SALIVARY GLANDS AND SALIVA
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Salivary gland tumours

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Salivary gland tumours are a relatively rare and morphologically diverse group of lesions. Although most clinicians and pathologists will have encountered the more common benign neoplasms, few have experience of the full range of salivary cancers, which are best managed in specialist centres. This review considers some current areas of difficulty and controversy in the diagnosis and management of these neoplasms. The classification of these lesions is complex, encompassing nearly 40 different entities, but precise classification and terminology is essential for an accurate diagnosis and for the allocation of tumours to prognostic groups. For many salivary tumours diagnosis is straightforward but the wide range of morphological diversity between and within tumour types means that a diagnosis may not be possible on small incisional biopsies and careful consideration of the clinical and pathological features together is essential. Although tumour grading is important and helpful, it is not an independent prognostic indicator and must be considered in the context of stage. Large malignancies tend to have a poor prognosis regardless of grade and even high-grade neoplasms may do well when they are small. A helpful guide to management of salivary cancers is the '4 cm rule'.
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Introduction

Salivary gland tumours are a morphologically and clinically diverse group of neoplasms, which may present considerable diagnostic and management challenges to the pathologist or surgeon. Salivary gland

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tumours are rare with an overall incidence in the Western world of about 2.5–3.0 per 100 000 per year. About 80% of all lesions are benign, hence salivary malignancies are particularly rare, comprising less than 0.5% of all malignancies and about 5% of cancers of the head and neck. When one considers that there are almost 40 named epithelial tumours in the latest World Health Organization (WHO) classification (Seifert and Sobin, 1991) it is evident that some tumours are very rare indeed and may be the subject of only a few case reports. Because of their rarity, individual clinicians are only infrequently required to manage these lesions and most cancers are managed in specialist centres. This, coupled with the degree of morphological diversity, makes this group of lesions one of the most interesting and challenging in the head and neck.

The literature on salivary gland tumours is very large and there are a number of excellent current texts on the histopathology of these lesions (Ellis, Auclair and Gnepp, 1991; Dardick, 1996; Ellis and Auclair, 1996; Cheuk and Chan, 2000). This short review will not attempt to repeat these works by embarking on a description of the clinicopathological features of each entity. Rather, we will address some broad issues and will highlight some current areas of difficulty or controversy among the epithelial tumours of the salivary glands.

Classification and epidemiology

The classification of salivary gland tumours is essentially based on morphology. In essence, the current WHO (Seifert and Sobin, 1991) and Armed Forces Institute of Pathology (AFIP) (Ellis and Auclair, 1996) classifications are simple lists of tumour types divided by their microscopic appearance based on recognizable morphological patterns. Recently, the classification of salivary gland tumours has been challenged, particularly by surgeons (Watkinson, 2001) who feel that a list based, at worst, on 'pattern matching' has little to commend itself in modern surgical oncological practice. Thus there is a view that the diagnosis of salivary gland tumours is

merely a case of matching the pattern of the lesion to a name - perhaps using a simple atlas to do so.

As will become apparent this is not the case, in fact, the comprehensive classifications have developed because of the wide morphological diversity of the tumours and the need to reach a precise diagnosis. Eveson (2001a) in particular has presented a robust defence of the current WHO classification, pointing out that the purpose of a classification is to provide a framework for an accurate diagnosis. Thus it is the responsibility of the pathologist to provide a precise diagnosis which can be used by the surgeon to group entities into broader prognostic groups relevant to management. The extensive WHO and AFIP classifications allow accurate diagnosis so that lesions can be correctly categorized. It is by study of subsequent clinical behaviour that prognostic groupings of individual diagnostic entities can be established.

Experience tells us that inaccurate terminology may lead to inappropriate management. In the 1972 WHO classification (Thackray and Sobin, 1972) two carcinomas were termed tumours, mucoepidermoid *tumour* and acinic cell *tumour*. Both were known to have the potential to metastasize, but debate at the time made their true nature uncertain. Hence *tumour* was used, with the result that clinicians may have regarded these lesions as benign. Similarly the term *monomorphic adenoma* was a term used to lump all, apparently benign, lesions that were morphologically homogeneous. In fact it became a diagnostic term for a wide range of lesions that did not meet the criteria for pleomorphic adenoma and included clearly monomorphic entities such as basal cell adenoma but also Warthin's tumour, which is not monomorphic. Worse, this imprecise term implied that all monomorphic lesions were adenomas making it easy to overlook or misclassify monomorphic malignancies such as some adenoid cystic carcinomas, basal cell adenocarcinoma and clear cell carcinoma. A further example of the advantages of precise terminology is the *polymorphous low grade adenocarcinoma*. This lesion was first fully characterized in 1984 (Evans and Batsakis, 1984), but prior to that it must have been diagnosed as another entity, most probably as adenoid cystic carcinoma, or pleomorphic adenoma. Clearly there are implications for the inappropriate management of some patients before the entity was recognized, but the inclusion of this lesion into published series of adenoid cystic carcinomas will have distorted our views on the clinicopathological features and behaviour of this neoplasm.

With few exceptions, the terminologies used in the classifications do not give an indication of tumour grade or behaviour, although an earlier AFIP classification did divide all malignant tumours into low, medium and high grade (Ellis and Auclair, 1991a). Clinicians, in particular, find this useful, but the main disadvantage is that some tumours (for example mucoepidermoid carcinoma, adenoid cystic carcinoma) find themselves in more than one category. Pathologists may also find it difficult to place an individual tumour into a specific grouping and are often concerned that the categories may be used too

rigidly as tumour behaviour may be unpredictable and giving a lesion a label of 'low grade' might result in inappropriately conservative management of a malignancy that still retains the potential to metastasize (see discussion of polymorphous low grade adenocarcinoma below). Recently the issue has been further confused by the inclusion of both 'low' and 'intermediate' grade mucoepidermoid carcinoma into the low grade category (Cheuk and Chan, 2000). This issue will be discussed in more detail later in this review. Overall therefore the current classifications, with an emphasis on listing morphological types of tumour, may be complex, and may not always help the clinician in planning treatment. They are however, essential for providing an accurate diagnosis, for the reporting of case series and for the further development of management strategies.

There are a number of published studies describing the distribution of salivary gland tumours by site and diagnosis (Spiro *et al*, 1973; Eveson and Cawson, 1985; Spiro, 1986; Auclair *et al*, 1991; Renehan *et al*, 1996a) and these will not be analysed in detail. It should be noted that there are quite significant differences between these series, probably because of their different backgrounds. Some (Spiro, 1986) are derived from specialist surgical units while others (Eveson and Cawson, 1985; Auclair *et al*, 1991) are based on data from specialist pathology units and may include difficult, referred cases. However, the largest and most detailed series is that derived from the files of the AFIP presented first in 1991 (Auclair *et al*, 1991) and updated in the latest Fascicle (Ellis and Auclair, 1996).

The most common salivary gland tumour is the *pleomorphic adenoma* which comprises about half of all tumours and 65% of parotid gland tumours. It is also the most common minor gland lesion representing 40% of intraoral tumours and about 50% of those on the palate. The parotid gland is the single most common site for any salivary neoplasm, with about 70% of all tumours arising at this site of which about 85% are benign. It is important to recognize that the frequency of benign lesions varies by site. About 60% of submandibular, 50% of minor gland and only 10% of sublingual lesions are benign. Furthermore, at some sites benign lesions are very rare. In the tongue and retromolar area virtually 100% of salivary neoplasms are malignant. In the lips, most tumours (70%) are benign and *basal cell* and *canalicular adenomas* are particularly frequent at this site. It should be noted that most labial salivary tumours are in the upper lip. Neoplasms in the lower lip are relatively rare and salivary lesions at this site are usually simple mucoceles.

The most common malignant salivary gland tumour is the mucoepidermoid carcinoma, which comprises about 10% of all tumours and 35% of malignant tumours. In the AFIP series, adenocarcinoma NOS (not otherwise specified) is the second most common malignancy followed by acinic cell carcinoma which had an incidence of 17%. However, this is higher than other reported series, which show an incidence of 4–10% with adenoid cystic carcinoma as the second most common malignant tumour with an incidence of about 20%. This

discrepancy is probably because acinic cell carcinoma is a difficult diagnosis and thus constitutes a high proportion of lesions referred to the AFIP for consultation.

In the minor salivary glands, reports suggest that polymorphous low grade adenocarcinoma, which is becoming increasingly recognized, is a common malignancy. Waldron, El-Moftly and Gnepp (1988) found that 26% of minor salivary gland tumours were polymorphous low grade adenocarcinomas, and in an African population, Van Heerden and Raubenheimer (1991) found it to be the most common intraoral salivary gland malignancy.

Approaches to the diagnosis of salivary gland tumours

Salivary tumours are a particular challenge to the diagnostic pathologist. This is mainly because of the complexity of the classification and the rarity of many of the entities, which may show a broad spectrum of morphological diversity. 'Pattern matching' using an atlas or even past experience can seem to be a worthwhile and rewarding exercise as many tumours have aesthetically pleasing patterns which, to the unwary, may appear to be characteristic or even diagnostic. However, this is a futile and very risky exercise because many different lesions may share common patterns. Furthermore, hybrid lesions may be seen (Seifert and Donath, 1996), and morphological diversity in individual lesions is so common as to be a characteristic feature of salivary tumours in general. Typical examples include adenoid cystic carcinoma, polymorphous low grade adenocarcinoma and pleomorphic adenoma which can show such variable and similar features as to make a diagnosis on a small biopsy impossible. A diagnosis based on haematoxylin and eosin stained sections remains the gold standard in salivary gland pathology, but some recent developments in immunocytochemistry have been helpful and have a number of specific applications (see below).

These problems are further compounded by the difficulty that may be encountered in differentiating benign from malignant. Many salivary carcinomas are cytologically bland with little evidence of the mitotic activity or cellular pleomorphism, which are often the clue to malignancy at other sites. The key determining factor in establishing the malignant nature of a salivary gland tumour is the demonstration of an infiltrative margin. These problems are compounded by the frequent use of small incisional biopsies to obtain a preoperative diagnosis, but in small biopsies it may not be possible to give a precise diagnosis. Some of these problems will be highlighted below.

Areas of controversy and diagnostic difficulties

Pleomorphic adenoma

Pleomorphic adenoma is the most frequently encountered and best described of the salivary gland tumours. The lesion shows a number of characteristic features (Table 1) that in most cases enable a diagnosis to be made. However, the characteristic heterogeneity of the morphological patterns may also cause confusion and difficulty particularly in small incisional biopsies. Areas of pleomorphic adenoma may resemble or be identical to a range of other tumour types including polymorphous low grade adenocarcinoma, adenoid cystic carcinoma, basal cell adenoma and epithelial-myoepithelial carcinoma. In addition pleomorphic adenomas may contain areas, or show metaplastic changes which resemble other tumour types (Dardick, 1996). (Table 2). For the unwary pathologist these may lead to a misdiagnosis. Particular care is needed when examining incisional biopsies from the palate, which is a site at which any of these tumours could arise. The pathologist must consider the site and the clinical history, but in some cases the characteristic morphological diversity of the lesion may only become apparent when the lesion has been excised and examined in its entirety.

Carcinoma in pleomorphic adenoma (malignant mixed tumour)

Malignant mixed tumours represented 2.2% of all salivary tumours and 6.5% of malignant tumours in the AFIP series. Gnepp and Wenig (1991) calculated the average incidence from 58 reported series to be 3.6% of all tumours and 11.7% of malignancies, with a range from 2.8 to 42.4%. Although debated in the older

Table 1 Characteristic features of pleomorphic adenoma

Feature	Comments
Morphological diversity	Variable appearance of the epithelium with ductal structures, sheets and islands of cells
Stromal changes	The stroma is typically eosinophilic and hyalinized but also shows myxoid, mucoid or chondroid change
Bilayered ducts with clear outer cells	The outer cells are myoepithelial cells
'Melting' of myoepithelial cells from the ducts into the stroma	Single myoepithelial cells become engulfed in the stroma
Lobular pattern	The tumour has an irregular lobular margin resulting often in the appearance of pseudoinvasion of the capsule.
Plasmacytoid or hyalinized cells	Altered myoepithelial cells, reported to be characteristic of more solid palatal lesions (Lomax-Smith and Azzopardi, 1978)

Table 2 Cellular features and metaplastic changes in pleomorphic adenoma

Feature	Resemblance
Morphological diversity	Polymorphous adenocarcinioma
Bilayered ducts and cribriform pattern	Adenoid cystic carcinoma
Bilayered ducts with clear outer cells	Epithelial-myoepithelial carcinoma
Sheets of epithelioid or basaloid cells	Basal cell adenoma or adenocarcinoma
Myxoid stroma	Myxoma, neural tumours
Chondroid stroma	Chondrosarcoma
Plasmacytoid cells	Plasmacytoma
Spindled myoepithelial cells	Sarcoma or soft tissue tumour
Squamous metaplasia	Squamous carcinoma
Oncocytic metaplasia	Oncocytoma

literature, carcinoma in pleomorphic adenoma is now an accepted entity and it is recognized that there is a progression of benign to malignant change in pleomorphic adenoma (Eveson and Yeudall, 2001). This is supported by both clinical and histological evidence. Carcinomas in pleomorphic adenoma arise in an older age group than benign lesions and are usually larger and longer standing lesions. The average age of presentation in the AFIP series was 60 years compared with 47 years for benign lesions, with corresponding figures from a UK series of 63 and 46 years (Eveson and Cawson, 1985). Auclair and Ellis (1996) reported that malignant tumours were twice the size (4.5 cm) of their benign counterparts and had been present for an average of 76.5 months, which was almost twice the duration of benign lesions. They were also more frequently encountered in the submandibular gland. Histologically, the primary criterion for diagnosis is the presence of carcinoma in an otherwise benign and typical pleomorphic adenoma. However, in practice, the residual benign lesion may be focal and difficult to find, or may have been completely overtaken by the malignant component. The diagnosis may not therefore always be apparent. Clues to the diagnosis of carcinoma in pleomorphic adenoma may come primarily from the clinical history of a large longstanding lesion, with evidence of recurrence or a previous lesion. Histological evidence that a carcinoma may have arisen in a pleomorphic adenoma includes areas of hyalinization of the stroma with focal calcifications, and of morphological diversity in the type of carcinoma (Eveson, 2001b).

The overall malignant change rate in pleomorphic adenoma has been estimated at about 6% (Gnepp, 1993) but there are at present no histological features that are predictive of which benign lesions may transform. Features suggested as predictive include cytological atypia, increased mitoses, invasion of the capsule, hypercellularity, hyalinization or scarring and focal calcifications. However some of these features, including atypia, mitoses and capsular invasion, are commonly seen in typical benign pleomorphic adenomas (Waldron, 1991; Eveson, 2001b) and some pleomorphic adenomas, especially on the palate, may be hypercellular. In an analysis by Auclair and Ellis (1996) none of these features were predictive of malignant change. Indeed cytological atypia was more often seen in lesions that did not progress. The only feature which showed any evidence of being predictive was the presence of a hyalinized stroma and of focal calcifications. However, the authors point out that any pleomorphic adenoma may progress and that all lesions should be managed accordingly.

In some lesions, foci of carcinoma or of dysplasia may be seen which are confined within the capsule. Such lesions are termed *non-invasive carcinoma*, or *intracapsular* or *in situ carcinoma*. Provided that the capsule has not been breached these lesions have the same prognosis as benign pleomorphic adenoma. The presence of dysplasia, however, supports the concept of progression and of a spectrum of change from benign to malignant. Brandwein *et al* (1996) have shown that 70% of dysplastic lesions have an aneuploid DNA content suggesting that they are histologically distinct from benign lesions. Eveson and Yeudal (2001) reviewed the molecular evidence and suggested a progression model for benign to malignant change involving loss of heterozygosity (LOH) at multiple chromosomal locations, activation of the *PLAG1* gene and mutations in *c-myc*, *p21* and *p53*.

A further area of controversy is the role that recurrence may play in the aetiology of carcinoma in pleomorphic adenoma. Clearly if a malignant lesion arises at a site of a previous benign pleomorphic adenoma, then it is associated with recurrence. However, some reports have suggested that repeated recurrence and the associated surgical interference might be a factor in progression. Overall however, malignant transformation in recurrent disease is rare, and there is no evidence that recurrent pleomorphic adenomas should be regarded as inherently more malignant or potentially malignant (Myssiorek, Ruah and Hybels, 1990). In a large series of recurrent pleomorphic adenomas (Renehan, Gleave and McGurk, 1996b) there were no cases of malignant transformation in patients with one recurrence only. In three patients with three or more recurrences, malignant change was seen, but all three had received postoperative radiotherapy. This suggests that radiotherapy may be a risk factor for malignant change. Radiotherapy is only used to manage gross tumour spillage, or multifocal recurrent disease (Slevin and Natvig, 2001), but in large series the

incidence of malignant change in such lesions has been less than 2% (Watkin and Hobsley, 1986; Renehan *et al*, 1996b; Renehan, 2001). A further argument against the role of recurrence and repeated surgical intervention as a factor in malignant transformation is that while recurrence rates have dropped dramatically from 40 to 50% 70 years ago, to less than 2% today (Langdon, 2001) there is no evidence of a reduction in the incidence of carcinoma in pleomorphic adenoma. This supports the view that some pleomorphic adenomas may be inherently potentially malignant from the outset (Brandwein *et al*, 1996; Eveson and Yeudall, 2001).

Management of pleomorphic adenoma
Recently there have been significant changes in the surgical management of pleomorphic adenoma. Enucleation, with associated recurrence rates of over 40% (Langdon, 2001), is clearly a thing of the past and totally inappropriate. The treatment of choice has become partial or formal superficial parotidectomy (Snow, 2001), which has resulted in low morbidity and recurrence rates as low as 0% (Leverstein *et al*, 1997). However, even using this technique the surgical specimen is not fully surrounded by normal gland and exposed tumour capsule is usually encountered on the deep aspect where tumour has been dissected from the facial nerve (Lam *et al*, 1990). Provided this capsule is intact, tumour does not recur. This observation led to the development of *extracapsular dissection* as a treatment (Gleave, 1995). In this approach, the tumour and its capsule are carefully dissected from the adjacent parotid gland. This more conservative approach is associated with low rates of morbidity (facial nerve damage and Frey's syndrome) and shows recurrence rates of 2% (McGurk *et al*, 1996; Hancock, 1999).

An important element of this surgery is the histopathological examination of the specimen. Histologically the pathologist will not see an 'adequate' surround of normal tissue, but this should not be interpreted as inadequate excision or 'close' margins. Furthermore, shrinkage during fixation, and retraction of the capsule during specimen dissection may result in no capsule being visible microscopically – leading again to potential misreporting as 'incompletely excised'. The key element to diagnosis in these cases is that the specimen should be delivered intact to the pathologist, surgeons must resist the temptation of bisecting the tumour to examine the cut surface. If there has been accidental surgical rupture, this should be noted and the pathologist informed. The pathologist can then undertake an examination of the whole specimen before it is dissected to confirm that the capsule is macroscopically intact. If there is any doubt, then the surgeon should be consulted.

Polymorphous low grade adenocarcinoma
Polymorphous low grade adenocarcinoma is a relatively recently described tumour that remains controversial because it is often misunderstood and because it is difficult to diagnose and has an unpredictable beha-

viour. It was first described simultaneously as terminal duct carcinoma (Batsakis *et al*, 1983) and lobular carcinoma (Freedman and Lumerman, 1983), names that alluded to its putative origin in intercalated (terminal) ducts and to its microscopic similarity to lobular carcinoma of the breast. Subsequently Evans and Batsakis (1984) coined the term polymorphous low grade adenocarcinoma which describes its variable morphological appearances and apparent low grade behaviour.

Polymorphous low grade adenocarcinoma is almost exclusively a tumour of minor salivary glands with about 60% arising in the palate, up to 20% in the cheek and about 12% in the upper lip (Ellis and Auclair, 1996). Occasional cases have been described in the parotid gland, but only in the context of carcinoma in pleomorphic adenoma. In the AFIP series polymorphous low grade adenocarcinoma represents about 7% of minor salivary gland tumours and 20% of those that are malignant. They suggest that it is twice as common as adenoid cystic carcinoma in the minor glands and may be the third most common of all salivary tumours after pleomorphic adenoma and mucoepidermoid carcinoma (Ellis and Auclair, 1996).

Diagnosis is usually quite straightforward on an excised specimen. The tumour shows an infiltrative growth pattern, morphological diversity and a striking cytological uniformity with a bland nuclear morphology and a uniform pale 'washed out' appearance giving the impression that the section has been inadequately stained (Wenig and Gnepp, 1991; Castle *et al*, 1999). The characteristic patterns include lobules or sheets of uniform epithelial cells, tubules and duct-like structures and islands with a microcystic or cribriform pattern. Seen in their entirety, this diversity may establish the diagnosis, but in small incisional biopsies, where only a single pattern may be apparent, the lesion can easily be mistaken for a pleomorphic adenoma, adenoid cystic carcinoma or a basal cell lesion. Its propensity for the palate and indolent clinical features make confusion with pleomorphic adenoma or adenoid cystic carcinoma even more likely. Polymorphous low grade adenocarcinoma also shares the feature of perineural infiltration with adenoid cystic carcinoma. Examination of the margins of the lesion is a useful aid to diagnosis. The tumour has a characteristic pattern with columns and rows of single cells infiltrating adjacent tissues and salivary gland, and extending up to the overlying epithelium. At low power the appearance is of swirling lobules and columns of tumour enveloping adjacent structures.

Some tumours show a papillary cystic pattern, which may be focal or extensive. Wenig and Gnepp (1991) consider that lesions with a predominant papillary cystic pattern should be classified separately under the category of *papillary cystadenocarcinoma* and that this should include *low grade papillary adenocarcinoma* (Mills, Garland and Allen, 1985). This distinction is made on the basis that predominantly papillary lesions are more aggressive in their behaviour (Slootweg and Muller, 1987). The AFIP accept this distinction in the

latest Fascicle (Ellis and Auclair, 1996). Nevertheless it is accepted that focal areas with a papillary cystic pattern may be seen in many polymorphous low grade adenocarcinomas (Wenig and Gnepp, 1991). In a recent series Evans and Luna (2000) showed 'more than focal' papillary areas in 17 of 40 cases (43%) and described focal areas in some of the remaining 23 cases. Although they do not define 'more than focal', they state, and their illustrations show, that tumours otherwise showed the morphological diversity typical of polymorphous low grade adenocarcinoma. Overall, of the 40 cases, 13 had local recurrence, six had cervical lymph node metastases, three had distant metastases and five patients died of disease. Patients with a papillary lesion showed a greater chance of cervical metastases (6/17) but not of distant metastases. Local recurrence was associated with incompleteness of excision and final outcome was similar in both groups. These findings illustrate two important points. First, that although papillary areas may be associated with metastases, the overall behaviour of this lesion is unpredicatable. Secondly, that polymorphous low grade adenocarcinoma is not always a low grade lesion - 15% had cervical metastases, 7.5% had distant metastases and 12.5% died of disease. These figures are at odds with the findings of Wenig and Gnepp (1991) who record a rate of cervical metastasis of 6% and state that distant metastases and death are not attributed to polymorphous low grade adenocarcinomas. The experience of Evans and Luna probably represents a more contemporary experience with this tumour and agrees with our experience that this lesion has an unpredictable behaviour. Occasional cases infiltrate aggressively with widespread destruction of maxillary bone and early regional metastases.

Overall therefore, although the lesion is moderately indolent, the term 'low grade' may lead to misunderstanding and inappropriately conservative management. There is no good reason why this tumour, whose behaviour is unpredictable, should be the only salivary gland tumour with a statement of grade in its name. We now believe that the term *polymorphous adenocarcinoma* is more appropriate for this tumour, and suggest that management should be as for other salivary carcinomas, with wide surgical excision and postoperative radiotherapy for large lesions or where the margins are in doubt (Slevin and Frankenthaler, 2001)

Clear cell tumours

Many types of salivary gland tumour may show focal areas of clear cell change but this rarely hampers the correct diagnosis. Occasionally however, clear cells may predominate making a precise diagnosis difficult (Eveson, 1992). The clarity of the cells is either because of accumulation of a product that does not stain with haematoxylin and eosin, or to processing artifact with shrinkage of cell contents. Non-staining products include mucus, lipids and glycogen, but in the salivary glands most clear cells are either empty or contain glycogen. In general, all clear cell tumours are malignant, but there are important exceptions, which must be identified.

Clear cell carcinoma is the only salivary gland tumour that, by definition, is composed entirely of clear cells (Simpson *et al*, 1990; Ellis and Auclair, 1991b). It does not feature in the WHO classification, but is included as an intermediate grade carcinoma in the original AFIP classification (Ellis and Auclair, 1991a) and as clear cell adenocarcinoma in the latest Fascicle (Ellis and Auclair, 1996). It is rare, comprising less than 2% of salivary tumours, and has a slight predominance for the minor glands (60%), with the parotid and palate being the most frequent sites overall. It is composed of sheets or nests of clear cells which contain glycogen. However, diastase-resistant periodic acid Schiff (PAS) positivity may not always be uniformly apparent because glycogen is not well preserved in routinely fixed tissues and many clear cells may be negative. Mucus production is not seen. In some cases dense hyalinized bands of collagenous connective tissue separate the clear cells (Ellis and Auclair, 1991b), giving a distinctive appearance which was later reported as a 'new' tumour type called *hyalinizing clear cell carcinoma* (Milchgrub *et al*, 1994).

Other tumours, especially acinic cell and mucopidermoid carcinomas, may contain focal areas of clear cells or may show extensive clear cell change to the extent that the true nature of the tumour is difficult to determine. It needs to be emphasized therefore that a diagnosis of clear cell carcinoma cannot be made on a small incisional biopsy and that it is essentially a diagnosis by exclusion (Eveson, 1992; Ellis, 1998). One needs to make a careful search of the whole tumour and carry out appropriate special stains to exclude other lesions (Table 3). *Mucoepidermoid carcinoma* is rarely predominantly clear and typical mucous cells and

Table 3 Characteristics of clear cells in tumours in which clear cells may predominate

	Glycogen	Mucus	Other features
Clear cell carcinoma	Yes	No	High mol wt cytokeratin-positive
Mucoepidermoid carcinoma	Yes	Yes	Mucous and epidermoid cells
Acinic cell carcinoma	No	No	Acinar differentiation, intercalated duct cells
Oncocytoma	Yes	No	PTAH-positive, rare in minor glands, multifocal
Epithelial-myoepithelial carcinoma	Yes	No	Cuboidal eosinophilic luminal cells, clear cells are calponin & S100-positive
Renal cell carcinoma	Yes	Never	Prominent vascular pattern, RCC antigen-positive, high mol wt cytokeratin-negative

epidermoid cells are usually easy to find. The clear cells in mucoepidermoid carcinoma may contain glycogen but some cells also contain mucus - a feature not seen in clear cell carcinoma. *Acinic cell carcinoma* may, on occasions, be extensively clear, but typical acinar differentiation and areas of intercalated duct cells can usually be found. In this case, cells may be amylase positive or contain PAS positive granules. The clear cells however, usually do not contain glycogen or mucus.

Epithelial-myoepithelial carcinoma is characterized by the presence of clear cells, but it is a biphasic tumour, composed of cuboidal luminal cells surrounded by clear albuminal cells, which are thought to be myoepithelial cells. Many examples of epithelial-myoepithelial carcinoma show areas entirely composed of clear cells and in occasional examples the biphasic pattern may be inconspicuous. The clear cells may contain glycogen and are also S100, actin and calponin positive suggesting that they are myoepithelial cells. Interestingly, the albuminal myoepithelial cells of a number of tumours are often clear; including pleomorphic adenoma and adenoid cystic carcinoma, but clear cell change is not a common feature of myoepithelioma.

The major exception to the malignant nature of clear cell tumours is *oncocytoma* or *multifocal oncocytic hyperplasia* both of which often contain glycogen-rich clear cells but may occasionally be composed entirely of clear cells (Ellis, 1988; Palmer *et al*, 1990). In these cases the diagnosis must be confirmed by searching for typical granular eosinophilic oncocytes, which may also be positive with the phosphotungstic acid haematoxylin (PTAH) stain. Oncocytomas are usually well-demarcated tumours and a characteristic feature is that they may be multifocal. *Sebaceous adenomas* (and carcinomas) are rare, but may also contain clear cells. In these lesions the cells do not contain glycogen but are usually foamy and contain lipids which can be demonstrated with fat stains on frozen sections.

A further major consideration in the diagnosis of clear cell tumours is to exclude the possibility of a metastasis. In particular, metastatic renal cell carcinoma is typically composed of sheets or islands of clear cells, which are glycogen-rich, but always negative for mucus. Renal cell carcinomas often have a prominent vascular pattern and may be positive for the renal cell carcinoma-associated (RCC) antigen by immunocytochemistry. Also, unlike salivary carcinomas, they do not express high molecular weight keratins. On occasions, if it is not possible to confirm a salivary origin for a clear cell neoplasm, then clinical investigation to exclude a primary renal carcinoma may be justified.

Immunohistochemistry

Because many types of salivary gland tumours share microscopic appearances, and others may show a range of appearances, a characteristic immunophenotype for a given salivary gland tumour would be of great help, especially in small biopsies. The numerous studies that have been undertaken have mainly concentrated on the cytokeratins, S100, actins (and components such as calponin), epithelial membrane antigen, vimentin and carcinoembryonic antigen. Unfortunately, none of these markers has proved specific or consistent enough to be reliably used in a diagnostic context. Indeed Cheuk and Chan (2000) describe the immunophenotypes of salivary gland tumours as 'disappointingly anarchic'. Nevertheless, there is now some evidence to suggest that expression of the product of the *c-kit* proto-oncogene (CD117) and glial fibrillary acidic protein (GFAP) might help in distinguishing three of the commonest salivary gland tumours which also share morphological features, namely pleomorphic adenoma, polymorphous adenocarcinoma and adenoid cystic carcinoma. CD117 mutations have been reported in several neoplasms of different ontogeny. However, amongst salivary gland tumours adenoid cystic carcinoma was positive in 47 of the 55 (85.5%) cases stained (Holst *et al*, 1999; Jeng, Lin and Hsu, 2000). Only four polymorphous adenocarcinomas have been tested, all of which were CD117-negative (Jeng *et al*, 2000). The latter tumour also lacks expression of GFAP which, by contrast, is strongly positive in pleomorphic adenoma (Curran *et al*, 2001). Thus, in a small biopsy where the diagnosis lies between adenoid cystic carcinoma and polymorphous adenocarcinoma, or between polymorphous adenocarcinoma and pleomorphic adenoma, immunohistochemistry for CD117 and GFAP might provide some additional guidance. Clearly, however, there is as yet insufficient data to categorically depend on these phenotypes for diagnosis. GFAP will not, of course, distinguish a pleomorphic adenoma from carcinoma-ex-pleomorphic adenoma, nor does staining for proliferation markers such as Ki-67 have any benefit in distinguishing benign from malignant tumours (Lazzaro and Cleveland, 2000), although pleomorphic adenoma and carcinoma-ex-pleomorphic adenoma have yet to be directly compared in this respect.

Grade, stage and prognosis

In earlier classifications, the AFIP divided all malignant salivary tumours into three grades, low, intermediate and high (Ellis and Auclair, 1991a), but this distinction did not appear in the latest Fascicle (Ellis and Auclair, 1996). Clinicians generally support such a scheme because it provides a useful reference point as a guide to management of individual lesions. The grouping of tumours into various prognostic categories was driven by pathologists who carefully classified the tumour types and built up archives of lesions that could be called upon for correlation to clinical outcomes (McGurk, 2001). Thus clinical experience has enabled us to categorize, for example, papillary adenocarcinomas as low grade and salivary duct carcinoma as high grade. Such information is valuable as it may assist the oncologist in planning treatment. It does not, however, require a rigid system and pathologists in particular are reluctant to rigidly categorize lesions where the behaviour may be unpredictable. The problem is compounded by lack of agreement as to where tumours should be placed. Cheuk and Chan (2000), for example,

categorize 'intermediate grade mucoepidermoid carcinoma' as a low grade tumour, and Renehan *et al* (1999) grade all adenoid cystic carcinomas as intermediate grade. A further problem is that some lesions appear in all three categories, although in these cases, there is quite good evidence that a histological grading scheme is of some value. Squamous cell carcinoma and adenocarcinoma NOS are graded in a similar way to extra-salivary lesions according to degree of tumour differentiation, but in other tumours, grading may be more complex. The AFIP and WHO classifications concur that grading may be of value in some cases but WHO only explicitly suggests grading mucoepidermoid carcinoma, and only gives two grades without detailed guidelines (Seifert and Sobin, 1991). They point out that the grades are part of a spectrum of features and 'have no absolute significance in individual cases'. Apart from adenocarcinoma NOS, the AFIP suggests grading schemes for mucoepidermoid carcinoma and adenoid cystic carcinoma.

In the case of mucoepidermoid carcinoma, there is good evidence that grading has prognostic significance. Grading is based loosely on the prevalence of cell types and cystic areas and on features of aggressiveness or cytological atypia, but has mostly been subjective. More recently, based on the AFIP experience, Goode, Auclair and Ellis (1998) described a more objective scheme based on numerical scores given to histological features (Table 4). Brandwein *et al* (2001) have modified this scheme to give greater weight to features of invasion. They examined the interobserver error of the two schemes and showed that the AFIP scheme tended to downgrade tumours, perhaps explaining reported cases of aggressive behaviour in low grade lesions. Brandwein *et al* (2001) claimed that their grading scheme is more sensitive in delineating tumours into more realistic behavioural groups. In the AFIP series 5% of patients with grade 1 lesions in the major glands metastasized or caused death (Goode *et al*, 1998), but with the new grading scheme Brandwein *et al* (2001) found that all grade 1 tumours were also stage I and that none metastasized. Also, all patients with grade 1 lesions were

disease free at 10 years, compared with about 70% with grade 2 lesions and less than 40% with grade 3. In this study however, stage was also found to be important. Over 90% of patients with stage I or II tumours were disease free at 10 years compared with less than 30% with stage III or IV disease (Brandwein *et al*, 2001). The authors point out, that although grade is useful, stage does seem to be a better indicator of prognosis, a view also emphasized in the AFIP Fascicle (Ellis and Auclair, 1996).

Grading of adenoid cystic carcinoma is generally quite straightforward as it depends primarily on the morphological pattern of the tumour. Three patterns are recognized: *cribriform*, *tubular* and *solid*, and tumours are categorized according to the predominant pattern (Batsakis, Luna and el-Naggar, 1990; Tomich, 1991). The cribriform or Swiss-cheese pattern is the most characteristic and most common pattern, comprising 43.5% of all lesions with the tubular pattern in about 35% and solid in 21% (Perzin, Gullane and Clairmont, 1978). Most authorities agree that the solid adenoid cystic carcinoma is a high grade lesion with reported recurrence rates of up to 100% compared with 50-80% for the tubular and cribriform variants (Tomich, 1991). In some reports, no patients with the solid variant survived 10 years (Nascimento *et al*, 1986).

Reports vary as to the behaviour of tubular and cribriform lesions. Perzin *et al* (1978) reported the tubular type to have the best outcome with regard to recurrence and survival, but others found the cribriform pattern to be the most favourable (Nascimento *et al*, 1986). The AFIP categorize solid adenoid cystic carcinoma as high grade and both tubular and cribriform types as intermediate grade (Ellis and Auclair, 1991a). At the Memorial Sloan Kettering Cancer Centre adenoid cystic carcinomas are graded according to the proportion of solid areas (Spiro, 2001a). Predominantly solid lesions are grade 3 (high grade). Predominantly cribriform or tubular lesions are grade 1 (low grade) and lesions with equal solid and cribriform/tubular areas are intermediate.

Unfortunately, regardless of grade or pattern, all adenoid cystic carcinomas have a protracted course and ultimately a poor outcome. Using the Memorial Sloan Kettering scheme, grade 1 and 2 lesions show similar outcomes at 5 years (approximately 85% survival) but at 10 years all grades do equally badly with overall survival of less than 50% (Spiro, 2001a). Most adenoid cystic carcinomas are widely infiltrative at diagnosis with early bone involvement. Although perineural infiltration is seen in over 50% of cases, it does not appear to be an independent factor in prognosis, rather being associated with solid, large or aggressive lesions (Barrett and Speight, 2001). Adenoid cystic carcinomas typically show frequent recurrences and late distant metastases. Overall, between 35 and 50% of lesions show distant metastases, usually to lung or bone, compared with only 10% with regional lymph node metastases (Matsuba *et al*, 1986; Spiro, 1997). This factor and an unusually slow biological growth result in a relatively favourable 5-year survival, but poor longer

Table 4 Grading schemes for mucoepidermoid carcinoma

Histological feature	Score	
	AFIP (Goode et al, 1998)	Brandwein et al (2001)
Cystic component < 25%	2	2
Neural invasion	3	3
Necrosis	3	3
Mitoses > 4/10 hpf	3	3
Anaplasia (nuclear atypia)	4	2
Invasion in small nests and islands	NI	2
Lymphatic or vascular invasion	NI	3
Bone invasion	NI	3
Grade I (low grade)	0–4	0
Grade II (intermediate grade)	5–6	2–3
Grade III (high grade)	7–14	4 or more

NI – features not included in the AFIP scheme.

term outcome. Typical figures include reports of 5 and 10 years survival of 62.4 and 38.9% (Hickman, Cawson and Duffy, 1984), 88.2 and 42.5% (Conley and Dingman, 1974) and 79 and 54% (Spiro, 2001a), respectively. Twenty year survival has been reported to be as low as 20% (Conley and Dingman, 1974) and Nascimento *et al* (1986) reported 0% survival at 10 years for patients with high grade lesions.

Although grade is important in guiding oncologists as to the possible biological behaviour of a tumour, it cannot be considered in isolation from clinical factors and therefore *stage* cannot be ignored. The most significant work on this topic comes from the experiences and resources of the Memorial Sloan Kettering Cancer Centre (reviewed in Spiro, 2001b) which shows that clinical stage, particularly tumour size, is the critical factor in determining the outcome of salivary gland cancer, and is more important than histological grade. For a detailed consideration of this issue, readers are referred to his considerable literature on this topic (Spiro, 1986; Armstrong *et al*, 1990; Spiro *et al*, 1991; Spiro and Huvos, 1992; Spiro, 2001a,b). Essentially, a stage III or IV tumour is not likely to do well, regardless of grade. In one study of mucoepidermoid carcinomas and minor gland adenocarcinomas (Armstrong *et al*, 1990), it was shown that low grade lesions did well, but that high grade lesions did equally well if they were in stages I or II. The impact of high grade lesions on survival was only apparent if the lesions were also high stage (III and IV). In a similar study, it was later demonstrated that patients with small but high grade adenoid cystic carcinomas had a better prognosis than previously thought. (Spiro *et al*, 1991; Spiro and Huvos, 1992). In mucoepidermoid carcinomas Plambeck, Friedrich and Schmelzle (1996) showed that, although overall survival rates at 5 and 10 years were 91.9 and 89.5%, respectively, all the patients who died were stage III or IV and in this group the equivalent survival rates were 63.5 and 52%. Similar findings on a range of tumour types have been reported from a number of centres (O'Brien *et al*, 1986; Renehan *et al*, 1999; Spiro, 2001b).

A widely used but little reported guide to the management of salivary gland cancers is *the 4 cm rule*. Tumours that are less than 4 cm (T1 or T2) do well regardless of histological type or grade (McGurk, 2001).

Tumours less than 4 cm show better survival and less risk of loco-regional or distant metastasis (Table 5). It has also been shown that adjuvant radiotherapy has a distinct survival advantage for patients with tumours over 4 cm, but has little benefit for smaller tumours. (Armstrong *et al*, 1990; Frankenthaler *et al*, 1991; Renehan *et al*, 1999), suggesting that, along with positive margins, tumours over 4 cm are an absolute indication for postoperative radiotherapy (Slevin and Frankenthaler, 2001).

Summary and conclusions

Salivary gland neoplasms are a diverse and difficult group of tumours, which are best treated within specialist centres. Even the most common benign neoplasms – especially pleomorphic adenoma – need careful surgical management and follow-up. Because of the morphological diversity both between and within tumour types, the gold standard for diagnosis remains careful histological examination of an excised specimen. Diagnosis on small incisional biopsies may be impossible, especially in the case of clear cell tumours and in differentiating between polymorphous adenocarcinoma, pleomorphic adenoma and adenoid cystic carcinoma.

Although the current classifications for salivary gland tumours appear to be unnecessarily complex they are essential for pathologists to provide a precise diagnosis. Careful use of established terminology has allowed accurate reporting of case series and the prospective accumulation of prognostic information. Over time this has enabled tumour types to be grouped into grading categories, which act as a useful guide to behaviour. Grading of individual tumours, however, is difficult and has only been shown to be useful in adenocarcinoma NOS, mucoepidermoid carcinoma and adenoid cystic carcinoma. Polymorphous low grade adenocarcinoma, for example, is labelled as 'low grade', but its behaviour is unpredictable and recent experience shows that it does not do as well as other low grade lesions. There no longer seems to be any justification for this tumour to be the only salivary gland neoplasm with a statement of grade to be included in the name. This neoplasm should be renamed *polymorphous adenocarcinoma*.

Table 5 The 4 cm rule: evidence of improved outcome for tumours less than 4 cm

	Tumour size		
	< 4 cm	> 4 cm	Reference
5-year survival [a]	> 90%	< 40%	Renehen *et al* (1996a)
5-year survival	> 75%	< 40%	Spiro (1986)
Occult neck metastases	4%	20%	Armstrong *et al* (1992)
Occult neck metasases	8%	19%	Frankenthaler *et al* (1993)
Risk of distant metastases [b]		1.60	Gallo *et al* (1997); Gallo (2001)
Risk of distant metastases [b]		8.49	Renehan (2001)

[a]Analysis includes high grade tumours only
[b]Cox hazard ratios

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Overall, when considering prognosis, stage is probably more important than grade. The size of tumour at presentation is a strong predictor of prognosis and the *4 cm rule* has proved to be a useful clinical guide to behaviour and outcome.

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