. However, Seifert *et al* (1986) recorded that none of the well differentiated mucoepidermoid carcinomas metastasized. Of the poorly differentiated tumours, 50% metastasized to lymph nodes and 25% to more distant sites.

Tumours that may be expected to have a poorer prognosis are those which are predominantly solid and have a preponderance of epidermoid cells. These are thought to have the strongest potential for metastasis and should be treated accordingly. Seifert *et al* (1986) suggest that their five-year survival rate is only 40%, but by contrast, the five-year survival rate for low-grade mucoepidermoid carcinomas is probably approximately 85%.

A follow-up study by Jensen *et al* (1988) on 39 mucoepidermoid carcinomas has reported 5-, 10- and 15-year survival rates of 92% for low-grade tumours, 47.4%, 47.4% and 35.5% for intermediate grade, and zero for high-grade tumours.

Analysis, by Hickman *et al* (1984) of survival rates from reports of several series, adequate in size and relevant data, amounting to a total of 749 cases, suggest that the overall five-year survival rate (taking no account of tumour grade) is 70.7% (95% confidence interval) and the ten-year survival rate is 50.0% (95% confidence interval).

Batsakis and Luna (1990) have suggested detailed criteria for separating mucoepidermoid carcinomas into three grades:

➤ Grade 1 is characterized by macro- and microcysts, daughter cyst proliferation from larger cysts, differentiated mucous and epidermoid cells often in equal proportions, minimal-to-moderate numbers of intermediate cells, minimal or absent pleomorphism and rare mitoses, pools of extravasated mucin with stromal reaction and broad front, often circumscribed invasion.

➤ Grade 2 is characterized by absence of macrocysts, few microcysts, solid nests of cells, preponderance of intermediate cells with or without epidermoid differentiation, sometimes sparse mucin-producing cells, less-conspicuous large duct-cell population, fibrosis separating groups of cells, slight-to-moderate pleomorphism, a few mitoses and more prominent nuclei and nucleoli, well-defined invasive property, lack of circumscription and peripheral inflammatory reaction.

➤ Grade 3 is predominantly solid and characterized by absence of macrocysts, few differentiated cells, especially mucin-positive cells, considerable pleomorphism, prominent nucleoli and readily found mitoses, obvious invasion of soft-tissue including perineural and intravascular, sometimes with desmoplasia of the stroma round clusters of invasive cells but a less prominent inflammatory reaction. The cell constituents range from poorly differentiated to recognizable epidermoid and intermediate to ductal-type adenocarcinoma with participation of epidermoid and intermediate cells or, it is suggested, the tumour may be predominantly glandular and microcystic.

These proposed criteria, however, have not as yet been correlated with outcome.

Our own multivariate analysis of 89 mucoepidermoid carcinomas (Gleeson *et al*, unpublished data) was based on fewer microscopic criteria of malignancy, but showed that necrosis was one of the strongest correlates with a poor prognosis. Prominent necrosis was also found to be associated with aggressive behaviour of acinic cell carcinomas by El-Naggar *et al* (1990). By contrast, we have found that the degree of circumscription and the solid or cystic nature of mucoepidermoid carcinomas bore little relation to their outcome. Otherwise, our findings are consistent with the grading proposed by Batsakis and Luna (1990) and such findings as perineural or intravascular invasion - features that are either clearly present or absent and not dependent on subjective assessment - were useful and reliable guides to prognosis.

Hamper *et al* (1989b) reviewed the history of ideas about grading mucoepidermoid carcinomas and applied cytophotometric analysis to 46 mucoepidermoid carcinomas. They found that those showing diploid histograms usually had a favourable course while those with atypical histograms had a poor prognosis.

Using immunocytochemistry, flow cytometry and clonal dilution studies Ross *et al* (1992) concluded that the intermediate cells were reserve cells capable of division and differentiation into squamous or mucous cells. They also showed by xenograft studies that only the intermediate cells were capable of active invasion and that they were present in greater numbers in high-grade tumours.

Previous reports, mentioned earlier, on prognosis relating to grade have been based on simpler microscopic criteria and any agreement is only of a general nature. Objective quantification of the variables within such grading systems is also not possible. It is likely therefore that though broad categories of 'low grade' and 'high grade' would be universally accepted, agreement on what constituted borderline cases would be difficult to obtain. It is also unlikely that precise grading could be made on a frozen section during operation.

Treatment

Total conservative parotidectomy (Chapter 9) is the treatment of choice for low-grade mucoepidermoid carcinomas. In a very few cases where a small tumour is localized to the lower pole, it would be reasonable to limit the resection to a superficial parotidectomy. Radical parotidectomy and, where appropriate, sacrifice of the facial nerve or neck dissection or both is required for tumours which are recognized by their clinical manifestations or by frozen section to be high grade, and are usually followed by radiotherapy.

Though some mucoepidermoid carcinomas are radiosensitive, radiotherapy alone is not sufficiently reliably effective. Moreover, since the diagnosis of low-grade mucoepidermoid carcinoma will usually have been made after parotidectomy for an apparently benign tumour, radiotherapy is also unlikely to have been considered as the first line of treatment. Radiotherapy may however be given to supplement radical surgery of high-grade tumours.

Acinic Cell Carcinoma

Acinic cell carcinomas account for about 2% of all salivary gland tumours and approximately 10% of malignant epithelial tumours in both our material and in the Hamburg salivary gland register (Seifert *et al*, 1986). Over 90% of them are found in the parotid glands, and they account for only 2% of the tumours of the minor glands.

Clinical features

Acinic cell carcinomas affect women at least twice as frequently as men and the peak incidence is between the sixth and eighth decades.

These tumours typically form rounded, well-circumscribed swellings and particularly in their early stages, are indistinguishable clinically from benign tumours. They only occasionally cause pain but poorly differentiated acinic cell carcinomas may sometimes be fixed or cause facial palsy.

Though it is a rare event, acinic cell carcinomas also appear to be more frequently bilateral or to be present in two different glands, than any other carcinoma. Gnepp *et al* (1989) have found 12 such cases and report two cases of acinic cell carcinoma associated with Warthin's tumours.

Microscopy

Acinic cell carcinomas usually appear circumscribed even though the capsule may be incomplete. The most common and readily recognizable appearances of these tumours are the solid and microcystic types, but several subtypes can be distinguished and description of them illustrates how widely the microscopic appearances of these tumours can vary. However, these variations in the configurations of low-grade tumours are of little value in forecasting their behaviour.

Low-grade tumours

Solid type

In typical examples, the tumour cells are in dense sheets (Fig. 7.16) but usually with scattered small microcysts, which are little larger than the cells and give the field a sieve-like appearance. The tumour cells closely resemble the basophilic, rounded polyhedral cells of serous acini; the cytoplasm is granular, period acid-Schiff-positive and contain zymogen (Fig. 7.17). They are frequently in acinar configurations with basally placed nuclei but there is little or no duct formation (Fig. 7.18) and the microcysts form either by accumulation of dammed up secretion or by rupture of cells and coalescence of intracytoplasmic vacuoles. The stroma is usually inconspicuous but occasionally there are foci or a widespread infiltrate of lymphocytes or fibrous tissue proliferation.

Microcystic type

This has a lattice-like or lacy appearance with both serous-type and more compressed cells (Fig. 7.19). Occasionally the microcysts coalesce to form larger cystic cavities (Fig. 7.20) and some of the cells may be vacuolated. Ellis and Gnepp (1988) have found vacuolated cells in 34% of their material and consider them to be fairly distinctive for acinic cell carcinomas. As well as the acinic cells, smaller, cuboidal intercalated duct cells may be seen. These have amphophilic or weakly eosinophilic cytoplasm and central nuclei. Occasional clear cells and their transition from granular cells may also be seen (Fig. 7.21). Variable numbers of lymphocytes may be present in the stroma and may form a conspicuous feature (Fig. 7.22).

Papillary cystic and follicular types

These are less common. The papillary cystic type is probably formed by coalescence of microcystic spaces leaving strands of tumour cells round vascular cores (Fig. 7.23). Such papillary cystic patterns may form the whole or only part of the tumour. The follicular pattern (Fig. 7.24) usually forms only part of the tumour and is only rarely predominant. It can resemble a thyroid follicular carcinoma, having rounded follicle-like spaces filled with eosinophilic amorphous material and lined by cuboidal cells (Fig. 7.25).

Clear-cell type

Clear cells as mentioned earlier, may be a minor or, rarely, the main feature of acinic cell carcinomas and in the latter case may have to be differentiated from other clear-cell tumours (Fig. 7.26). Another rare finding is that of lamellated, psammoma-like bodies (Fig. 7.27), which may be associated with a fibrous stromal reaction. Yet another variant has uniformly basophilic epithelial cells, typically in an acinar arrangement (Figs 7.28 and 7.29). Their appearance suggests that these cells are mucin-producing, but though they are periodic acid-Schiff-positive, they are negative for specific mucin stains.

High-grade tumours

Most acinic cell carcinomas are well differentiated, but this gives little indication of how they will behave. Occasional examples have a more obviously malignant appearance (Fig. 7.30). These show widespread mitotic activity and pleomorphic cells with large vesiculated nuclei containing prominent nucleoli or undifferentiated areas with, occasionally, foci of necrosis (Fig. 7.31). However, they should still be recognizable by the persistence of some granular cells.

Differential diagnosis

Difficulties mainly arise in the case of papillary cystic, follicular and clear-cell types.

Differentiation of acinic cell carcinomas which are wholly of papillary cystic or follicular from thyroid tumours is, as mentioned earlier, occasionally difficult. Ellis and Gnepp (1988) report that, unexpectedly, acinic cell carcinomas frequently stain positively with mucicarmine but thyroid carcinomas may also contain intracellular mucin (Mlynek *et al*, 1985). This problem may therefore have to be resolved by immunostaining for thyroglobulin

or, if this fails, by investigation of the patient for a primary thyroid tumour.

Clear-cell types have to be differentiated from other clear-cell tumours if no granular cells are evident, as discussed later.

Seifert *et al* (1986) have described variants of acinic cell carcinomas, aspirates of which were rich in lymphocytes and showed partial oncocytic differentiation; they thus resembled Warthin's tumours. However, we have not seen variants with oncocytic differentiation in our material.

Behaviour and grading

Even cytologically benign acinic cell carcinomas can be invasive (Figs 7.32 and 7.33) and this behaviour appears to correlate with a potential for local recurrence or more distant spread. Nevertheless, a reasonably good correlation between the degree of differentiation and prognosis has been reported by Evans and Cruikshank (1970), Batsakis *et al* (1990) and Seifert *et al* (1986). By contrast, Ellis and Gnepp (1988) in an analysis of 244 cases, found that no one tumour pattern or type was strongly indicative of a poor prognosis. However, they found that infiltrative growth, multinodularity and stromal hyalinization were frequently seen in tumours that recurred or metastasized, and that an intercalated duct-cell type of tumour was slightly more frequent among those which metastasized.

In a further attempt to predict prognosis, Hamper *et al* (1990a) applied DNA cytometry to 55 acinic cell carcinomas but found no correlation between the DNA content of the tumours and whether they were diploid or near-diploid, and prognosis. In an analysis of the outcome in 40 of these cases, they found that of 12 patients with low-grade tumours, 10 (83.3%) had an unfavourable outcome, 5 (42%) had recurrences and 5 (42%) died from their tumours; of 28 patients with high-grade tumours, 15 (53.6%) had an unfavourable outcome, 12 (42.9%) had recurrences and 7 (25%) died from their tumour. In view of the numbers involved, these figures were not significant except in so far as they showed no difference in outcome in relation to differentiation. By contrast, El-Naggar *et al* (1990) also applied flow cytometry in a retrospective assessment of 15 acinic cell carcinomas and found that only patients having tumours showing aneuploidy, but none of those with diploid tumours, died or had metastases within a 10-year period. Other features associated with aggressive behaviour were prominent necrosis, tubuloductal differentiation and dedifferentiation areas.

Overall, local recurrence has been reported in 20% of acinic cell carcinomas, metastases to regional lymph nodes in 10% of cases and death from distant metastases in approximately 6%, by Spiro *et al* (1978), Jack (1981) and Ellis and Corio (1983), respectively. Seifert *et al* (1986) reported that 36% of well-differentiated tumours had lymph node but no distant metastases, whilst the figures for poorly differentiated tumours were 50% and 27%, respectively.

Ellis and Gnepp (1988) in reviewing 244 cases, found a local recurrence rate of 12%, metastases in 8% and a 6% death rate in a mean period of 8.9 years (range 3 months to 34 years). Retrospective analysis of 101 reported cases with usable data, by Hickman *et al* (1984) suggested an expected five-year survival rate of 82% and a 10-year survival rate of 68%.

Exceptionally long periods of follow-up were recorded by Lewis *et al* (1991) in their study of 90 patients. They had been followed for at least 10 years or until death and calculated determinate survival probabilities were 90% at five years, 83% at 10 years and 67% at 20 years.

In the cases analyzed by Lewis *et al* (1991), the primary treatment group of 63 patients had been followed for up to 45 years; the remainder (27 patients), who had been referred for recurrent disease, were followed-up for a median period of 12 years. Forty-four per cent of the patients had local recurrences, 19% had metastases and 25% died from their disease. Local recurrences first appeared up to 30 years after presentation and death followed up to 38 years later. Clinical features associated with a poor prognosis were pain or fixation, signs of gross invasion and local excision rather than parotidectomy. Microscopic features associated with a poor prognosis were a desmoplastic stromal reaction, atypia or increased mitotic activity.

Treatment

In view of the uncertainty about the prognostic value of the histological findings, even well-differentiated acinic cell carcinomas should be treated by total conservative parotidectomy with preservation of the facial nerve whenever possible. However, if the tumour has to be peeled off and is therefore intimately related to the nerve, it should be sacrificed. Poorly differentiated tumours, with preoperative facial weakness, should be treated by radical parotidectomy followed by radiotherapy.

Adenoid Cystic Carcinoma ('Cylindroma')

Adenoid cystic carcinomas formed 5% of 3500 epithelial salivary gland tumours in our material, and 23% of the carcinomas. They comprised 28% of parotid salivary gland tumours but had a much higher relative frequency in the submandibular and minor glands where, overall, > 70% of adenoid cystic carcinomas were found. The palate is by far the most frequent site in minor glands.

Clinical features

The peak age incidence is in the sixth decade (range 12-72 years) and the female-to-male ratio is 1.3.

In most cases, the tumour is slow growing and this slow rate of growth is mirrored by the late appearance of recurrences. Nevertheless, adenoid cystic carcinoma frequently causes pain as a result of its well-known propensity for infiltration of nerves. It should be noted that pain in the distribution of one or several cranial nerves can be caused by an occult adenoid cystic carcinoma which may elude diagnosis for a considerable period. Malins and Farrow (1991), for example, describe facial pain lasting for 18 months and 7 years respectively before the causative adenoid cystic carcinomas were detected. In the first case, the tumour was 1.5 cm and in the second, 1 cm in diameter. The difficulty in finding some adenoid cystic carcinomas is enhanced by their predilection for arising in minor glands which extend as far back as the pharynx.

Facial palsy is another common manifestation of their invasiveness and Seifert *et al* (1986) quote a frequency of facial palsy in 20%, 40% and 65% for the cribriform, tubular and solid types, respectively.

Microscopic features

There are several variants of which the cribriform is the single most common type and the most readily recognizable. However, it is important to note that although many adenoid cystic carcinomas are instantly recognizable, there can be wide variation between the appearance of individual fields, of which some can look deceptively benign.

Cribriform type

In typical cribriform adenoid cystic carcinomas, the cells are small and darkly staining with little cytoplasm (Fig. 7.34). Usually they form oval islands of cells containing many microcystic spaces which are more often surrounded by myoepithelial than duct-lining cells (Fig. 7.35). There are also duct-like structures which have a double-layered wall of duct-lining cells surrounded by an outer layer of myoepithelial cells; they usually contain PAS positive material (Fig. 7.36). However, these duct-like structures are rarely seen cut longitudinally.

The stroma is fibrous and contains elastic fibres. Formation of basophilic hyaline material by myoepithelial cells is also sometimes prominent (Fig. 7.37). This material frequently surrounds the epithelial cells as a thick band, may form the major component of the stroma and also fills the cribriform spaces (Fig. 7.38).

As with other subtypes of adenoid cystic carcinoma, perineural and sometimes intraneural spread may be conspicuous.

Hyaline type

Overproduction of hyaline material can lead to such distension of the cyst-like spaces and attenuation of the cells as to give a lace-like appearance (Figs 7.39 and 7.40), or it may break up the tumour pattern completely, leaving only thin strands of cells forming incomplete outlines to coalescing globules of hyaline material. Less often, formation of hyaline material is restricted within small groups of cells, so that a reticular or lattice-like appearance is produced. A somewhat similar appearance may be seen in parts of pleomorphic adenomas as shown earlier, and can cause diagnostic confusion. In extreme cases, so much hyaline material is formed that the tumour pattern is totally destroyed and only minute clumps of cells or single duct-like structures are scattered in a sea of mucoid or hyaline material (Fig. 7.41).

Tubular type

These form only 20-30% of adenoid cystic carcinomas and as the name implies, consist of small, dark, epithelial cells forming cords (Fig. 7.42) or duct-like structures with multilayered walls (Fig. 7.43), sometimes with an outer clear-cell layer, and surrounded by a hyaline stroma. Excessive hyalinization of the stroma in this variant can lead to disintegration of the cellular architecture (Fig. 7.44).

Solid (basaloid) type

Solid areas may be seen in addition to cribriform. Alternatively, they may occasionally predominate (Fig. 7.45) but are usually distinguishable from other small-cell carcinomas by the presence of sparse duct-like spaces or small foci of necrosis within the solid masses (Fig. 7.46). Mitotic activity is greater in the solid than other types of adenoid cystic carcinoma.

Behaviour and prognosis

Though usually slow growing, adenoid cystic carcinoma is invasive and infiltrative, and perineural spread is characteristic of, though by no means exclusive, to this tumour (Figs 7.47 and 7.48). Other important routes are bony canals, either those of haversian systems or those conveying arteries, and marrow spaces, nerves or other structures. The tumour can spread far into a bone by these routes, with relatively little bone destruction (Fig. 7.49) or radiographic evidence of its true extent. Alternatively, it may proliferate, with extensive bone destruction once well within the tissue.

Metastases are usually late events and in most cases follow multiple recurrences. In many cases, lymph-node involvement is due to invasion by contiguous tumour rather than by lymphatic permeation or embolization (Fig. 7.50), hence the apparently anomalous finding of Seifert *et al* (1986) that distant metastases were considerably more frequently found than spread to the lymph nodes. Blood-borne metastases are mainly to the lungs or liver. However, secondary deposits retain the slow-growing character of the primary tumour. They frequently permit survival for many years and success has also been claimed for excision of isolated secondary deposits.

As noted earlier, pain is sometimes the first symptom and can long precede the discovery of an occult adenoid cystic carcinoma.

Grading

Seifert *et al* (1986) noted that lymph-node metastases were seen in none of the tubular, 4% of the cribriform and 33% of the solid types. Distant metastases were found in 36%, 58% and 67%, respectively. In a study of 19 cases, Santucci and Bondi (1989) concluded that the number of cystic spaces per square millimetre correlated well with the disease-free period or survival, within periods of follow-up up to 52 months after treatment.

Hamper *et al* (1990b) applied DNA cytometry and other criteria to 90 adenoid cystic carcinomas to assess the prognostic value of various features. Cytophotometry showed that diploid histograms were associated with the longest (median 128 months) survivals and atypical histograms with the shortest (median 65 months). Other unfavourable features were solid-type histology and tumour size (> 4 cm in diameter).

Because of their slow rate of growth, the prognosis of adenoid cystic carcinoma is considerably better than for adenocarcinomas, particularly in the short term. Analysis of reports of a total of 1065 adenoid cystic carcinomas (Hickman *et al*, 1984) suggested five- and ten-year survival rates of 62.4% and 38.9%, respectively. This compares with the five- and twelve-year survival rates of 73% and 39% reported by Blanck *et al* (1967) for 35 cases,

and of 76% and 33% obtained by Seifert *et al* (1986).

Treatment

The infiltrative growth pattern, the potential for spread along nerves and bony canals and the deterioration of prognosis with recurrences, presents a dilemma for any surgeon anxious to avoid a mutilating operation. Unfortunately, there is as yet no consensus as to the optimal approach nor any firm evidence that postoperative radiation improves the prognosis. However, it is generally accepted that radiotherapy improves local control and should therefore be considered for every patient with an adenoid cystic carcinoma.

Seifert *et al* (1986) suggest that for tumours ≤ 2.5 cm in size, comprehensive (supraradical) surgery is indicated. This comprises radical parotidectomy, sacrifice of the facial nerve and resection of surrounding tissues, including the mandible, maxillary tuberosities, mastoid process or temporal bone, and contents of the infratemporal fossa, to provide a wide margin of healthy tissue. Though an arbitrary figure has been given for the maximum size of tumour where supraradical surgery can be contemplated, much may depend on other factors such as the patient's age, attitude and general health. In the young otherwise healthy patient, supraradical surgery may be considered for larger tumours, in view of the greater potential expectation of life.

For those with more extensive disease, there is no certainty that wide excision with tumour-free margins can ever be obtained, so that it seems difficult to justify the functional and cosmetic deficits resulting from such procedures. Excision is therefore limited to radical parotidectomy with sacrifice of the facial nerve (to remove a possible path of spread of residual tumour) and, possibly, postoperative radiotherapy. As mentioned earlier it appears that a metastasis can sometimes be removed with beneficial effects on the outcome.

It is, nevertheless, still surprising that the more radical surgery of the Göttingen group (Seifert *et al*, 1986) gave no better results than the much earlier cases of Blanck *et al* (1967) where parotidectomy was carried out in only 3 of 35 cases and in 31 only local excision was performed. Indeed, Seifert *et al* (1986) admit that, despite their recommendation of supraradical surgery even for small tumours, the method of treatment had very little influence on the outcome and that they could not confirm any prolongation of survival as a result of giving radiotherapy.

Polymorphous Low-Grade Adenocarcinoma

The relatively recent recognition of this entity has meant that there is some variation in the terminology and, for example, the terms, lobular and 'terminal' duct carcinoma have also been applied to it. Alternatively some of these terms may represent subgroups of these tumours, which have a wide spectrum of appearances. However, the term 'polymorphous low-grade adenocarcinoma' describes the most striking feature of its appearances and, despite an infiltrative pattern of growth, the low potential for metastasis over periods of many years.

Clinical aspects

So far, > 200 cases have been reported. Most have been tumours of the minor glands with the palate as the site of predilection, but with some cases in the buccal mucosa, retromolar area, lip and tongue. Only four examples in the parotid gland have been reported, with one reported by Ritland *et al* (1993). Vincent *et al* (1994) evaluated 204 cases including 15 of their own and analyzed the sites of 173 tumours; 87 of them had arisen in the palate. Patients are mostly between 50 and 75 years, the mean age being 65 years; women may be slightly more frequently affected.

The clinical features of these tumours are usually nondescript in that they form firm painless swellings but may later ulcerate.

Microscopy

In contrast to the variety of microscopic architectural patterns produced by this tumour, there is cytological uniformity with bland-appearing nuclei. The latter are pale and ovoid with a finely speckled pattern of chromatin and small or inconspicuous nucleoli. The cytoplasm is usually scanty but more columnar cells may surround some of the cell masses.

The main microscopic patterns include:

- Solid (lobular) masses of cells surrounded by fibrous tissue (Fig. 7.51).
- Cribriform areas (Fig. 7.52).
- Duct-like structures with mucinous or hyaline stroma and hyaline material present in the spaces in the cribriform areas.
- Strands or fascicles of cells sometimes in concentric arrangements (Fig. 7.53).
- Papillary structures or a papillary cystic pattern (Fig. 7.54).

Fibrous bands between different areas of the tumour are sometimes conspicuous (Fig. 7.55). The concentric arrangements of cells, to which the term 'targetoid' has been applied, sometimes surround nerve fibrils or blood vessels, or may form a solid whorl of uniform tumour cells (Figs 7.56 and 7.57).

In 22 polymorphous low-grade adenocarcinomas, Slootweg (1993) analyzed the frequency of lobular, papillary cystic, trabecular-tubular and cribriform configurations. The last was the least common (6 of 22), lobular and papillary cystic patterns were present in the great majority and 50% showed trabecular-tubular configurations. By contrast, papillary cystic patterns were infrequent in metastases and there was a clear distinction between these tumours and papillary cystic adenocarcinomas.

Perineural invasion and, despite partial circumscription by fibrous tissue, infiltration of surrounding structures by strands of tumour cells can be seen. Nevertheless, unlike more malignant neoplasms, substantial amounts of normal salivary gland tissue and fat can persist in the depths of the tumour (Fig. 7.58).

If the term 'terminal duct carcinoma', is used, it implies the presence of tubules, cut transversely or obliquely. These cells have distinctly visible cytoplasm and resemble intercalated duct cells. The overall pattern may therefore resemble that of a tubular adenoma or the tubular variant of adenoid cystic carcinoma. Solid masses of tumour cells may also project into and largely fill enlarged duct spaces. However, the term 'terminal duct carcinoma' is unhelpful in that it is questionable whether terminal ducts are recognizable as an anatomical entity and, as already mentioned, the tubules seen in some of these tumours resemble intercalated ducts, where indeed Batsakis *et al* (1992) believe they originate.

Reported electron microscopic findings include true glandular structures with luminal junctional complexes and microvilli projecting into lumens containing homogeneous material. Myoepithelial cells were not identified. In addition, there were pseudoglandular spaces with a smooth lining of basement membrane lacking well-defined junctional complexes near the luminal surfaces.

An incidental finding is that tyrosine-rich crystalloids may be widespread in the stroma.

Four cases were reported by Gnepp *et al* (1988) who reviewed the histopathology and carried out immunohistochemistry on this material. In summary, they suggest that where extensive cribriform areas and perineural invasion in a polymorphous low-grade adenocarcinoma cause difficulties in diagnosis, it can be distinguished from adenoid cystic carcinoma particularly by the staining of > 90% of polymorphous low-grade adenocarcinoma tumour cells with EMA. By contrast, EMA stained only the true luminal cells of adenoid cystic carcinomas. Carcinoembryonic antigen (CEA) staining was positive for only 5-15% of cells, and both muscle-specific actin and CEA staining were usually negative in cribriform areas of polymorphous adenocarcinomas. Vincent *et al* (1994) therefore concluded that the histological features rather than special stains were more useful for differentiating polymorphous low-grade adenocarcinomas from other tumours. However, they also noted the frequency with which many cases of polymorphous low-grade adenocarcinomas had been misdiagnosed, most frequently as monomorphic adenomas or adenoid cystic carcinomas.

Behaviour and prognosis

As mentioned earlier, these tumours are infiltrative and locally invasive but as far as can be determined, rarely metastasize. Admittedly the numbers reported have been small and there are few cases which have been followed for prolonged periods. But of those that have been followed for periods up to 20 years, distant metastases have not been recorded.

Vincent *et al* (1994) found an overall recurrence rate of 17% for 116 cases where follow-up information was available. These appeared from 1 to 19 years after initial treatment. These workers suggested that polymorphous low-grade adenocarcinomas having a predominantly papillary configuration should be categorized as papillary cystadenocarcinomas since the latter have a stronger tendency to metastasize, as described earlier.

Treatment

Despite the relatively benign nature of this tumour, local recurrence has been frequent among the reported cases, but in some of these at least, the resection margins had not been adequate or the tumours had been misdiagnosed as benign. Excision should therefore be as radical as possible to obtain a good surgical clearance. In view of the usual sites for these tumours, both early recognition and complete excision without significant complications should be possible.

Epithelial-Myoepithelial (Intercalated Duct) Carcinoma

This tumour was originally described by Donath and Seifert (1972) and since then has been described in detail by Corio *et al* (1982); approximately 40 cases have been reported. A similar example was shown as the last of a series of so-called 'duct carcinomas' reported by Kleinsasser *et al* (1968), but salivary duct carcinomas are now categorized as a separate group as described later.

Clinical features

The mean age of affected patients appears to be about 60 years and the peak age incidence of the tumour is in the seventh and eighth decades although occasional examples have been in young adults. Women have been predominantly affected in the ratio of 2:1.

Over 80% of these tumours have been in the parotid glands. The majority have given rise to otherwise asymptomatic swellings, but a minority have caused pain or facial weakness.

Microscopy

The tumour is typically multinodular and though it appears circumscribed, like pleomorphic adenomas, the capsule may be thick in part, incomplete or have tumour nodules extending through it.

Duct-like structures or larger spaces are characteristically present. Alternatively, such structures may be absent and the cells are predominantly in an organoid (thecal) pattern with a well-defined basal membrane.

The cells are characteristically of two types, namely small dark cells lining the duct-like spaces, and large glass-clear cells which surround the dark cells and usually predominate (Fig. 7.59). The dark cells are usually roughly cuboidal, eosinophilic and have little cytoplasm. The clear cells are considerably larger, of rounded polyhedral shape and can usually be shown by periodic acid-Schiff staining to contain glycogen, but are mucicarmine-negative (Fig. 7.60). In some areas of these tumours, there may be solid sheets of clear cells without any distinguishing features (Fig. 7.61).

The lumens of the duct-like or larger spaces sometimes contain eosinophilic periodic acid-Schiff-positive material. The basal membrane surrounding the organoid nests of tumour cells also stains positive, and may be considerably thickened and hyaline in appearance.

In some cases, there are cyst-like spaces into which there are papillary projections of tumour cells and there is thus a variety of patterns and of numbers of clear cells in individual tumours or within a single example.

Electron microscopy has confirmed that the dark cells are epithelial and that the clear cells are myoepithelial in that the cytoplasm contains myofilaments, pinocytotic granules, glycogen and lipofuscin. The small, dark cells by contrast are ductal epithelium with microvilli on some points on the luminal surface. They contain tonofilaments and are joined by desmosomes.

Immunohistochemistry has confirmed that the clear cells are strongly S-100 protein and myosin positive but have variable keratin reactions. This seems, therefore, to be a useful means of confirming the myoepithelial nature of clear cells in epithelial-myoepithelial carcinomas here clear cells are overwhelmingly predominant. Though neoplastic myoepithelial cells may become S-100 positive, the long held belief that normal myoepithelial cells were S-100-positive appears now to be questionable. Assumptions about the histogenesis of salivary gland tumours such as epithelial-myoepithelial carcinomas may possibly therefore have to be reassessed.

Behaviour and prognosis

Mitoses are rarely seen, but the potential of epithelia-myoepithelial carcinomas for invasion is shown by the occasional finding of perineural infiltration or intravascular growth (Fig. 7.62). Not surprisingly, these tumours have recurred in a significant number of reported cases (13 of 37). Two patients have died with metastases which have been in lymphnodes, lung and kidney. Seifert *et al* (1986) suggest that five-year survival rate is 65%.

Treatment

Although often regarded as of low-grade malignancy, the behaviour of reported cases suggests that total conservative or radical parotidectomy should be carried out. The latter is appropriate particularly if there is preoperative facial weakness. In the case of other glands, *en bloc* resection should be carried out.

Clear-Cell Tumours

Clear cells can be seen in a variety of salivary gland tumours, but are frequently few in number. It is apparent that there is no single entity that can be categorized as a clear-cell tumour and clear-cell formation can result from a variety of processes. These include sparsity of organelles, intracytoplasmic accumulation of materials such as glycogen, mucus, lipids or clear secretory granules, or hydropic change or fixation artifact.

It is also doubtful whether there is any such entity as a clear-cell adenoma. Many, such as Batsakis (1980), believe that all clear-cell tumours should be regarded as low-grade carcinomas and this view is supported by Ellis and Gnepp (1988). Nevertheless, the latter, like most other workers, include the clear-cell variant of oncocytoma, among the clear-cell tumours.

Varieties of clear-cell tumours

A variety of clear-cell tumours is, therefore, described here to give an adequate picture of the present state of knowledge. However, it must be admitted that some clear-cell tumours remain difficult to fit into any of the recognized categories.

Clear-cell oncocytoma

This is a rare variant of a rare tumour and its name is something of an internal contradiction.

The characteristics of oncocytomas have been described earlier but, exceptionally, in these tumours there can be transition from typical oncocytes to clear cells, which on even fewer occasions form a high proportion or the major component. The tumour then appears as a circumscribed mass of rounded polyhedral clear cells, with small, dark eccentric nuclei, arranged in an organoid pattern and surrounded by thin fibrous septa (Fig. 7.63). As noted in Chapter 6, clear cells are most frequently found in multinodular oncocytic hyperplasia and in associated oncocytomas.

While a high proportion of cells of an oncocytoma can thus be glass-clear, at least a few cells remain eosinophilic, contain a small amount of eosinophilic material or appear granular.

Staining of these clear cells with PTAH, which should be taken up by the many mitochondria of oncocytes, is sometimes unreliable. However, PTAH staining is sometimes intense and includes the oncocytic duct cells of adjacent normal salivary tissue. Periodic acid-Schiff staining may show variable amounts of glycogen, but mucicarmine staining is negative. Ellis and Gnepp (1988) suggest that the appearance of the clear cells in oncocytomas is largely due to fixation artifact. This seems to be confirmed by electron microscopy which shows many of these cells to lack any organelles or to have only swollen mitochondria limited to the periphery of the cells. Similar clear-cell transformation may also be rarely seen in oncocytosis. However, Davy *et al* (1994) have shown by electron microscopy that the cytoplasm of these clear cells is occupied by glycogen with margination of the chromatin and organelles.

Unlike other clear-cell tumours, the clear-cell variant of oncocytoma appears to be benign.

Mucoepidermoid and acinic cell carcinoma

These tumours sometimes contain foci of glass-clear cells or rarely, such cells predominate. However, closer examination of the material should establish these tumours as mucoepidermoid (see Fig. 7.) or acinic cell carcinomas (see Fig. 7.26) as the case may be. According to Ellis and Gnepp (1988) clear cells appearing in acinic cell carcinomas are fixation artifacts, while the clear cells found in mucoepidermoid carcinomas sometimes contain glycogen but only rarely mucin.

Such tumours are not normally therefore categorized as clear-cell tumours but merely variants of well-recognized neoplasms.

Epithelial-myoepithelial carcinoma

This tumour, the main type of clear-cell tumour, has been described earlier (see Fig. 7.64).

Sebaceous carcinoma

Occasionally one of these rare tumours consists largely of clear rather than foamy cells, but in such cases the characteristic lobular configuration may assist in making the diagnosis (Fig. 7.65).

Metastatic renal cell carcinoma (hypernephroma)

When clinical or any other features suggest that a clear-cell tumour of a salivary gland is a secondary deposit, the kidney is the only important source. The other possible source of a secondary deposit, in a salivary gland, of a clear-cell tumour is a parathyroid carcinoma with *wasserhelle* (water-clear) cells, but this appears to be no more than a theoretical hazard.

In the case of a renal cell carcinoma, difficulties arise because metastases are frequently its first sign and renal disease is unsuspected. The 'classical' triad of gross haematuria, pain in the loin and a renal mass is late in appearance and present in only 10% of patients. However, microscopic haematuria alone can be found in 60% of patients and about 50% of patients have non-specific systemic symptoms such as fever, fatigue or loss of weight.

Microscopy

Renal cell carcinoma consists of solid groups of clear cells with small eccentric nuclei in an organoid or trabecular arrangement (Figs 7.66 and 7.67). The blood vessels are typically dilated and form scattered sinusoids; foci of haemorrhage and deposits of haemosiderin may be seen. Granular cells may also be present and in some cases predominate.

The clear cells are usually uniform size and show little or no atypia but those which show nuclear and cellular pleomorphism, and mitotic activity are less likely to be confused with primary salivary gland tumours.

Differentiation from epithelial-myoepithelial salivary gland tumours can be difficult. Ellis and Gnepp (1988) suggest that a helpful distinguishing feature of epithelial-myoepithelial carcinoma is that small blood vessels can be seen running between the groups of tumour cells, but there are typically large sinusoids in renal cell carcinomas. In addition, if unblocked material is available, the demonstration of abundant fat is typical of renal cell carcinomas but unfortunately, is not invariably present. Glycogen is common to both epithelial-myoepithelial and renal cell carcinomas.

If doubt remains, intravenous urography and if necessary a computerized tomography or ultrasound scan need to be carried out. If a renal cell carcinoma is present, a salivary gland metastasis is likely to mean that the prognosis is poor. However, some of these tumours grow unexpectedly slowly and removal of both the primary tumour and metastasis has occasionally resulted in a cure.

Hyalinizing Clear-Cell Carcinoma of Salivary Gland

Milchgrub *et al* (1994) have presented 11 cases of yet another type of clear-cell carcinoma of salivary glands in which the epithelium was surrounded by hyalinized bands with foci of myxohyaline stroma. Despite some microscopic resemblances to epithelial-myoeepithelial carcinoma, immunohistochemistry and electron microscopy failed to show myoeepithelial cells. They noted four earlier examples which had been illustrated but not characterized as a distinct entity.

The patients comprised eight females and three males. Ages ranged from 34 to 78 years with a mean of 55 years. Minor salivary glands were most frequently affected (nine cases). There was a single case in the parotid gland and another in the larynx.

Microscopy

The tumour cells formed trabeculae, cords or nests and infiltrated any residual acini or other soft tissues such as the overlying oral mucosa. They were mostly round to polygonal with clear, periodic acid-Schiff-positive cytoplasm and central nuclei. The nuclear membranes frequently appeared indented with a suggestion of lobulation. Mitotic activity was noted in only two cases. In 10 of the 11 cases reported by Milchgrub *et al* (1994), there were polygonal cells with eosinophilic granular cytoplasm mingling with the clear cells and appeared to represent transition between the two types.

The tumour cells were immunoreactive for low- and high-molecular weight keratins and epithelial membrane antigen. In two cases there was CEA reactivity. Immunoreactivity for S-100 protein, smooth muscle actin and muscle-specific actin was consistently negative. Electron microscopy failed to show any cells with myoeepithelial differentiation, zymogen, mucin or dense core neurosecretory granules.

A distinctive feature was the stroma which was desmoplastic in both the primary tumours and metastasis. It sharply outlined the trabeculae and nests of tumour cells and enhanced the streaming effect where the tumour cells were aligned in slender cords. In five cases, the stroma was hyalinized and periodic acid-Schiff-positive and, though resembling amyloid, was Congo red-negative. In eight tumours there were also foci of loose myxoid stroma. Perineural invasion was seen in most cases but vascular invasion was absent. Electron microscopy showed a prominent continuous layer of basal lamina surrounding most tumour cell nests.

Eight of the eleven tumours reported by Milchgrub *et al* (1994) had originally been reported as other types of carcinomas such as poorly differentiated adenocarcinoma, epithelial-myoeepithelial carcinoma, mucoepidermoid carcinoma, acinic cell carcinoma, squamous cell carcinoma, carcinoma in pleomorphic adenoma or calcifying epithelial odontogenic tumour.

Behaviour and management

One of the patients reported by Milchgrub *et al* (1994) presented with cervical nodal metastases but no metastases developed in the remaining nine cases. Clinical follow-up ranged in duration from 6 months to 11 years with no evidence of recurrent disease in any of the patients. Hyalinizing clear-cell carcinoma therefore appears to be of low-grade malignancy and wide excision possibly supplemented by radiotherapy appears to be the treatment of choice.

Salivary Duct Carcinoma (Excretory or Large Duct Carcinoma)

These tumours were originally described by Kleinsasser *et al* (1968) who termed them 'duct carcinomas' because of their histological resemblance to duct carcinomas of the breast. Nevertheless, probably only two of the five cases that he presented can be regarded as duct carcinoma in its present connotation. Also the term, 'duct carcinoma' might cause confusion with several other types of salivary gland carcinomas which also arise from duct cells and in particular, with what has been termed 'terminal duct carcinoma' (low-grade polymorphous adenocarcinoma) and the 'intercalated duct carcinoma' (epithelial-myoeithelial carcinoma). Moreover, Seifert *et al* (1986) use the term 'duct carcinoma' for the epithelial-myoeithelial carcinoma.

Any confusion caused by the different terminologies is particularly unfortunate in that duct carcinomas, as described here, are significantly more aggressive than other salivary duct carcinomas. To resolve these difficulties the term 'excretory (large) duct carcinomas' was coined, and Chen and Hafez (1981) found reports of 12 acceptable examples. Eleven of these arose from Stenson's duct and one from the excretory duct of a minor salivary gland in the palate. Luna *et al* (1987) described 30 cases and Afzelius *et al* (1987) reported another 12. Six more cases have been reported by Simpson *et al* (1991) from among 212 parotid gland tumours seen in a 12-year period. The incidence of these tumours is therefore likely to be greater than previously suspected. Overall however, Barnes *et al* (1994) believed that few more than a hundred cases had been reported in the English-language literature.

Clinical features

In reviewing 104 cases including their own, Barnes *et al* (1994) concluded that duct carcinomas affected major salivary glands, particularly the parotids, in 96% of cases, were three times as common in males as in females, and affected patients > 50 years (range 22-91 years). Growth is typically rapid and may be associated with pain or facial palsy. The cervical lymph nodes may be involved at the time of presentation.

Microscopy

Four patterns, namely, papillary, cribriform, solid and a rare comedo type, may be seen (Figs 7.68 and 7.69). The tumour is actively invasive. The cells are moderately large with eosinophilic cytoplasm and may contain periodic acid-Schiff-positive granules but are mucicarmine-negative. The nuclei are large, hyperchromatic and pleomorphic, with prominent nucleoli, and mitoses are frequent.

The tumour cells form nodular masses in a fibrovascular stroma in which there may be small amounts of mucin and a light inflammatory infiltrate. The stroma may show areas of eosinophilic hyalinization. Perineural and intraneural invasion is relatively frequent. Vascular invasion and intralymphatic emboli may also be seen. Cribriform and papillary cystic patterns may sometimes be seen in adjacent nodules. The comedo type is characterized by extensive central necrosis within duct-like structures as in comedo carcinoma of the breast but other areas of necrosis are also common. Duct carcinomas of salivary glands may induce dense fibrosis like scirrhous-duct carcinomas of the breast.

Delgao *et al* (1993) reviewed the immunocytochemistry, electron microscopy and results of treatment of 15 duct carcinomas of which three had arisen in pleomorphic adenomas. Men were affected in the ratio of 4:1. All 15 tumours stained positively for one or more of five commercially available 'breast-specific' markers but oestrogen receptor stains were uniformly negative in 11 that were tested.

Behaviour and prognosis

As mentioned earlier, the growth of duct carcinomas is typically rapid and aggressive. The tumour is infiltrative and lacks clearly defined boundaries. Variations in the microscopic appearances do not appear to correlate with the behaviour sufficiently well to be of predictive value, except insofar as the comedo type may have the worst prognosis. However, Simpson *et al* (1991) noted that there was little difference in the survival times of patients with tumours showing less well-defined areas of necrosis than the comedo type and that the longest survival was in a patient whose tumour showed no necrosis.

Nine of 12 cases reported by Chen and Hafez (1981) developed metastases and eight died. Of the three remaining patients, only one had remained free of recurrence after six years. Of the six patients reported by Simpson *et al* (1991), all died within 6-28 months except one who was alive after 68 months, but who also had metastases.

Despite total or radical parotidectomy, radical neck dissection and/or radiotherapy in the majority of cases, only three of the 15 patients reported by Delgado *et al* (1993) were alive and without disease after 2-5 years. Unexpectedly, two of these three patients had tumours with intraductal growth patterns and comedo-like necrosis. One had arisen in a pleomorphic adenoma but unlike most of the 12 other cases, none of them had lymph-node metastases.

In their analysis of 104 cases, Barnes *et al* (1994) found that one-third of patients experienced local recurrences, 59% experienced regional nodal spread and 49% developed distant metastases particularly to lungs and bone. Sixty-five per cent of these patients died from their disease usually within four years, but all of those with distant metastases died. Tumour ploidy as determined in 12 of their 13 cases appeared to have little prognostic significance.

Treatment

In view of reported behaviour of this tumour, radical treatment appears to be necessary in the hope of improving the chances of survival. Supplementary irradiation is frequently

given but its value is uncertain.

Radical parotidectomy or *en bloc* resection of other salivary glands when feasible, appears to be the treatment of choice. Neck dissection even when there is no clinical involvement of nodes may be indicated. Though Seifert *et al* (1986) reported a five-year survival rate of 65% with such treatment, their criteria for definition of duct carcinoma are in doubt and more recent reports suggest that $\leq 70\%$ of patients may die within three years.

Basal Cell (Basaloid) Adenocarcinoma

Twenty-one cases of basal cell adenocarcinomas were described by Ellis and Gnepp (1988) who considered them to be malignant counterparts of, and sometimes difficult to distinguish histologically from, basal cell adenomas, particularly the membranous variant. One of these tumours caused facial pain and another, facial palsy. Twenty-nine cases have been reviewed by Ellis and Wiscovitch (1990). However, illustrative of the difficulties in terminology are 24 cases of basaloid adenocarcinoma reported by Chomette *et al* (1991) who regarded them as variants of adenoid cystic carcinoma. Gallimore *et al* (1994) in reporting three cases of what they termed 'basaloid carcinomas' also distinguished one of them which they regarded as a typical basal cell adenocarcinoma from the others which were high-grade tumours. Raslan *et al* (1995) have described the immunohistochemical and ultrastructural findings in a case and reviewed the literature.

The peak age incidence appears to be in the sixth decade and all patients have been adults. The parotid glands are the usual site.

Microscopy

Basal cell adenocarcinomas usually consist of multiple nodules of basaloid epithelial cells of two types. One type is small and dark with scanty cytoplasm. The other cells are larger, polygonal or more elongated, with eosinophilic or amphophilic cytoplasm and a pale basophilic nucleus, and frequently surrounded by the smaller cells. Palisading of the peripheral cells is less prominent than in basal cell adenomas, but the configurations of the benign and malignant types are similar (Figs 7.70 and 7.71). Like basal cell adenomas, solid, trabecular, tubular and membranous types may be recognized but frequently more than one pattern is present. In the tumour nodules, the larger cells may form small whorls in which there is sometimes squamous differentiation. Small lumens or tubules are occasionally present. Cellular and nuclear pleomorphism, foci of necrosis and moderate mitotic activity are sometimes seen, but are not conspicuous.

A distinctive feature is the frequent presence of sharply defined, hyalinized, periodic acid-Schiff-positive perinodular basal lamina which can also be enclosed as intercellular droplets. Also suggestive of the relationship of these basal cell adenocarcinomas to membranous basal cell adenomas is their association with dermal cylindromas of the scalp, as in two cases described by Ellis and Gnepp (1988).

Perineural, intravascular growth or invasion of surrounding tissues is frequently evident. Such infiltration may be seen in cytologically benign tumours of this type and is an

important feature distinguishing them from basal cell adenomas. Williams *et al* (1993) studied the immunohistochemistry of 11 basal cell adenomas and 23 basal cell adenocarcinomas but concluded that it was not possible to distinguish them by this means.

Behaviour and prognosis

Limited data are available. In the largest series so far reported (Ellis and Wiscovitch, 1990), follow-up of the 29 patients was incomplete. Of 25 patients on whom information was available, seven had recurrences, metastases developed in three, but 10 remained alive and well for 5-10 years after diagnosis. One of the infiltrative tumours recurred more than once and finally metastasized after nearly 11 years. Gallimore *et al* (1994) noted that the well-differentiated tumour they described, had been present for three years before treatment but by then was causing severe pain and facial palsy and had extended into the nasopharynx and skull base. The two less well-differentiated examples that they described grew rapidly. One developed extensive metastases to lymph nodes and the other died within weeks, probably from a cerebral metastasis.

Treatment

On the basis of their reported behaviour, these tumours are generally regarded as relatively low-grade adenocarcinomas in most cases. They probably require at least total conservative parotidectomy, though Ellis and Wiscovitch (1990) noted local recurrence in 28% of their cases and lymph-node involvement in 12%. Adjuvant radiotherapy may be advisable.

If there is involvement of the facial nerve or lymph nodes or both, radical parotidectomy and neck dissection is required.

Sebaceous Carcinoma

Although sebaceous differentiation is sometimes seen in the parotid glands and occasionally seen in pleomorphic adenomas, sebaceous tumours of salivary glands are uncommon. Out of 125 salivary sebaceous neoplasms reviewed by Gnepp (1983), 52 were sebaceous adenomas or lymphadenomas, 19 were sebaceous carcinomas, only three were sebaceous lymphadenocarcinomas while 51 were other tumours containing some sebaceous differentiation. Most of these sebaceous neoplasms were in the parotid glands. The peak age incidence was in the seventh decade.

Baillet *et al* (1992) showed that rare though they were, sebaceous carcinomas of salivary glands were the most frequent extraocular sebaceous carcinomas in the head and neck region. Of 91 of these tumours, 26 were in the parotid and one in the submandibular gland. Eighteen per cent of the patients with salivary gland tumours died from their disease within two to five years and only 46% were apparently tumour-free after a mean follow-up period of four years.

Sebaceous lymphadenocarcinomas have more recently been categorized as 'sebaceous carcinoma' with 'lymphoid stroma' as described below.

Sebaceous carcinomas give rise to painful masses, varying degrees of facial palsy and may become fixed to the overlying skin.

Microscopy

Sebaceous carcinomas consist of sebaceous cells showing variable degrees of cellular pleomorphism and nuclear atypia. The cells form sheets or nests (Figs 7.2 and 7.73). Despite apparent encapsulation, there is infiltration of surrounding tissues and perineural invasion may also occasionally be seen.

In isolated cases, oncocytes and foreign-body reactions to extravasated sebum, with histiocytes and giant cells, have been described. However, a dense lymphoid stroma with germinal follicles is, by definition, absent.

Although the typical features of sebaceous carcinomas have been described, the differentiation of low-grade examples from sebaceous adenomas may be difficult. In addition, some epidermoid carcinomas show foci of sebaceous differentiation. The presence of fat but absence of mucin may be useful in differentiating sebaceous tumours from mucoepidermoid carcinomas.

Behaviour and prognosis

Of 18 cases for which follow-up data were available, survival ranged from 8 months to 13 years, but five patients died from their disease within 5 years of diagnosis. The longest survival (13 years) was in a 22-year-old patient. The treatment of these cases ranged from local excision to parotidectomy with, in some cases, postoperative radiotherapy or chemotherapy.

Treatment

In view of the reported recurrences after limited resections, as radical a parotidectomy as possible, in keeping with the clinical presentation, is probably the treatment of choice.

Sebaceous Carcinoma with Lymphoid Stroma (Sebaceous Lymphadenocarcinoma)

The parotid glands are the most frequently affected but this tumour does not appear to have any distinctive clinical features. Unlike undifferentiated carcinoma with lymphoid stroma, its sebaceous counterpart has no special racial distribution.

Microscopy

The essential features are foci of sebaceous cells which show varying degrees of loss of differentiation, in a dense lymphoid stroma, sometimes with follicle formation. Intermingled with the malignant sebaceous cells are foci of apparently benign sebaceous tissue and there may be foreign-body reactions to extravasated sebum. This may be helpful in the differential diagnosis, though granulomatous reactions can also be seen in infarcted Warthin's tumours. There is partial encapsulation but local invasive activity.

Behaviour and prognosis

Limited information is available about these rare tumours. One patient had had the tumour for 20 years, while another had a solitary lung metastasis more than 13 years after treatment. Overall, these tumours appear to be of lower-grade malignancy than sebaceous adenocarcinomas without lymphoid stroma.

Treatment

In view of the potential of these tumours for metastasis, total conservative parotidectomy appears to be advisable but more radical surgery may be dictated by the preoperative behaviour of the tumour.

Oncocytic Carcinoma (Malignant Oncocytoma)

This must be the most uncommon of all primary salivary gland tumours.

Clinical features

The parotid gland is chiefly affected and only isolated cases have been reported in other glands. Most patients have been over 45 years and their mean age has been about 65 years. There seems to be no significant difference in sex distribution.

The usual manifestation has been an asymptomatic swelling but pain has been reported in a few cases.

Microscopy

Many of the earlier cases do not fulfil the two essential criteria of having oncocytes as the tumour cells and clear evidence of malignancy. Fifteen cases fulfilling these criteria, from the files of the AFIP, have been reviewed and nine further cases of oncocytic adenocarcinoma have been reported by Goode and Corio (1988) who have attempted to define its characteristics. All showed invasive activity or involvement of lymph nodes, and, in the majority of cases, gross pleomorphism. An initial diagnosis of oncocytic adenoma had been made in several cases. However, even Goode and Corio (1988), though they recognize malignant change in an oncocytic adenoma as a category, do not distinguish it from adenocarcinoma with extensive oncocytic change. They also believe that cytologically benign oncocytomas can occasionally metastasize as discussed in Chapter 6. One reason may be that, as Sugimoto *et al* (1993) have shown, a malignant variant and its metastases can show remarkably little cellular pleomorphism and very few mitotic figures.

The tumour cells resemble those of a benign oncocytoma in that they are rounded or polygonal and have distinctly eosinophilic, granular cytoplasm, but differ in that there is noticeable pleomorphism, both nuclear and cellular, and variable numbers of mitoses (Fig. 7.74). Also unlike benign oncocytoma, the cells may be in solid masses, cords, trabeculae or in papillae with small cysts, as well as in the expected alveolar arrangement. The oncocytic nature of these cells may be confirmed by staining with PTAH or BAAF to confirm mitochondrial proliferation, or may be established unequivocally by electron microscopy.

The malignant nature of such tumours, irrespective of their cytology, is confirmed by evidence of invasion of surrounding tissues, such features as perineural infiltration or by the appearance of metastases.

Behaviour and prognosis

Oncocytic carcinomas have a high incidence of recurrence after local excision and this has been followed by metastasis. Of the 30 cases reviewed by Ellis and Gnepp (1988), 12 had cervical lymph node and eight had distant metastases. Eight patients died from their tumours.

Unfavourable prognostic features, Goode and Corio (1988) suggest, are a large primary tumour and, microscopically, a predominantly cystic pattern or gross pleomorphism or both.

Treatment

Information is limited, but the behaviour of many of the reported cases of this rare tumour suggests that as radical a parotidectomy as is consistent with the preoperative clinical behaviour is probably the treatment of choice. Prophylactic neck dissection may have to be considered in view of the high reported incidence of nodal disease. Supplementary radiotherapy may also be considered though its value is uncertain.

Adenocarcinoma Not Otherwise Specified

The term 'adenocarcinoma (not otherwise specified)' is restricted to those carcinomas showing formation of duct-like structures without significant variation on this theme and lacking any features of a pleomorphic adenoma. These typical adenocarcinomas are described first; mucinous and papillary cystic adenocarcinomas are readily recognizable variants.

Other types of salivary carcinomas, which do not resemble typical adenocarcinomas which arise in such tissues as the gut, have been identified in increasing numbers as described in earlier sections. The inclusion of such subtypes into the general category of 'adenocarcinoma' in the past has made it difficult as yet to interpret earlier reports of behaviour.

Adenocarcinomas (all major types) formed 5% of 3500 epithelial salivary gland tumours, and 23% of carcinomas in our material. They comprised 3% of parotid but 5% of submandibular, 11% of sublingual and 13% of tumours of minor glands. However, the Göttingen and Hamburg registries record that they form between 10 and 12% of malignant salivary gland tumours.

Clinical features

The peak age incidence for adenocarcinomas is between the sixth and eighth decades; men appear to be more frequently affected than women in the ratio of almost 2:1. Rapid growth, pain, fixation to deep or superficial tissues and occasionally, ulceration through the skin are typical signs and symptoms in a significant number of patients. Seifert *et al* (1986) noted that 40% of adenocarcinomas caused facial palsy.

Microscopy

Even when carcinomas arising in pleomorphic adenomas or other tumours are excluded, several subtypes of salivary gland adenocarcinomas can be identified, as mentioned earlier, and inevitably also, variable degrees of differentiation are seen. Seifert *et al* (1986) recognized tubular, papillary and rare solid variant. A more recent tendency is to categorize members of this diverse group as separate entities as indicated in the classification (see Table 6.2, p. 82).

Tubular type

This, the most readily recognized form of adenocarcinoma, is characterized by production of ducts formed by cells showing variable degrees of atypia (Fig. 7.75). The quality of differentiation of the ducts may sometimes be unrelated to the degree of atypia of the surrounding cells; well-formed ducts may be produced by cells showing gross atypia and vice versa.

Papillary cyst adenocarcinoma

This has a predilection for the palate and is rare in the major glands. The typical appearances are folds of epithelium projecting, as papillary or frond-like ingrowths, into irregular cystic spaces. This epithelium may be multilayered and have columnar or goblet-shaped mucous cells on its surface. Small foci of solid epithelium, some of the cells of which may have clear cytoplasm, may also be seen.

The epithelium may, as with comparable thyroid carcinomas, lack any cytological features of malignancy, with the result that it appears to be benign (Fig. 7.76). In addition, some areas of polymorphous low-grade adenocarcinomas show a conspicuous papillary cystic pattern and may in the past have been categorized as papillary adenocarcinomas (Fig. 7.77).

Mills *et al* (1984) reported five cases from the palate and their microscopic features, and also reviewed seven earlier cases. The misleadingly bland appearance of the cells of many papillary cystadenocarcinomas is emphasized by the fact that three of these five cases were initially interpreted as benign. One of them, which had shelled out freely at operation, caused the death of the patient 33 years after the original diagnosis, despite extensive surgery and radiotherapy. In another such case seen by us, a patient who had a tumour categorized as a papillary cystic adenoma of the palate, which was widely excised, remained asymptomatic for 15 years but then died with widespread metastases. It is doubtful therefore whether it is justifiable to accept the existence of a papillary cystic adenoma, except in the terms described in Chapter 6, and it is probably wise to regard all papillary cystic salivary gland tumours as carcinomas, though of very low-grade in some cases. In one of the patients reported by Mills *et al* (1984), metastases appeared in the regional lymph nodes 21 years after presentation. Of the seven earlier cases reviewed by them, only three patients were alive and without evidence of tumour, approximately 42 months after treatment. Of the five more recent patients, two had had recurrences seven and eight years respectively, after initial treatment. Mostofi *et al* (1993) found 22 reports of low-grade papillary cystic adenocarcinomas of minor salivary glands and confirmed that 27% of them recurred between 1 and 19 years after treatment. However, the period of follow-up of seven of those without recurrences was only three years or less.

High-grade papillary cystadenocarcinomas may also be seen but should not be difficult to recognize.

Mucinous adenocarcinoma

Mucin secretion may be prominent in adenocarcinomas, as described by Blanck *et al* (1971), and an uncommon variant is the mucin-secreting adenocarcinoma resembling its counterpart from the breast. Microcysts may also form (Figs 7.78 and 7.9). In the differential diagnosis, mucoepidermoid carcinomas may have to be distinguished.

Behaviour and prognosis

Typical adenocarcinomas usually grow rapidly, are aggressively invasive, and spread to regional lymph nodes and more distant sites. As with most other carcinomas, the prognosis depends on the rapidity of development of the tumour and its extent at operation. Poorly differentiated tumours have frequently involved lymph nodes when first seen and have a correspondingly poor prognosis. By contrast, well-differentiated papillary cystadenocarcinomas may behave in a benign fashion for many years as described earlier. Probably for this reason, adenocarcinomas of minor salivary glands appear to have a better prognosis than those arising in the parotid glands according to Seifert *et al* (1986).

It is not possible to give accurate five- and ten-year survival rates as most series have been small and there is sometimes doubt as to how widely the term 'adenocarcinoma' has been interpreted. The figure of a five-year survival rate of 40%, given by Seifert *et al* (1986), is probably as good a guide as any.

Treatment

Radical parotidectomy or *en bloc* resection of other glands is probably unavoidable in most cases; neck dissection may also be necessary. These tumours are not highly radiosensitive; nevertheless, postoperative radiotherapy is frequently given. Even this may not be curative, but in the case of low-grade papillary-cystic adenocarcinomas, many years of normal life are possible before recurrences appear.

Sclerosing Adenocarcinoma

This exceedingly rare type of tumour which does not seem to have been described elsewhere, appears to be a counterpart of sclerosing carcinomas of the breast. It induces fibrosis of the gland but tumour cells surround duct-like or microcystic spaces (Fig. 7.80). The tumour cells tend to be compressed by the fibrous stroma so that their carcinomatous nature may be difficult to discern and the appearances may mimic inflammatory sclerosis or a Küttner tumour. Careful examination is therefore required to recognize the malignant nature of this lesion (Fig. 7.81).

Epidermoid (Squamous-Cell) Carcinoma

Squamous metaplasia is a common feature of pleomorphic adenomas, but primary epidermoid carcinomas of salivary glands are rare. In some series, the incidence may have been inflated by the inclusion of microscopically similar tumours such as poorly differentiated mucoepidermoid carcinomas, squamous-cell carcinomas originating in the skin or oral mucosa, and metastatic tumours.

In the series of Seifert *et al* (1986), squamous-cell carcinomas accounted for 10% of all salivary gland carcinomas or 2.0% of all epithelial tumours. In our material, it formed only 5% of salivary gland carcinomas or 1% of epithelial tumours. The most common site is the parotid gland, though this tumour is relatively more frequent in the minor and submandibular glands; in our material, none was found in the sublingual glands.

Clinical features

The elderly are predominantly affected and in our material, the mean age was 71 years and the range 50-90 years. Males predominated over females in the ratio of 2.4:1.

In most cases, the history is relatively short and the tumour is often hard and fixed. The regional lymph nodes are involved early and facial palsy is common.

Microscopy

The appearances range from well-differentiated tumours, consisting of sheets of squamous cells with clearly visible intercellular bridges and abundant keratinization (Fig. 7.82), to poorly differentiated examples with smaller cells having relatively little cytoplasm and without keratin formation. Active invasion and destruction of surrounding tissues is evident. The stroma is fibrovascular and contains a predominantly lymphocytic infiltrate. In short, the appearances are those of squamous-cell carcinomas in general.

Mucin production is not seen and if detected by appropriate stains, the tumour is probably a poorly differentiated mucoepidermoid carcinoma. However, squamous-cell carcinomas are reported by Takeuchi *et al* (1981) to have a high glycosaminoglycan content.

In parotid gland material, it may be impossible to decide whether or not a squamous-cell carcinoma is a primary tumour.

Behaviour and prognosis

Squamous-cell carcinomas tend to invade and spread rapidly, and involve regional lymph nodes at a relatively early stage. The five-year survival rate is probably about 40% but no large series of these uncommon tumours exists to establish either the prognosis or optimal mode of treatment with certainty.

Treatment

Radical parotidectomy (or *en bloc* resection of other salivary glands) and, if necessary, neck dissection, followed by postoperative radiotherapy, is the most appropriate form of treatment. A major factor which may limit the extent of the excision is the patient's age.

Squamous Carcinoma of Stenson's Duct

Carcinoma of Stenson's duct is even more rare than squamous-cell carcinomas of the parotid gland parenchyma and Haar *et al* (1991) could find fewer than 20 reports in the English literature.

Those affected range between 40 and 80 years and the usual presentation is a localized tender swelling. This may dilate the duct, produce a filling defect radiographically and thus simulate an inflammatory lesion. The diagnosis may therefore be delayed attempts to deal with the lesion by antimicrobial treatment. The patient's prognosis is likely to be adversely affected, as happened in the case shown here.

Microscopy

These tumours range from well to poorly differentiated, but otherwise typical squamous-cell carcinomas, and the origin from the lining epithelium of Stenson's duct should be discernible. The duct may fill with keratin (Fig. 7.3). At the time of diagnosis, this may be obscured by the spread of the tumour, but its precise site of origin probably does not significantly affect either the management or prognosis.

Carcinoma of Stenson's duct must be distinguished from a carcinoma arising from a nearby minor buccal gland.

Management

Treatment is by radical excision and radiotherapy. Because of its superficial origin, symptoms and diagnosis should be earlier than in the case of intraglandular squamous-cell carcinomas unless the picture has been complicated by inflammation. However, so few cases have been reported and the follow-up periods have been so short that it is not possible to gain any useful idea of the prognosis.

Other primary carcinomas of Stenson's duct

The majority of reported carcinomas of Stenson's duct have been squamous as described earlier, but of twelve carcinomas of Stenson's duct reviewed by Haar *et al* (1991), five were mucoepidermoid carcinomas.

Adenosquamous Carcinoma

Adenosquamous carcinoma is a rare neoplasm which, as the name implies, shows both adenoid and squamous differentiation. There have been reports of such tumours in many sites in the body and Gerugthy *et al* (1968) described ten cases, of which five were in the nasal

or laryngeal areas and five in the mouth. Ellis and Gnepp (1988) have found that this tumour, when in salivary glands, only affects minor oral glands. They reviewed 40 cases from the Armed Forces Institute of Pathology (AFIP) files.

The main sites affected appear to be the floor of the mouth, posterior tongue and faucial area. Male patients have outnumbered females in the ratio of 2:1 and the peak age incidence has been in the sixth and seventh decades. Clinically, the tumour appears similar to a squamous-cell carcinoma of the mouth.

Microscopy

Distinction should be made between adenosquamous carcinoma and pseudoglandular areas in a squamous-cell carcinoma. This latter appearance, which according to Ellis and Gnepp (1988) is seen only in carcinomas of the oral aspect of the lower lip, results from malignant acantholysis of the epidermoid cells to produce pseudolumens (Fig. 7.84).

Adenosquamous carcinoma has distinct and separate areas of adenocarcinoma and of epidermoid carcinoma and thus differs from mucoepidermoid carcinoma, in which glandular and epidermoid differentiation are contiguous. Ellis and Gnepp (1988) consider that squamous carcinoma or carcinoma *in situ* of the overlying epithelium, with underlying adenocarcinomatous change, is an important criterion of diagnosis (Figs 7.85 and 7.86). The adenocarcinoma is typically of ductal type and can be seen intermingling with the squamous carcinoma, but separate areas of both types of carcinoma are also seen.

Gerughty *et al* (1968) speculated that adenosquamous carcinoma might originate from excretory duct epithelium with spread to the oral mucosa. The reserve cells of the excretory duct epithelium, it is suggested, have the potential for both ductal and epidermoid differentiation. However, the association between a superficial squamous-cell carcinoma with a deeper adenocarcinoma could also be interpreted as the intermingling of two separate primary tumours.

Behaviour and prognosis

The limited information from the few reported cases suggest that adenosquamous carcinoma is aggressive. All five cases reported by Gerughty *et al* (1968) spread to the regional lymph nodes, even though they were only 1 cm in size when biopsied. Three of the five also metastasized to the liver and lung.

Treatment

Radical parotidectomy or *en bloc* resection of other glands appears to be necessary. Radiotherapy and prophylactic neck dissection should be considered but their effect on survival is unknown.

Undifferentiated and Neuroendocrine Carcinomas

The term 'undifferentiated carcinoma', as defined by the World Health Organization, is applied to carcinomas which do not show any microscopic features which allow them to be included in any of the categories already described. These tumours should also be distinguished from another entity, namely, 'undifferentiated carcinoma with lymphoid stroma' which is described later.

Undifferentiated tumours comprised 5% of malignant salivary gland tumours in the Hamburg registry (Seifert *et al*, 1986) and 8% in the BSGTP material. This represents between 1.4% (Seifert *et al*, 1986) and 1.9% (BSGTP) of all epithelial tumours. They were most frequently found in the parotid glands (63% of all the undifferentiated carcinomas in our material), formed a modest proportion (11%) of sublingual gland tumours and submandibular gland tumours (4%) but were rare in other glands.

In contrast with these figures, Hui *et al* (1990) have noted that in some reports, undifferentiated carcinomas had been considered to form $\leq 30\%$ of malignant salivary gland tumours. Of 32 tumours which had been so designated previously, these workers had to exclude 16 because they failed to fulfil the necessary criteria when a variety of stains and immunohistochemistry were used. Exclusions fell into the following categories: (1) non-epithelial tumours; (2) metastatic tumours such as oat-cell carcinoma of the lung; and (3) 'lymphoepithelial carcinoma' (undifferentiated carcinoma with lymphoid stroma). They also noted that some tumours had been designated undifferentiated on insufficient material or were found on further examination to be better differentiated than was earlier thought. In assessing previous reports, therefore, these considerations should be borne in mind.

Gnepp and Wick (1990) found that approximately 41 of these tumours had been reported. Nagao *et al* (1982) in reporting 18 undifferentiated carcinomas of the parotid glands, found that 12 were small-cell in type and the remainder, large-cell. Hui *et al* (1990) in their re-examination of 16 undifferentiated carcinomas of salivary glands reported that 12 of them were small-cell (≤ 30 microm in diameter) and four were large-cell types.

Small-cell carcinomas, according to Gnepp and Ellis (1988) account for between 0.3 and 3% of salivary gland tumours and this variation in reported incidence presumably also results from variations in the criteria of categorization used in different centres. Gnepp *et al* (1986) suggest that true anaplastic small-cell carcinomas form only about 1% of undifferentiated carcinomas.

Clinical features

Gnepp and Wick (1990), in reviewing and re-examining previously reported cases, showed that of 11 patients with small-cell carcinomas, all except one were adults over 30 years, seven were over 65 years and there was little difference in the sex incidence. The mean age of the 16 patients reviewed by Hui *et al* (1990) was 67 years but there was a male predominance of 3:1. In the latter's series, patients complained of a non-tender mass that had been enlarging over a period of 1-7 months. The parotid glands are predominantly affected. Facial palsy is particularly common with this type of tumour and was present in 60% of the

patients of Seifert *et al* (1986). As might be expected of poorly differentiated tumours also, growth is rapid and the incidence of lymph-node metastases on presentation is high.

Microscopy

The nature of the cell of origin is not obvious by light microscopy and the usual picture is of almost non-descript sheets of cells. These cells may be predominantly round, large or small or spindle-shaped. The small-cells are almost featureless, uniform in size with round or oval nuclei and dense chromatin, inconspicuous nucleoli and scanty cytoplasm; mitoses may be frequent (Fig. 7.87). Large-cell undifferentiated carcinomas typically consist of round cells or three times larger than those of the small-cell variant and have vesiculated nuclei with several nucleoli.

The small-cell tumours may resemble lymphomas. However, immunohistochemistry should enable the necessary distinction to be made.

The tumour cells form sheets, irregular clusters, organoid nests or combinations of these features and there may be areas of necrosis. Small-cell carcinomas of salivary glands resemble oat- or intermediate-cell carcinomas of the lung but may show rudimentary duct formation. Crush artifacts may be seen.

A lymphocytic infiltrate of variable density is frequently present in a scanty fibrovascular stroma. Invasion and destruction of normal structures is usually obvious. Hui *et al* (1990) found that the most important feature suggesting a poor prognosis was neural invasion.

Small-cell neuroendocrine tumours

Like oat-cell carcinomas of the lung, neuroendocrine cells have been identified mainly in small-cell carcinomas of salivary glands (Fig. 7.88). However, the latter, like many other neuroendocrine cell tumours (Sobol *et al*, 1989) do not appear to produce active hormones, though occasional cases of salivary gland carcinomas associated with endocrine disturbances have been reported as discussed later.

Neuroendocrine cells in these tumours have been identified by their argyrophil properties (Grimelius staining) or chromogranin A staining, immunoreactivity and electron microscopy in the various reports (Fig. 7.89).

Chromogranin A positivity is regarded as a reliable marker of neuroendocrine cells since it is not produced by non-endocrine cells. However, the reliability of chromogranin for identifying neuroendocrine cells does not appear to have been confirmed by Gnepp and Wick (1990) who studied 11 small-cell carcinomas of major salivary glands. These tumours had previously been examined by electron microscopy and neuroendocrine granules had been found in eight. Immunostaining, using the avidin-biotin-peroxidase technique, was carried out for a variety of antigens. Keratin was the only antigen detected in all the tumours and epithelial membrane antigen was found in eight. Vimentin staining was positive in only two and neither of these had neuroendocrine granules. However, all the tumours were positive to some of the stains, and all except vimentin corresponded with the presence of neuroendocrine

granules to a variable degree. All the neuroendocrine granule-containing cells stained positively for NSE, Leu-7 and keratins but only one of them was chromogranin-positive. All but a few of the tumours lacking neuroendocrine cells also stained positively for keratins, Leu-7 and NSE. On the basis of these findings therefore, Gnepp and Wick (1990) concluded that even when electron-dense core granules could not be detected, all small-cell carcinomas of major salivary glands had some neuroendocrine characteristics.

Hui *et al* (1990) in their 16 undifferentiated carcinomas found ultrastructural evidence of neuroendocrine differentiation in five of the small-cell and in one of the large-cell carcinomas; four other small-cell carcinomas had no distinguishing ultrastructural features. Like Gnepp *et al* (1986), they found that none of the small-cell tumours that showed ductal differentiation contained neurosecretory granules.

Histogenesis

The origin of neuroendocrine cells in salivary gland tumours is speculative, but the most obvious assumption is that they are derived from the neural crest and are part of the neuroendocrine (APUD) tissue that is widely distributed in the body, particularly in the gastrointestinal tract, where it can give rise to the carcinoid syndrome. Disseminated neuroendocrine cells have also been found in normal parotid tissue but only on rare occasions. Nevertheless, there is little evidence for the presence of neural crest (Kulschitzky) cells in normal salivary tissue. More probably, therefore, undifferentiated duct cells become capable of neuroendocrine granule production in a comparable fashion to small-cell carcinomas of the lung and can develop electron microscopic features in common with the latter. This ectopic hormone production may be the result of abnormalities of expression of regulating genes rather than an origin in neuroendocrine cells.

Differential diagnosis

Some of the difficulties have been discussed earlier. Basal cell adenocarcinomas or solid (basaloid) adenoid cystic carcinomas may also be confused with undifferentiated carcinomas, but it is particularly important to distinguish them, as basal cell adenocarcinomas appear to be of considerably lower-grade malignancy.

The possibility of the salivary gland tumour being a metastasis from an asymptomatic primary in the lung or elsewhere, must also be considered as the prognosis is then likely to be hopeless. Bronchogenic carcinomas are one of the most frequent sources of metastases to many sites and in approximately 4% of them symptoms are first caused by secondary deposits. A case of bilateral parotid metastases from an oat-cell carcinoma of the lung has been reported by Cantera and Hernandez (1989), but metastases of bronchogenic carcinomas to salivary glands appear to be rare though they may form deposits in juxta-glandular nodes.

Behaviour and prognosis

Undifferentiated carcinomas are actively invasive and metastasize early. Although Gnepp *et al* (1986) estimated that the two- and five-year survival rates for neuroendocrine tumours were 70% and 46%, respectively, in the later series reported by Gnepp and Wick (1990), all but three of the nine patients in whom the outcome was known, had died within

periods of 1-51 months. The three remaining were alive and well after at least six years. Similarly Hui *et al* (1990) found that > 50% of their patients had recurrences after 2-26 months and a similar proportion had regional or distant metastases. Over 60% of these patients died from their disease within 2-54 months and only 25% were living without evidence of tumour for periods of ≤ 2 cm in diameter were alive after five years.

It is not possible to compare these survival rates with those of histologically similar carcinomas of the lung as most of the latter are too extensive for excision at the time of treatment and are treated by chemotherapy. Nevertheless, a 35% five-year survival rate has been reported after excision of operable, oat-cell lung tumours.

It does not seem that the presence of neuroendocrine features in undifferentiated salivary gland tumours confers any prognostic advantage and like chromogranin-positive tumours of some other sites such as the uterine cervix, colon or bladder may be particularly aggressive.

Treatment

The available data suggest that undifferentiated carcinomas should be widely excised and neck dissection carried out for clinically involved nodes. Postoperative radiotherapy is advisable. Metastasis when it takes place appears to be mainly via the bloodstream.

In the series reported by Hui *et al* (1990), all 16 patients had excision and 10 patients had ipsilateral neck dissections. All patients had postoperative radiotherapy and 10 patients had chemotherapy for recurrences or distant metastases. Nevertheless, as already described, the survival rates were poor.

Other types of neuroendocrine salivary gland tumours

Sugawara and Hagen (1988) reported ectopic adrenocorticotrophic hormone (ACTH) production and Cushing's syndrome, associated with a tumour that they categorized as an adenoid cystic carcinoma in which high levels of immunoreactive ACTH were found. The patient had widespread metastases and died before the effect of removal of the salivary gland tumour could be assessed, but at autopsy the pituitary gland appeared normal. Earlier reports of ectopic ACTH production by salivary gland tumours include those of Cox *et al* (1970) and Marks *et al* (1975).

Also in contrast to small-cell endocrine tumours, Eusebi *et al* (1982), reported a neuroendocrine parotid gland carcinoma, which resembled a clear-cell tumour, had an organoid pattern and was associated with a carcinoid of the lung. Structurally, therefore, this tumour had resemblances to a jugulotympanic paraganglionoma which can occasionally involve the parotid region.

Hayashi *et al* (1987) have also reported undifferentiated carcinomas of salivary glands which contained neurosecretory granules but also squamous and clear cells. Earlier, Hayashi *et al* (1987) had reported immunoreactive vasoactive intestinal polypeptide (VIP) and positive Grimelius staining in an acinic cell carcinoma of the parotid but not in any samples of other

common types of salivary gland tumours.

Carcinoma in Pleomorphic Adenoma (Ca Ex-Pleomorphic Adenoma) and Variants

The term 'dysplasia in pleomorphic adenoma (intracapsular carcinoma)', as described earlier, is given to carcinoma cells within the boundaries of a pleomorphic adenoma but lacking evidence of invasion of surrounding tissues (Fig. 7.90). This change has also been termed '*in situ* carcinoma'. If invasion can be confidently excluded, the tumour can be treated in the same way as a pleomorphic adenoma, but follow-up must be rigorous.

Malignant change in benign tumours in the body as a whole, is relatively rare. Over the years therefore, opinions have ranged from those that held that some pleomorphic adenomas were malignant from the start but that foci of carcinoma had been missed in the initial specimen, to the current view that carcinomas can genuinely arise in pleomorphic adenomas.

Convincing evidence of true carcinomatous change in a pleomorphic adenoma is the microscopic finding of both types of neoplasm in the same tumour. Further, the finding of foci of cellular atypia, mitotic activity and other signs suggestive of malignancy well within a pleomorphic adenoma (as described in the previous chapter) also suggests that an adenoma can undergo carcinomatous change.

Clinical features

The development of carcinoma in pleomorphic adenoma is suggested when localized tumours of many years standing show a sudden acceleration of growth or any other signs or symptoms typical of malignancy. It is clear that carcinoma develops mainly in long-standing pleomorphic adenomas; whereas the mean age incidence of the latter is 46 years, that of carcinoma in pleomorphic adenoma is almost two decades later. The frequency of carcinoma in pleomorphic adenoma also rises with its duration of existence (Eneroth *et al*, 1968) and the risk increases from about 1.5% after five years to nearly 10% after fifteen years. In the material analyzed by Seifert *et al* (1986), 87% of carcinomas in pleomorphic adenoma developed after one or more recurrences and had an average latent interval of 16 years. In the remaining 13%, the duration of existence of the untreated pleomorphic adenomas was seven years.

The frequency of malignant change in recurrent pleomorphic adenomas underscores the necessity to eradicate pleomorphic adenomas at the first operation as discussed in Chapters 6 and 9.

Carcinoma in pleomorphic adenoma is one of the most common types of carcinoma of salivary glands. In our material, it accounted for 5% of all epithelial tumours and 20% of carcinomas of salivary glands. A similar figure is reported by Seifert *et al* (1986). In the parotid and sublingual glands, it was the most common type of carcinoma, but in the submandibular and minor salivary glands, adenoid cystic carcinoma was more frequently encountered. Overall, however, 80% of these tumours arose in the parotid glands.

As mentioned earlier, the mean age of those affected is 63 years with a peak incidence also in the seventh decade. There appears to be little difference in sex distribution. The typical history is that of a long-standing and slowly growing tumour, the growth rate of which has suddenly accelerated or which has started to become painful or shown other clinical signs suggestive of malignancy.

Microscopy

The salient features are the juxtaposition of typical pleomorphic adenoma and a carcinoma (Fig. 7.91). The latter is usually an adenocarcinoma or poorly differentiated, and in most cases there is an abrupt transition from the adenoma. Mucoepidermoid, adenoid cystic or squamous-cell carcinomas are less common. More than one type of carcinoma can arise in a pleomorphic adenoma (Thackray and Lucas, 1974), but this is rare.

Some pleomorphic adenomas become increasingly hyalinized over the course of years and it is often in one of these scarred nodules that carcinomas develop (Figs 7.92 and 7.93). As a consequence, such nodules should be closely examined for signs of malignancy (Fig. 7.94).

Carcinoma developing in a multinodular recurrence of a pleomorphic adenoma may be evident in only one of the nodules so that both the benign and malignant parts of the tumour can be seen side by side (Fig. 7.95).

It must be emphasized that, in making this diagnosis, the microscopic features of malignancy should be unequivocal with clear signs of destruction of normal tissues or invasion and not merely those of intracapsular atypia as mentioned earlier.

Confident recognition of the primary adenoma is sometimes difficult. Little of it may remain or what remains may have degenerated. Remnants of the myxochondroid stroma and cartilage, in particular, appear to be most persistent components. The diagnosis of carcinoma in pleomorphic adenoma is unlikely to come to mind if the adenomatous element is not obvious but it is important to recognize this possibility because of its effect on the prognosis.

Behaviour and prognosis

Once malignant change has developed, the behaviour is that of the carcinomatous component. However, it appears that the prognosis of carcinoma in pleomorphic adenoma is poorer than that of comparable carcinomas developing *de novo*. Seifert *et al* (1986) quote a five-year survival rate of only 25% while Thackray and Lucas (1974) suggest that the majority of patients die within three years.

Treatment

Radical parotidectomy with sacrifice of the facial nerve and neck dissection, if necessary, is required.

Myoepithelial Carcinoma (Malignant Myoepithelioma)

As described in Chapter 6, spindle-shaped myoepithelial cells can occasionally predominate in pleomorphic adenomas and, rarely, a pure spindle cell myoepithelioma may be seen. Malignant change involving these myoepithelial cells is rare. Cases have been reported by Crissman (1971), Dardick (1985), Singh and Cawson (1988), and Di Palma and Guzzo (1991) who also reviewed previous reports. Despite its distinctive appearances, myoepithelial carcinoma must be regarded as a variant of carcinoma in pleomorphic adenoma.

In the case reported by Singh and Cawson (1988), the malignant myoepithelial component had developed in, and overgrown, a pleomorphic adenoma to form a giant tumour (775 g) which extended down to the clavicle and had been present for fifteen years. There was no pain or facial palsy.

Microscopy

The most obvious feature is the pseudosarcomatous proliferation of the myoepithelial cells which are predominantly spindle-shaped, with pleomorphic hyperchromatic nuclei. Abnormal mitoses may be present (Figs 7.96 and 7.97). The cell cytoplasm is fibrillar or vacuolated and there is strongly positive staining for actin, vimentin and S-100 protein. Interspersed among the spindle cells may be multinucleate giant cells and occasional plasmacytoid cells. Any contiguous pleomorphic adenoma (Fig. 7.98) shows the expected variety of appearances including myxochondroid differentiation and calcification, but transition of some of the cells to pleomorphic, malignant spindle-shaped myoepithelial cells may also be seen. Previously reported cases such as those reported by Crissman *et al* (1977) and Dardick (1985) showed generally similar features but the latter also described the ultrastructural changes. This patient had no evidence of recurrence or metastases after three years.

Benign plasmacytoid myoepitheliomas have been said to have no potential for malignant change. However, Di Palma and Guzzo (1993) reported two among eight malignant myoepitheliomas. These showed moderate to marked atypia and infiltrative growth.

Treatment

Too few cases have been reported to be certain that the prognosis of myoepithelial carcinoma is any more favourable than that of the more common type of carcinoma in pleomorphic adenoma. Radical parotidectomy with neck dissection, if necessary, seems therefore to be the most appropriate form of treatment.

Carcinosarcoma

Though a potential for sarcomatous change in the mesenchymal products of the myoepithelial cells might be expected and sarcomas of salivary glands are occasionally found, malignant change in both types of cellular components of pleomorphic adenomas is exceptionally rare. Batsakis (1982) mentions four examples that he had seen and there have been a few scattered reports, such as three examples among 40 cases of malignant mixed tumours found by Tortoledo *et al* (1984). More recently, Ellis and Gnepp (1988) identified

five cases from the AFIP files and Toynton *et al* (1994), have added another which arose in the lip of a 32-year-old male.

Clinical features

Limited information is available from the few reported cases. Those from the AFIP files were in patients from 58 to 66 years old, apart from one of 29 years. In a remarkable case reported by Jacobson *et al* (1973), the patient was an 8-year-old girl with a pleomorphic adenoma of the parotid gland. It recurred repeatedly over a period of 39 years and finally metastasized to the regional lymph nodes and humerus. Though not reported as such, the metastasis appears from the illustration to be sarcomatous. In our material, a carcinosarcoma in the palate of a female aged 60 years, caused pain and ulceration. Despite radical surgery, the patient developed bilateral cervical nodes within a period of weeks and died shortly afterwards. The relief of pain from the palatal lesion was soon replaced by excruciating pain from the neck, and required large doses of opioids for its control.

Microscopy

The epithelial component consists of moderately well to poorly differentiated carcinoma in most cases (Fig. 7.99), but papillary cystadenocarcinoma and epithelial-myoeipithelial carcinoma have also been described by Ellis and Gnepp (1988).

The sarcomatous component has usually been chondrosarcoma (Fig. 7.100) or osteosarcoma, as might be expected from the chondroid differentiation commonly seen in the stroma of pleomorphic adenomas. In a case reported by Talmi *et al* (1990), a fibrosarcoma was associated with ductal carcinoma in a parotid tumour. In the case reported by Toynton *et al* (1994), the carcinoma was largely undifferentiated but with some acinar differentiation while the mesenchymal component was a fibrosarcoma.

Differentiation from pseudosarcomatous change in a myoeipithelioma can be made by immunohistochemistry.

Behaviour and prognosis

Little information is available but it seems likely that the sarcomatous component would worsen the prognosis. This seems to be borne out by the patients reported by Tortoledo *et al* (1984) all of whom died from their disease, as did our patient. However, the patient reported by Talmi *et al* (1990), whose tumour was only 1.5 cm in diameter, remained well 11 months after operation.

Treatment

Information about these rare tumours is little better than anecdotal, but radical surgery seems to be indicated for early cases and may at least provide some palliation of pain, but, in advanced cases, the decision as to whether any surgery is likely to be of long-term or even of short-term benefit may be exceedingly difficult.

Metastasizing Pleomorphic Adenoma

Foote and Frazell (1954) described cytologically benign pleomorphic adenomas which were invasive and could metastasize. Moreover, the secondary deposits retained the benign cytological features of the primary growth. This type of carcinoma is sometimes termed 'malignant mixed tumour' to distinguish it from carcinoma in pleomorphic adenoma. However, this term is sometimes also interpreted to mean both sarcomatous and carcinomatous change in a tumour. The present terminology is by no means entirely satisfactory but despite the variety of meanings applied to the term 'malignant mixed tumour', it seems to be widely favoured.

Metastasizing pleomorphic adenoma illustrates the difficulty, by no means unique to salivary gland tumours, of predicting malignant behaviour from cytological appearances alone. This problem is one where, like carcinoma in pleomorphic adenoma, aspiration cytology might be misleading.

Since Foote and Frazell (1954) drew attention to these tumours, there have been few other reports and little clinical data have accumulated. However, it is clear that they are considerably more uncommon than carcinoma in pleomorphic adenoma. Chen (1978) reported one case and reviewed seven others, while, from the many specimens in the AFIP files, Ellis and Gnepp (1988) found only two cases that had metastasized.

From among the 151 carcinomas in pleomorphic adenoma and 1918 pleomorphic adenomas in our material, only two metastasizing pleomorphic adenomas were found.

Clinical features

The limited data available suggest that the age range is wide and that the parotid gland has been the site in most cases. Qureshi *et al* (1994) reported a case in which a bone metastasis showed identical histopathology to a parotid gland pleomorphic adenoma treated 16 years earlier. There had been no local recurrence. In reviewing the literature they found 23 acceptable cases. Males and females were equally frequently affected. Patients' ages ranged from 12 to 73 years (mean age 35 years) and intervals between primary treatment and appearance of metastases ranged from 2 to 52 years (mean interval 19.8 years).

Microscopy

The diagnostic criteria are cytological features consistent with those of a pleomorphic adenoma, but with the difference that there are clear signs of local tissue invasion and destruction (Figs 7.101 and 7.102) or of metastasis. Absolute confirmation of the diagnosis is the development of metastases which reproduce the benign cytological characteristics of the primary. Lack of encapsulation, mild atypia or occasional mitoses are not sufficient for diagnostic purposes as these changes can be seen in pleomorphic adenomas. Greater degrees of cellular atypia, comparable to that in carcinomas but localized within the substance of a pleomorphic adenoma, as mentioned earlier, may precede development of carcinoma in pleomorphic adenoma, but are not, therefore, a feature of metastasizing pleomorphic adenoma which, by definition, is cytologically benign. Wenig *et al* (1992) found neither histological variables nor flow cytometry to be successful for predicting metastasis.

Behaviour and prognosis

Little information is available on the prognosis of these tumours. Their behaviour is that of carcinomas, but even though the cytology suggests that they are of low grade, this is of little help in view of their ability to metastasize and, rarely, to cause the death of patients.

Treatment

In view of the ability of these tumours to metastasize, wide surgical excision and neck dissection, if necessary, appears to be the treatment of choice.

Carcinoma in Warthin's Tumour

Malignant change in the epithelial component of Warthin's tumours has been reported on exceedingly rare occasions. These reports were reviewed by Seifert *et al* (1986) who quote cases of squamous-cell, adenocarcinoma and undifferentiated carcinomas developing in Warthin's tumours and show examples. Since then, Onder *et al* (1990) have reported a case of poorly differentiated adenocarcinoma in Warthin's tumour with severe dysplasia of the oncocyctic cells in other areas. They have also summarized the features of 14 previous reports in the English-language literature. These show that the carcinomas can be adenocarcinomas, squamous cell or undifferentiated. Bengoechea *et al* (1989) have reported an unusual case of an oncocyctic carcinoma in a Warthin's tumour with visible transition between the benign and malignant oncocytes.

To make the diagnosis of carcinoma in Warthin's tumour, it is necessary to find convincing evidence of the typical columnar epithelium undergoing dysplastic change and to exclude another, synchronous tumour. It is also necessary to exclude metastases into a Warthin's tumour and to distinguish the tumour from undifferentiated carcinoma with lymphoid stroma ('lymphoepithelial carcinoma').

Treatment

Virtually all the reported cases have metastasized and radical treatment therefore seems appropriate.

Lymphomatous change in Warthin's tumour is discussed in Chapter 8.

Undifferentiated Carcinoma With Lymphoid Stroma

The terminology is confusing. The tumour has also been termed malignant lymphoepithelial tumour and lymphoepithelial carcinoma. So-called 'benign lymphoepithelial lesion' is a lymphoproliferative disorder and not generally believed to be a neoplasm. The same histological appearances are characteristic of Sjögren's syndrome as discussed in Chapter 4. There is also a high risk of lymphoma in benign lymphoepithelial lesion, as discussed in Chapter 8. The term 'malignant lymphoepithelial lesion' is therefore misleading in that it suggests a relationship with benign lymphoepithelial lesion. Currently, therefore, to distinguish this tumour from lymphoma in a benign lymphoepithelial lesion, the clumsy term 'undifferentiated carcinoma with lymphoid stroma' is used for this tumour with an unusual

racial distribution and rarely associated with Sjögren's syndrome.

Clinical features

Undifferentiated carcinoma with lymphoid stroma is found in Arctic Eskimos, and accounts for the unusually high incidence of salivary gland cancer in these races. It is also found in Chinese, particularly from southern China. Saw *et al* (1986b) reported eight cases, seven of which were in southern Chinese and one in an Anglo-Chinese. A relationship with the Epstein-Barr virus has been suggested. In non-mongoloid patients, this tumour is rare, but two cases were reported in Britons (James and Ellis, 1986). Ellis and Gnepp (1988) reviewed cases from reports and found 73 cases in the AFIP files. Of these, 20 (27.4%) were in non-mongoloids. However, in view of the type of population represented in this material, it seems possible that these unusual (non-mongoloid) cases have been overrepresented.

Krishnamurty *et al* (1987) in a detailed review of this tumour in Alaskan Eskimos and American Indians, calculated that incidence rates per 100.000 of salivary gland cancer (of which undifferentiated carcinoma with lymphoid stroma accounts for approximately 75% of cases) in native Alaskans were 1.73 for men and 3.31 for women. The incidence of salivary gland cancer in these racial subgroups was, therefore, five times that of White American women. These workers also detailed the racial subgroups suffering from these tumours and found that among these native Alaskans, the majority were Yupic- or Inupiaq-speaking Eskimo and a minority were Athabaskan Indians who are a minority of the population there. Earlier, Hanji and Gohao (1983) in reporting nine cases and a review, estimated that for Eskimo populations in Greenland, northern Canada and Alaska, the incidence rate was 4.5 per 100.000 for males and 9.6 per 100.000 for females, and the rates for salivary gland cancer were therefore among the highest in the world.

The eight Chinese or Anglo-Chinese patients reported by Saw *et al* (1986) had a mean age of 49.4 years (range 15-72 years) and males predominated in the ratio of 5:3. In the 14 Alaskan patients reported by Krishnamurty *et al* (1987), the median age was 44 years for men and 39 years for women (range 17-70 years) and females predominated in the ratio of 11:4. Of 73 the patients reviewed by Ellis and Gnepp (1988), the age of affected patients ranged from 14 to 86 years, the mean age was 44 years and females predominated in the ratio of 1.5:1. Rarely, patients have had pre-existing or remnants of benign lymphoepithelial lesion, but only one patient (Delaney and Balogh, 1966) is known to have had Sjögren's syndrome. Overall, therefore, undifferentiated carcinoma with lymphoid stroma does not appear to be a sequel of benign lymphoepithelial lesion.

The exceptionally high incidence of otherwise rare tumours in mongoloid races in such widely disparate environments and of such different dietary habits, strongly suggests a genetic contribution to susceptibility. However, clustering of this tumour has been only recently reported among Eskimo families by Merrick *et al* (1986) who reported cases in five sisters of two families. The first familial cases in Whites were reported by Autio-Harmainen *et al* (1988) who described malignant lymphoepithelial tumours in both mother and daughter in a Finnish family with a dominantly inherited trait for trichoepithelioma.

Immunological findings

Immunological investigations have been carried out on a limited scale. Of 10 native Alaskans with these tumours, Krishnamurty *et al* (1987) found that none had SS-A or SS-B antibodies characteristic of Sjögren's syndrome, but two patients were SS-C (rheumatoid antinuclear antibody and reactive with extracts of Epstein-Barr virus-positive B-lymphocytes). Alaskans with either benign lymphoepithelial lesion or undifferentiated carcinoma with lymphoid stroma had titres of IgG antibodies to Epstein-Barr viral capsid antigen and to Epstein-Barr nuclear antigen, consistent with earlier Epstein-Barr viral infection. However, two patients showed a rise in titres of most Epstein-Barr viral antibodies with development of metastatic disease. By contrast, one patient with extensive metastases and two with spread to regional nodes showed no such rise in these antibody titres. Of eight patients reported by Saw *et al* (1986a), six had raised serum titres of IgA antibodies to Epstein-Barr viral capsid antigen.

Microscopy

The characteristic features are irregular, ill-defined islands of carcinomatous epithelium in a dense lymphocytic stroma (Fig. 7.103). The epithelial cells are pleomorphic, undifferentiated and often appear syncytial (Fig. 7.104). The nuclei are vesiculated, nucleoli may be prominent and there is variable mitotic activity. The stroma, by contrast, is lymphoplasmacytic and benign, but in high-grade tumours, lacks germinal centres. Saw *et al* (1986b) point out that reactive histiocytes can give the stroma a starry sky appearance.

Low-grade undifferentiated carcinoma with lymphoid stroma may be identifiable by more orderly arrangement of the tumour epithelium which sometimes shows palisading. Central necrosis and sometimes mitotic activity are also absent. The lymphocytic stroma may also be ductocentric and may show germinal follicles.

Low-grade undifferentiated carcinoma with lymphoid stroma may be identifiable by more orderly arrangement of the tumour epithelium which sometimes shows palisading. Central necrosis and sometimes mitotic activity are also absent. The lymphocytic stroma may also be ductocentric and may show germinal follicles.

These microscopic appearances are similar to, and may be indistinguishable from, those of the lymphoepithelial variant of nasopharyngeal carcinoma. The latter has an even higher incidence in these racial groups, than the similar-looking salivary gland carcinoma and the possibility that a salivary undifferentiated carcinoma with lymphoid stroma is a metastasis from an occult nasopharyngeal carcinoma should therefore be ruled out (Saw *et al*, 1986a).

Behaviour and prognosis

These tumours are actively invasive and metastasize to regional lymph nodes and distant organs. Follow-up of 73 cases by Ellis and Gnepp (1988) showed that there had been an 18% recurrence rate. Fifty-seven per cent had spread to the regional lymph nodes, 23% had more distant metastases and 35% of patients died from their disease. In the small group of Alaskan natives investigated by Krishnamurty *et al* (1987) low-grade tumours were identified in 6 of the 14 with undifferentiated carcinoma with lymphoid stroma. None of the

six patients developed metastases and were alive 5-22 years after treatment; by contrast, all patients with high-grade tumours died from their tumour or its complications within 8 months to 5 years after treatment. The eight patients reported by Saw *et al* (1986b) were alive and well after periods of 7 months to 9 years, apart from one patient who died of unrelated infection. All of these patients had received radiotherapy after excision of the tumour.

Treatment

In view of the aggressive behaviour of high-grade undifferentiated carcinoma with lymphoid stroma, radical excision is required and the high frequency of spread to regional lymph nodes suggests that prophylactic neck dissection should be performed.

Radiotherapy may be used to supplement surgery and must be used if complete resection of the tumour is not possible. However, the tumour is not particularly radiosensitive and there is no certainty that such treatment prolongs survival.

Note

1. N. Kulschitzky (1856-1925), Russian histologist; imprisoned and forced by the Communists to make soap but escaped in 1918, by walking with his family from Kharkov to Sebastopol, and migrated to London.