Oral Oncol, Eur J Cancer, Vol. 28B, No. 1, pp. 49–56, 1992
Printed In Great Britain

0964–1955/92 $5.00+0.00
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Histopathology of Malignant Salivary Gland Tumours*

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This report is based upon the Salivary Gland Register in Hamburg and on the second revised edition of the WHO Histological Typing of Salivary Gland Tumours. The group of malignant salivary gland tumours contains carcinomas, malignant non-epithelial tumours, malignant lymphomas and secondary tumours. The various carcinomas are classified in a continuous separate listing because the different types are distinguished not only by histopathology, but also by differences in prognosis and treatment. The term "tumour" is replaced by "carcinoma" in two entities: acinic cell carcinoma and mucoepidermoid carcinoma. New entities are: polymorphous low-grade adenocarcinoma, basal cell adenocarcinoma, salivary duct carcinoma and malignant myoepithelioma. Carcinoma in pleomorphic adenoma can be distinguished as non-invasive and invasive carcinoma, and carcinosarcoma. Malignant non-epithelial tumours are mostly malignant fibrous histiocytoma, malignant schwannoma and rhabdomyosarcoma. The large majority of malignant lymphomas are non-Hodgkin-lymphomas with high differentiation. Many lymphomas are associated with chronic immunosialadenitis (Sjögren's syndrome). Secondary tumours are mostly metastases from primary squamous cell carcinomas or from melanomas of the skin (head and neck area). Haematogeneous metastases are very rare (mainly from lung, kidney or breast).
Oral Oncology, Eur J Cancer, Vol. 28B, No. 1, pp. 49–56, 1992.

INTRODUCTION

THIS REPORT is based upon the cases recorded in the Salivary Gland Register in Hamburg [1] and on the second revised edition of the WHO Histological Typing of Salivary Gland Tumours [2, 3].

Principles of the new classification are:

The different types of carcinomas are distinguished not only by precise histopathological definitions, but also by differences in prognosis and treatment. Therefore, a continuous separate listing of the various carcinomas is given. The term "tumour" is replaced by "carcinoma" in two entities: acinic cell carcinoma and mucoepidermoid carcinoma. All varieties of these carcinomas are potentially capable of metastasising, regardless of their macroscopic or histological appearance.

In daily routine work the value of immunocytochemistry [4] is limited with the exception of the following conditions: Amylase for the identification especially of the clear cell variant of acinic cell carcinoma; S-100 protein, actin, myosin or other muscle-specific antigens for the identification of myoepithelial cells; Subtypes of cytokeratin and leucocyte common antigen (LCA) for the differential diagnosis of undifferentiated carcinomas from malignant lymphomas; CEA and thyroglobulin for the differential diagnosis of primary salivary gland carcinoma and metastases of thyroid carcinoma.

Cytochemical assessment of DNA content by means of scanning cytophotometry can be helpful in the evaluation of some types of carcinoma. Mucoepidermoid carcinomas show a strong correlation between biological behaviour and type of histogram [5], tumours with a poor prognosis being identified by their atypical tetraploid histogram. For adenoid cystic carcinomas [6], diploid tumours have longer clinical courses than atypical aneuploid ones. In addition, the measurement of argyrophil nucleolar organiser regions shows significant differences between adenomas and carcinomas [7–9]. The mean value of an adenoma is 1.5, the mean value of a carcinoma 2–4.5 with a maximal value of 9.0.

In histopathology four groups of malignant salivary gland tumours can be distinguished: Carcinomas, malignant non-epithelial tumours, malignant lymphomas and secondary tumours.

CLASSIFICATION OF CARCINOMAS

Acinic cell carcinoma

Acinic cell carcinoma [10–12] has a wide spectrum of histopathological and cellular features. Most common are the solid and microcystic patterns, rarer are the follicular and papillary-cystic pattern. Cell types are mostly serous-acinar cells, more rarely, intercalated duct or vacuolated clear cells. Other characteristics are female predominance, local recurrence and rare metastases. Most of the tumours are localised in the parotid gland. The occurrence in the minor salivary glands was observed mostly in the palate and the upper lip (Table 1).

The solid type contains large numbers of well differentiated acinar cells and most closely resembles the normal parotid gland parenchyma (Fig. 1). Periodic acid-Schiff stain will highlight the cytoplasmic granules. One of the curious features

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*Lecture on the occasion of the Course "Diseases of the Salivary Glands. Diagnosis and Treatment" in Amsterdam, 26–27 November 1991.
Received 21 Jan. 1992; accepted 13 Feb. 1992.

Table 1. Characteristics of acinic cell carcinoma

Pattern
Solid (50%)
Microcystic (30%)
Follicular (15%)
Papillary-cystic (5%)
Cell types
Serous acinar (75%)
Intercalated duct (20%)
Vacuolated (5%)
Female predominance
Local recurrence (45%)
Metastases (20%)
Mostly parotid gland
Minor salivary glands: palate, upper lip

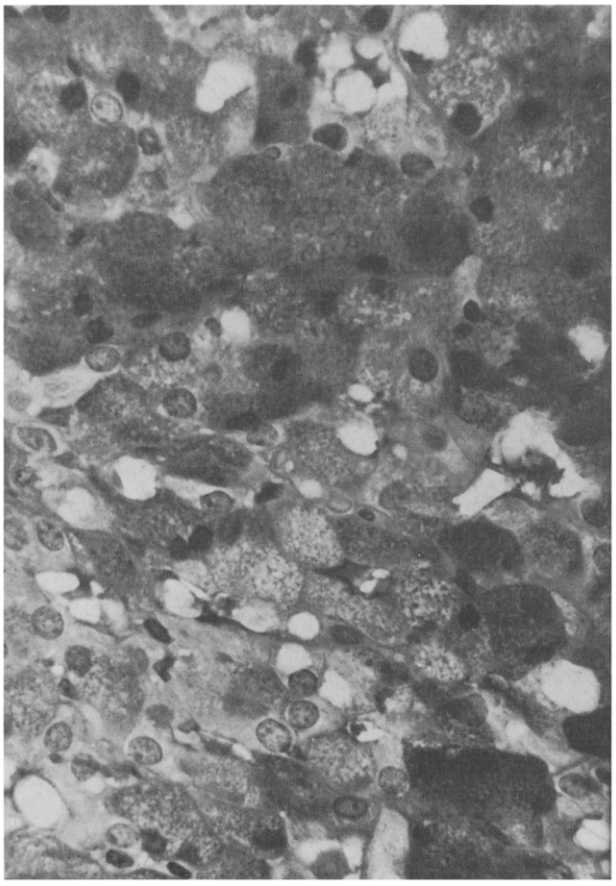

Fig. 1. Acinic cell carcinoma: well differentiated acinar cells with cytoplasmic granules similar to gland parenchyma. Haematoxylin–eosin. ×400.

of acinic cell carcinoma is the frequent association with a lymphoid infiltrate in the supporting stroma. The microcystic pattern shows numerous cystic spaces which are limited by acinar, intercalated duct-like and vacuolated cells. The follicular pattern has a thyroid-like appearance. The cystic spaces contain an eosinophilic material that simulates the appearance of colloid. Helpful for differential diagnosis is the positive reaction of amylase and the negative reaction of thyroglobulin.

The clear cell variant of acinic cell carcinoma can be distinguished from other carcinomas with clear cell predominance by the positive reaction of periodic acid-Schiff and amylase stain.

Acinic cell carcinomas are regarded as low-grade malignancies. As prognostic features gross invasion, desmoplasia, cellular atypia, increased mitotic activity, prominent necrosis and tubulo-ductal differentiation were proofed and discussed. But the results of many studies indicate that neither histological features nor special growth pattern seem to have an obvious value for the prognosis of a more favourable or worse clincal course. This is more dependent on local invasion and completeness of surgical removal.

Mucoepidermoid carcinoma

Mucoepidermoid carcinoma [13–16] contains three characteristic cell types: epidermoid cells, mucous-producing goblet-like cells and intermediate cells (Table 2). These cells form solid sheets, microcysts or macrocysts. In solid tumours epidermoid and intermediate cells usually predominate, whereas in mainly cystic tumours mucous cells tend to be more conspicuous. Special strains, such as periodic acid-Schiff reaction, Alcian blue or Astra blue are helpful in the diagnostic work, especially in the clear cell variant or in solid poorly differentiated tumours with sparse mucous cells. Mucoepidermoid carcinoma can be categorised into low- and high-grade malignancy.

The well-differentiated subtype consists of more than 50% mucous-producing cells. There is the typical biphasic cellular differentiation of epidermoid cells and cystic spaces which contain mucous production. In some areas the cystic spaces are surrounded by goblet-like cells with distinct mucous production (Fig. 2). The clear cell variant (Fig. 3) may be a problem for differential diagnosis, but the application of mucus stains, such as Astra blue is very helpful.

In the poorly-differentiated subtype mucous cells are rare, less than 10%. Intermediate and epidermoid cells are predominant. The detection of mucous-producing cells in some areas is important for the correct diagnosis (Fig. 4).

This classification provides groups with relatively good and poor prognosis, with respect to local recurrence and metastatic ability. The subtype of low-grade malignancy (Table 2) shows local recurrence in about 6%, a 5-year-survival of 95% and exceptionally rare metastases, whereas the subtype of high-grade malignancy has local recurrence in 80%, a 5-year-survival of only 30% and frequent metastases.

Prognostic factors for a favourable clinical course may be: adequate surgical procedures, broad pushing border, high differentiation, diploid DNA content and a value of argyrophil

Table 2. Characteristics of mucoepidermoid carcinoma

Cell types
Epidermoid
Mucus-producing (goblet-like)
Intermediate
Growth pattern
Solid sheets
Microcysts
Macrocysts
Subtypes
Well-differentiated (low-grade)
Poorly-differentiated (high-grade)
Grading
Recurrence: low grade 6%, high grade 80%
5-year survival: low grade 85%, high grade 30%
Metastasis: low grade rare, high grade frequent

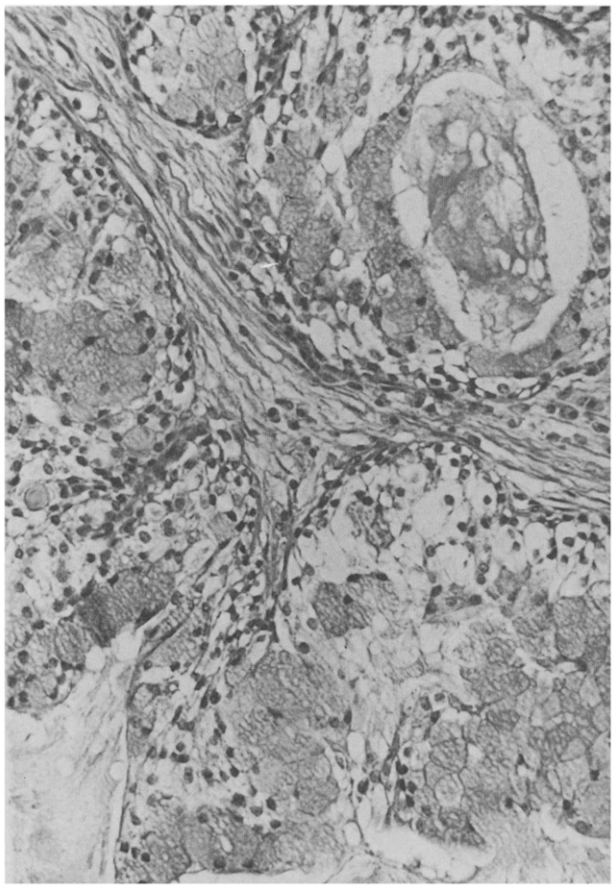

Fig. 2. Mucoepidermoid carcinoma: well-differentiated type with cystic spaces surrounded by goblet-like cells with mucous production. Astra blue. ×160.

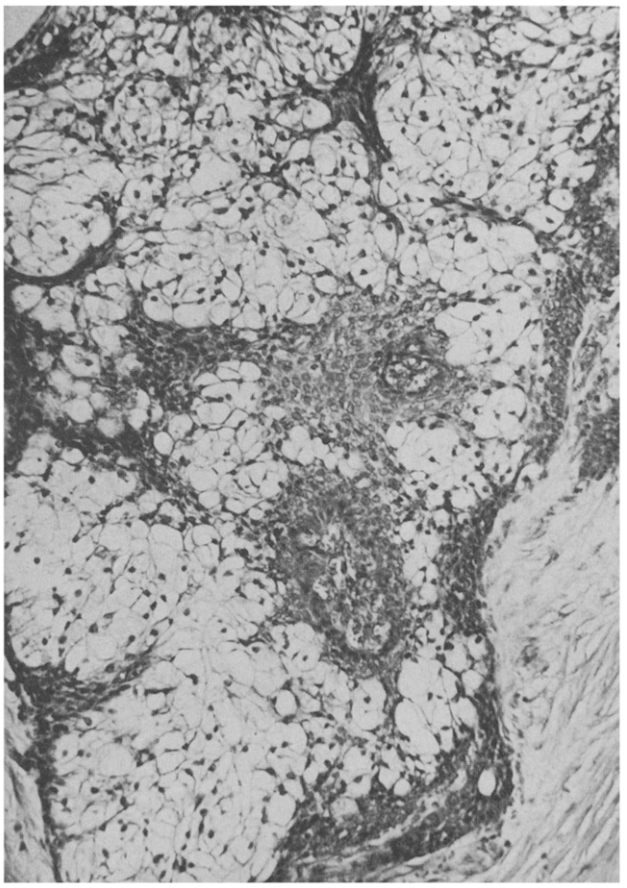

Fig. 3. Mucoepidermoid carcinoma: clear cell variant. Haematoxylin–eosin. ×100.

nucleolar organiser regions (AgNOR) of one [8]. Unfavourable clinical course is more frequent in cases of inadequate surgical procedures for primary cure, distinct local infiltrative growth, poor differentiation, atypical tetraploid DNA content and value of AgNOR over four. However, in individual cases, this grading is not absolute, and the quality of primary surgical excision is an important factor determining local recurrence and prognosis.

Adenoid cystic carcinoma

Adenoid cystic carcinoma [17–20] shows differences in the frequency of localisation: 2–6% of all parotid gland tumours, but 15% of all submandibular gland tumours and 30% of all minor salivary gland tumours. The histological patterns are glandular (cribriform) in 45%, tubular in 35% and solid in 10–20%.

The glandular type consists of numerous cylindrical spaces. Most of these are pseucocysts containing proteoglycans and basal membrane-like material, such as fibronectin. The true cysts contain secretory material. Perineural or perivascular spread without stromal reaction is very characteristic, as is intraosseous spread.

The tubular type consists of epithelial ductular strands or strands surrounded by hyaline desmoplastic tissue. Similar to the other types duct-lining cells and modified myoepithelial cells are the two cell types. The solid type (Table 3) is characterised by solid epithelial areas. Neoplastic cell nests contain few gland-like spaces (Fig. 5) and often central necrosis. Mitoses are few.

Tumours of glandular or tubular type have a better prognosis with regard to recurrences or duration of survival than the solid type which is characterised by numerous early recurrences, early metastases and higher mortality. In addition, factors associated with a poor prognosis are location in the minor salivary glands, advanced clinical stage, duration of symptoms (less than 1 year), solid pattern and positive surgical margins. But, in individual cases, all prognostic factors may be of limited predictive value as all adenoid cystic carcinomas, regardless of their histological types, are biologically aggressive and can give rise to metastases, even many years after excision of the primary tumour.

Polymorphous low-grade adenocarcinoma

Polymorphous low-grade adenocarcinoma [22–27] as a new tumour entity was first described in 1983 as "terminal duct carcinoma". But the term "polymorphous low-grade adenocarcinoma" gives a better definition of this carcinoma (Table 4): varied histological pattern (such as cords, tubules, papillae, glandular structures or solid aggregates) in combination with cytological uniformity of myoepithelial or luminal duct cells, infiltrative growth pattern, but very rare local recurrence or metastases only in the regional lymph nodes in about 10%. The tumour appears to arise almost exclusively in the minor salivary glands, particularly in the palate. Despite the microscopic evidence of invasion, the prognosis is good. The main microscopic pattern is lobular (Fig. 6). The cells are often

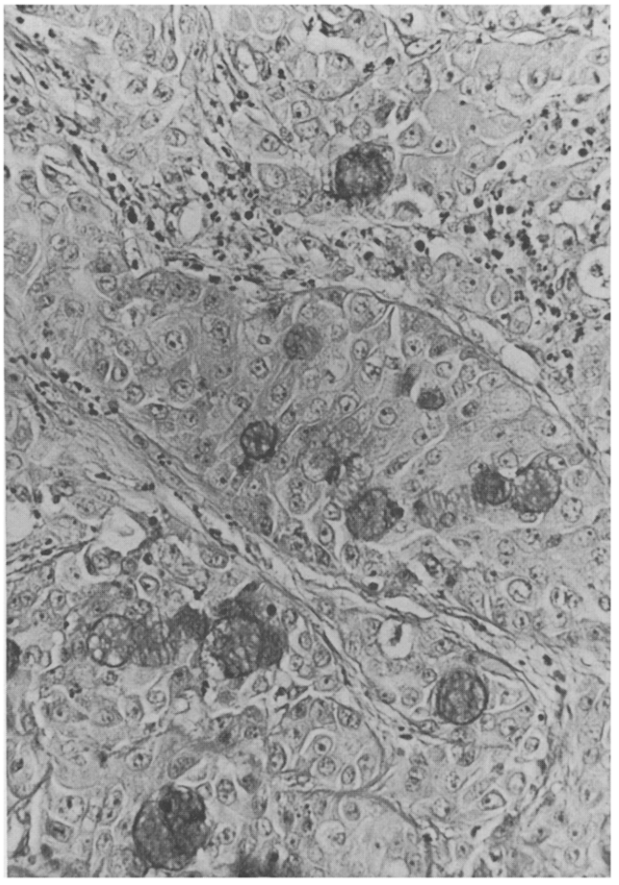

Fig. 4. Mucoepidermoid carcinoma: poorly-differentiated type with isolated mucus-producing cells. Periodic acid-Schiff. ×160.

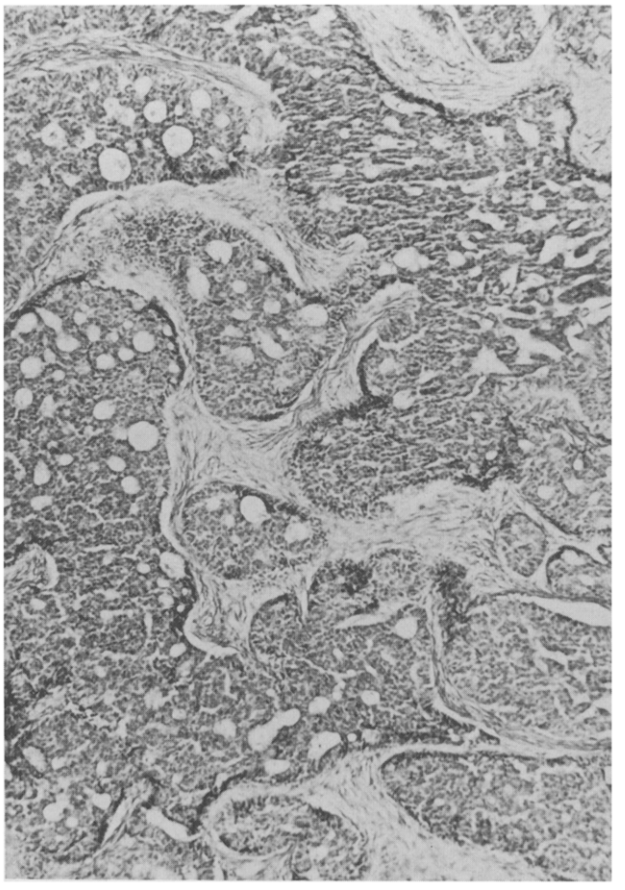

Fig. 5. Adenoid cystic carcinoma: solid type with few gland-like spaces. Haematoxylin–eosin. ×63.

pale, giving the impression that the section has been understained. The stroma shows areas of mucoid or hyaline appearance. In some areas confusion with adenoid cystic carcinoma or carcinoma in pleomorphic adenoma is possible.

Epithelial-myoepithelial carcinoma

Epithelial-myoepithelial carcinoma [28–30] usually has a good prognosis. The tumour arises predominantly in the parotid gland and shows a female predominance. The duct-like structure are composed of two cell types: an inner layer of duct lining cells with small dark cytoplasm and an outer layer of clear myoepithelial cells. There is considerable variation in the proportion of the both cell types: In typical cases the tumour cells form duct-like structures (Fig. 7). In cases with a predominance of clear cells, these cells form sheets or nests rather than duct-like structures. Perineural invasion can be observed, and even recurrence (in 30%) or metastases (in 10%).

Basal cell adenocarcinoma

Basal cell adenocarcinoma [31] is closely similar to basal cell adenoma with regard to the histological and cytological features of this new tumour entity (Table 5). The important criterion for malignancy is the invasive growth to the surrounding tissue (Fig. 8) including perineural or perivascular spread. The tumour is a low-grade adenocarcinoma with a relatively good prognosis. Recurrence is observed in 25%, but metastasis is less common, usually to regional lymph nodes.

Table 3. Signs of the solid type of adenoid cystic carcinoma

Dark epithelial islands
Cuboidal or ovoid cells
Hyperchromatic nuclei
Narrow areas of stromal tissue
Central necroses
Few mitoses
Rare cribriform spaces
Frequency: 10–20% of adenoid cystic carcinomas
Poor prognosis
Early recurrences
Early metastases
Frequent lethal evolution

The tumour occurs predominantly in the parotid gland and may be associated with dermal cylindroma.

The solid type is characterised by tumour cells arranged in islands with hyaline material on the outside of the cell nests. In some areas the cells form swirls with a squamoid appearance (Fig. 9). Perineural growth is also a characteristic feature. Basal cell adenocarcinoma must be distinguished from the solid type of adenoid cystic carcinoma.

Sebaceous carcinoma

Sebaceous carcinoma [32] is a rare tumour of low-grade malignancy. The sebaceous cells form nests or sheets with various degrees of cellular atypia. The cytoplasm is vacuolated and contains lipid droplets. Sebaceous lymphadenocarcinoma

Table 4. Characteristics of polymorphous low-grade adenocarcinoma

Minor salivary glands (palate)
Varied histologic pattern
Cords, tubules, papillae
Glandular and adenoid structures
Solid aggregates
Cytologic uniformity
Myoepithelial cells
Luminal epithelial cells
Immunohistochemistry
S-100-protein and EMA (more than 90%)
Keratin (75–90%)
Muscle-specific antigen (10–65%)
CEA (75%)
Infiltrative growth pattern
Rare recurrence or metastases

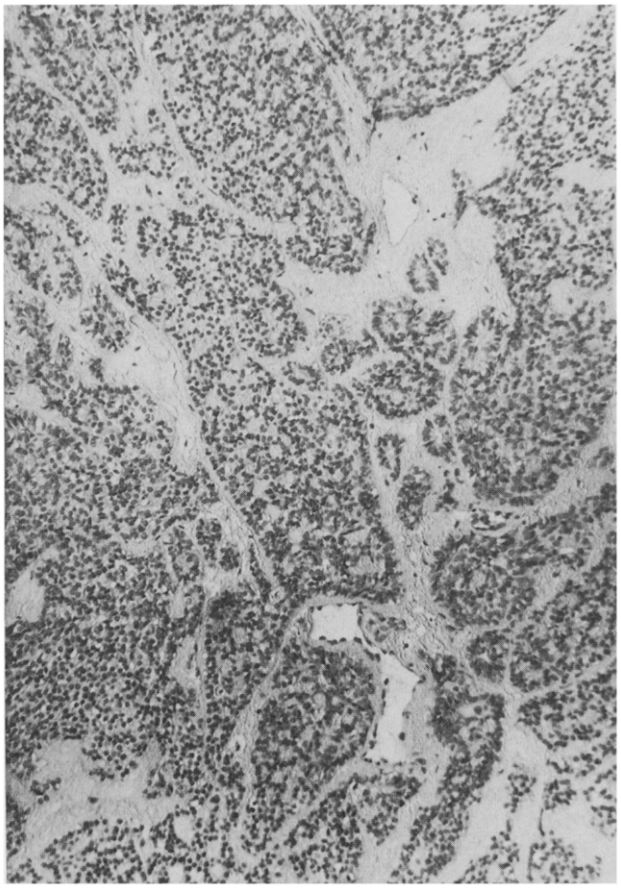

Fig. 6. Polymorphous low-grade adenocarcinoma: lobular pattern with glandular nests. Haematoxylin–eosin. ×63.

is a very rare variant, lying in a stroma of lymphocytes, with or without follicles. The tumour shows an infiltrating growth.

Papillary cystadenocarcinoma

Papillary cystadenocarcinoma is characterised by cysts and papillary endocystic projections. Malignancy is confirmed by infiltrative growth, mitoses and nuclear pleomorphism. It is a low-grade carcinoma which occurs more frequently in the minor salivary glands.

Mucinous adenocarcinoma

Mucinous adenocarcinoma as a rare tumour shows an abundant mucus production. Epidermoid or intermediate cells are not present. Cuboidal or columnar cells line the cysts. The mucus can be demonstrated by the periodic acid-Schiff reaction or by Astra blue staining.

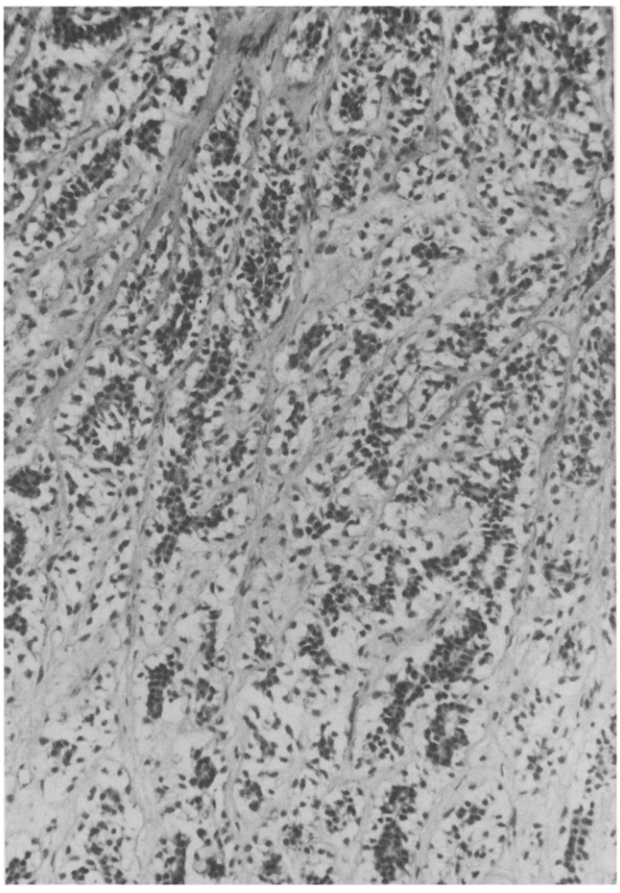

Fig. 7. Epithelial–myoepithelial carcinoma: duct-like structures with small dark cells on the inner layer and clear cells on the outer layer. Haematoxylin–eosin. ×63.

Table 5. Signs of basal cell adenocarcinoma

Mostly solid cell nests
Less frequent trabecular/tubular pattern
Small basal membrane structures
Infiltrative growth features
Perineural, intravascular
Recurrence (25%)
Metastases (10%)
Location predominantly parotid gland
Common occurrence with dermal cylindroma

Oncocytic carcinoma

Oncocytic carcinoma [33] is a very rare tumour and is composed of malignant oncocytic cells. In addition, the diagnosis of malignancy is based also on local infiltrative growth, perineural or perivascular invasion and metastasis. The prognosis is poor in relation to tumour size.

Salivary duct carcinoma

Salivary duct carcinoma [34, 35] as an extremely rare carcinoma resembles comedocarcinoma of the breast and has a high malignancy. The majority of patients succumb within 3 years. The histological features are nuclear pleomorphism, frequent mitoses, infiltrative growth and often central

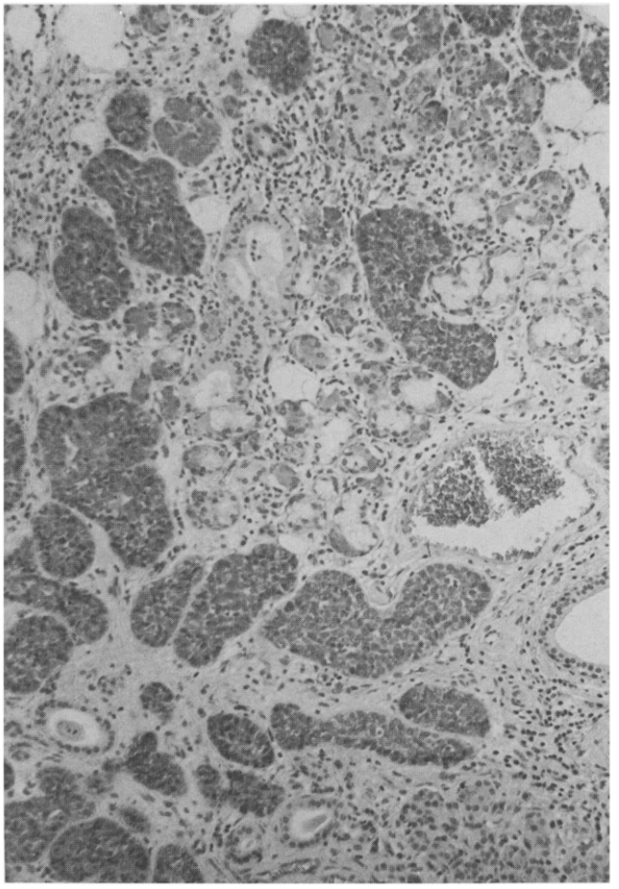

Fig. 8. Basal cell adenocarcinoma: solid type with infiltrating growth. Haematoxylin–eosin. ×250.

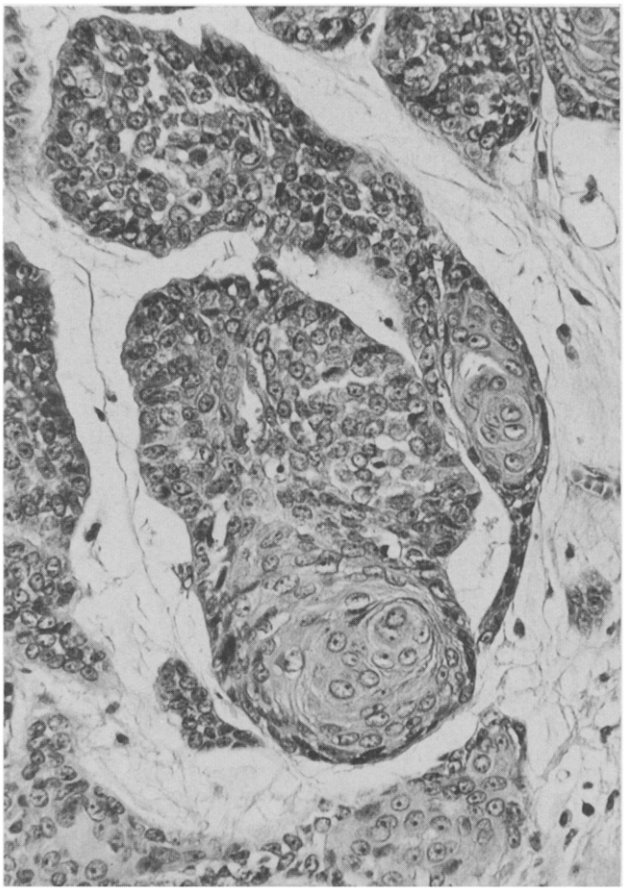

Fig. 9. Basal cell adenocarcinoma: swirls with squamoid appearance. Haematoxylin–eosin. ×40.

necrosis. The growth patterns are cribriform, looping or solid. At surgery, the tumour usually infiltrates adjacent tissues and involves cervical lymph nodes. The tumour occurs almost exclusively in the parotid. The glandular-cribriform pattern contains mostly central necrosis. Also the solid pattern shows distinct central necrosis. For this reason, the possibility of a metastasis of breast carcinoma must be excluded.

Myoepithelial carcinoma

Myoepithelial carcinoma [36] is a rare malignant tumour characterised by the following features: composition of atypical myoepithelial cells, increased mitotic activity and aggressive infiltrative growth. Most tumours occur in the parotid gland of adults over 50 years. Metastases are infrequent.

Carcinoma in pleomorphic adenoma

Carcinoma in pleomorphic adenoma [37–39] shows the following signs of malignancy (Table 6): cellular atypia and frequent mitoses, infiltrative growth, necrosis, haemorrhage, hyalinisation or calcification and progressive course. The evidence of a pre-existing pleomorphic adenoma should be found either in the histological slides or in the clinical data, such as earlier results of examination. The development can be observed in 3–4% of all pleomorphic adenomas. The incidence of malignancy correlates with the length of history of pleomorphic adenoma. The risk of developing malignancy is only about 1.5% up to 5-years, but increases to 9.5% after more than 15 years of the existence of a pleomorphic adenoma. The types of carcinoma are undifferentiated carcinoma,

Table 6. Characteristics of carcinoma in pleomorphic adenoma

Signs of malignancy
Cellular atypia, mitoses
Infiltrative growth
Necrosis, haemorrhage
Hyalinisation, calcification
Facial paralysis
Histological types of carcinoma
Undifferentiated carcinoma
Mucoepidermoid carcinoma
Squamous cell carcinoma
Different types of adenocarcinoma
Mixed differentiation
Subtypes
Non-invasive carcinoma
Invasive carcinoma
Carcinosarcoma
Metastasising pleomorphic adenoma

mucoepidermoid carcinoma, squamous cell carcinoma or carcinoma with mixed differentiation. Concerning infiltrative growth and pathohistological differentiation three subtypes can be distinguished (Table 6): non-invasive carcinoma, invasive carcinoma and carcinosarcoma resp. true malignant mixed tumour.

The term "non-invasive carcinoma" means circumscribed malignant areas in a pleomorphic adenoma without infiltration of the surrounding tissue. This term is preferred to "intracapsular carcinoma" or "carcinoma *in situ*". Patients with

non-invasive carcinoma have an excellent prognosis if the tumour is completely removed.

In invasive carcinoma the extent of invasion is a valuable guide to prognosis and biological behaviour. In carcinosarcomas the sarcomatous component shows mostly a chondrosarcomatous pattern. This true biphasic tumour is highly lethal, with a 5-year survival of 0%.

The most unusual and rarest variant is the metastasising pleomorphic adenoma, defined as a histologically benign tumour that manifests distant metastases composed of benign tumour structure.

Squamous cell carcinoma

This consists of epidermoid cells which form keratin or have intercellular bridges. Mucous secretion is not present. The distinction between primary squamous cell carcinoma of the salivary glands and metastases of primary skin carcinoma is difficult because the histological appearance is similar. The diagnosis may rest on clinical data.

Small cell carcinoma

Small cell carcinoma [40–42] is a tumour whose diagnosis should be made only after excluding the possibility of a primary tumour arising in the lung because the histology is similar. By electron microscopy and immunohistochemistry two variants can be distinguished: a neuroendocrine and a ductal variety.

Undifferentiated carcinoma

Undifferentiated carcinoma [43–45] is devoid of any phenotype expression, and cannot be placed in any other groups of carcinoma. A special subtype is the undifferentiated carcinoma with lymphoid stroma. The tumour is indistinguishable from carcinoma of the nasopharyngeal type. Therefore, it is essential to examine the upper respiratory tract before the diagnosis of a primary carcinoma of the salivary glands is accepted. The tumour has a relatively high incidence in Eskimos and in China. The description of "malignant lymphoepithelial lesion" is incorrect because the true nature of this tumour is an undifferentiated carcinoma with lymphoid stromal component.

MALIGNANT NON-EPITHELIAL TUMOURS

About 10% of all non-epithelial tumours are malignant. Sarcomas most frequently appear as malignant fibrous histiocytoma, malignant schwannoma or embryonal rhabdomyosarcoma.

MALIGNANT LYMPHOMAS [46, 47]

About 5% of all extranodal lymphomas (Table 7) and 40% of all head and neck lymphomas are localised in the salivary glands. The majority of salivary gland lymphomas are of non-Hodgkin type and in 2/3 of all cases well differentiated B-cell lymphomas with low-grade malignancy, especially immunocytomas or centrocytic–centroblastic lymphomas using the Kiel classification. Malignant lymphomas are usually associated with Sjögren's syndrome. The risk of development of a malignant lymphoma in patients with Sjögren's syndrome is 40 times higher than in a normal population. Malignant lymphomas can involve the salivary glands as the only manifestation of the disease or as part of a systemic spread. The primary lymphoma can be localised in the salivary gland parenchyma or the salivary gland lymph nodes.

Table 7. Characteristics of malignant lymphomas

5% of all extranodal lymphomas
40% of all head and neck lymphomas
Non-Hodgkin B-cell lymphomas (85%)
2/3 well differentiated, low grade malignancy
Association with Sjögren syndrome
Hodgkin lymphomas (15%)
Primary extranodal lymphomas of salivary gland parenchyma
Primary lymphoma of salivary gland lymph nodes
Secondary manifestation of primary extraglandular lymphomas

SECONDARY TUMOURS [48]

The distinction between primary malignant tumours of the salivary glands and metastases to the salivary glands is of practical importance for therapy and prognosis. Most metastases to the salivary glands develop from primary squamous cell carcinomas of the skin (head and neck region) or from melanomas of this region. 75% of these metastases are localised in the parotid gland. Haematogenous metastases in the salivary glands are relatively rare. They are mainly from three sites: lung, kidney and breast. Suspicion of metastases exists in the following types of carcinomas: small cell carcinoma, undifferentiated carcinoma with lymphoid stroma, neuroendocrine carcinoma, lobular or ductal carcinoma, clear cell carcinoma and squamous cell carcinoma.

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