Neoplasms and allied lesions of intraoral salivary glands

A clinicopathologic study

Jacqueline E. van der Wal

NEOPLASMS AND ALLIED LESIONS OF INTRAORAL SALIVARY GLANDS

A clinicopathologic study

CIP-GEGEVENS KONINKLIJKE BIBLIOTHEEK, DEN HAAG

Wal, Jacqueline Eleonore van der

Neoplasms and allied lesions of intraoral salivary glands:
a clinicopathologic study / Jacqueline Eleonore van der Wal.
-[S.l. : s.n.]. - Ill.
Thesis Vrije Universiteit Amsterdam. - With ref.
- With summary in Dutch.
ISBN 90-9005037-X
Subject headings: intraoral salivary glands / neoplasms

VRIJE UNIVERSITEIT

NEOPLASMS AND ALLIED LESIONS OF INTRAORAL SALIVARY GLANDS

A clinicopathologic study

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor aan
de Vrije Universiteit te Amsterdam,
op gezag van de rector magnificus
dr. C. Datema,
hoogleraar aan de faculteit der letteren,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de faculteit der tandheelkunde
op maandag 15 juni 1992 te 15.30 uur
in het hoofdgebouw van de universiteit,
De Boelelaan 1105

door

Jacqueline Eleonore van der Wal

geboren te Amsterdam

Drukkerij Elinkwijk bv, Utrecht
1992

Promotor : prof.dr. I. van der Waal

Copromotor : prof.dr. G.B. Snow

Referent : prof.dr. G. Seifert

Voor mijn moeder

Ter nagedachtenis aan mijn vader

CONTENTS

CHAPTER 1

INTRODUCTION AND AIM OF THE STUDY

INTRODUCTION

Salivary gland tumours account for about 3% of all head and neck neoplasms. The majority of these tumours are of epithelial origin and affect the major salivary glands, e.g. the parotid glands (80%), the submandibular glands (5%-10%) and the sublingual glands (1%). Approximately 10%-15% of all salivary gland neoplasms occur in the minor salivary glands of the oral cavity and upper aerodigestive tract.[1-3]

Salivary gland tumours constitute a heterogeneous group of lesions with great morphologic variation, which may present difficulties in histological classification. Until recently salivary gland tumours were classified histologically according to the first edition of the WHO-classification (1972).[4] In 1991 the second edition of the WHO-classification was presented.[5]

A correlation between the normal structure of the salivary gland and the histological aspects of salivary gland tumours can help us to understand morphologic classifications. Therefore, first of all a description of the histology of the normal salivary gland is given.

The common structure of all major and minor salivary glands consists of acini connected with a branching ductal system, composing so-called lobuli (Fig. 1). The acini lead to an intercalated duct which is connected to an interlobular striated duct. The striated duct empties in the extralobular excretory duct. The ducto-acinar unit is surrounded by a fibrovascular stroma. Myoepithelial cells are present around the periphery of the acini and the intercalated ducts.[6]

Salivary glands are classified as serous, mucous or seromucous, depending on the nature of their product. The minor salivary glands may represent any of the three types, depending on their location.

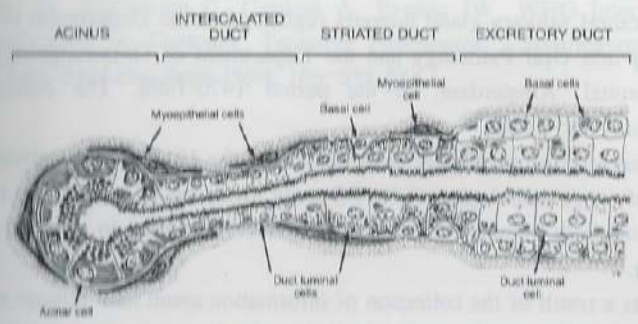

Fig. 1. Cellular organisation of the acini and ducts of a normal salivary gland. (From Burns BR, Dardick I, Parks WR: Intermediate filament expression in normal parotid glands and pleomorphic adenoma. Virchows Arch [A] 1988; 413: 103-112. With permission, Heidelberg, Springer-Verlag).

In Table 1 the morphologic similarity of some salivary gland tumours and the different epithelial structures of the salivary gland is shown. This similarity is not necessarily related to histogenesis.[6,7]

Table 1. Correlation between the normal structure of the salivary gland and salivary gland tumours[6]

Acinus	-	Acinic cell carcinoma
Intercalated duct	-	Pleomorphic adenoma
		Adenoid cystic carcinoma
		"Monomorphic" adenoma
		Epithelial-myoepithelial carcinoma
Striated duct	-	Warthin tumour
		Oncocytoma
Excretory duct	-	Mucoepidermoid carcinoma
		Adenocarcinoma
		Epidermoid carcinoma
		Ductal papilloma

AIM OF THE STUDY

The present study is confined to the epithelial tumours and tumour-like lesions of the intraoral salivary glands. Since the adenoid cystic carcinoma is the clinically most relevant intraoral salivary gland tumour, an important part of the study has been focused on the intraoral adenoid cystic carcinomas of the group of 101 intraoral salivary gland tumours. The aim of the last part of this study was to report some rare tumours and tumour-like lesions of the intraoral salivary glands.

In *chapter 2* an overview of the literature is presented, which is combined with a discussion of 101 intraoral salivary gland tumours registered at the Department of Oral & Maxillofacial Surgery and Oral Pathology and the Department of Otolaryngology of the Free University Hospital, Amsterdam, in the period 1970-1988. The collection of references ended January 1st, 1992.

In *chapter 3* the results of a histological re-evaluation of the 101 intraoral salivary gland tumours by a panel of (oral) pathologists (EORTC-study group on salivary gland tumours) are discussed, recording both interobserver and intraobserver variation in order to come to a consensus diagnosis.

In the meantime, as a result of the collection of information about new tumour entities a tentative revision of the WHO-classification of salivary gland tumours was elaborated.[8] In *chapter 4* this tentative histological classification has been applied to the 101 intraoral salivary gland tumours.

In *chapter 5* the possible value of postoperative radiotherapy in intraoral adenoid cystic carcinomas is discussed. The presence of perineural spread in relation to site, size, local extension and metastatic spread in the intraoral adenoid cystic carcinomas is described in

chapter 6. In *chapter 7* an unusual variant of intraoral adenoid cystic carcinoma, with squamous metaplasia is presented.

In *chapter 8* a case of sialadenoma papilliferum is presented. Finally, in *chapter 9* the clinical and histopathological findings of 12 cases of necrotizing sialometaplasia, a lesion that clinically and histologically may mimic malignancy, are described.

REFERENCES

1. Eveson JW, Cawson RA. Salivary gland tumours: A review of 2410 cases with particular reference to histological types, site, age and sex distribution. J Oral Pathol 1985; 14: 51-58.
2. Fitzpatrick PJ, Black KM. Salivary gland tumors. J Otolaryngol 1985; 14: 296-300.
3. Spiro RH. Salivary neoplasms: Overview of a 35-year experience with 2807 patients. Head & Neck Surgery 1986; 8: 177-184.
4. Thackray AC, Sobin LH. WHO International Histological Classification of Tumours. Nr. 7. Histological Typing of Salivary Gland Tumours. Geneva, World Health Organization, 1972.
5. Seifert G, Sobin LH. WHO International Histological Classification of Tumours. Histological Typing of Salivary Gland Tumours. Second edition. Springer Verlag, Heidelberg, 1991.
6. Martinez-Madrigal F, Micheau C. Histology of the major salivary glands. Am J Surg Pathol 1989; 13: 879-899.
7. Dardick I, van Nostrand AWP. Morphogenesis of Salivary Gland Tumors. A prerequisite to improving classification. Pathol Annu 1987; 22: 1-53.
8. Seifert G, Brocheriou C, Cardesa A, Eveson JW. WHO International Histological Classification of Tumours. Tentative Histological Classification of Salivary Gland Tumours. Path Res Pract 1990; 186: 555-581.

CHAPTER 2

CLINICOPATHOLOGIC ASPECTS OF INTRAORAL SALIVARY GLAND TUMOURS

A discussion of 101 patients and a review of the literature

2. CLINICOPATHOLOGIC ASPECTS OF INTRAORAL SALIVARY GLAND TUMOURS

2.1. Epidemiology

Salivary gland tumours account for 1% of all neoplasms of the body and for about 3% of all head and neck neoplasms. The incidence is about 1-2 cases per 100.000 population per year.[87] Racial and geographic variations in the frequency and distribution of salivary gland tumours do exist. For instance, there is a high prevalence of salivary gland tumours in Eskimos.[100,111,139]

The majority of salivary gland tumours are of epithelial origin. Non-epithelial salivary gland tumours account only for about 5% of all salivary gland neoplasms and most often occur in the major salivary glands.[5,10,64,141,143,148]

More than 90% of the salivary gland neoplasms are located in the major salivary glands; approximately 80% in the parotid glands, 5%-10% in the submandibular glands and less than 1% in the sublingual glands.[53,57,158] The remaining 10%-15% of the salivary gland neoplasms are found in the minor salivary glands of the oral cavity and upper respiratory tract. The distribution of the tumours registered at the Free University Hospital in Amsterdam is shown in Table 1. During an 18-year period 408 patients with a salivary gland tumour were seen. Thirty-five percent of these tumours arose in the minor salivary glands. This high percentage is probably due to a referral bias.

Table 1. Distribution of patients with a salivary gland tumour registered at the Free University Hospital according to localisation (1970 - 1988)

Localisation	Number	%
Parotid gland	238	58.3
Submandibular gland	26	6.4
Accessory glands, mouth*	101	24.7
Accessory glands, other sites	43	10.6
Total	408	100.0

* Including the sublingual glands.

Minor salivary gland tumours occur with an equal sex distribution.[28] However, a female predominance has been reported in Africans.[82] The majority of these salivary gland tumours are found in patients in their fourth to seventh decades.[53,90,140] Less than 5% of all primary salivary gland tumours occur in children with the parotid gland being the site of predilection.[5,61,101,106,142,149] A considerable number of these latter tumours are vascular in origin.[10,117] An exceptional entity is formed by the congenital salivary gland tumours,

such as sialoblastoma, embryoma, congenital basal cell adenoma and embryonal carcinoma.[50,79,137,152,170] The age and sex distribution of the 101 intraoral salivary gland tumours registered at the Free University Hospital is somewhat similar to the findings in the literature (Fig. 1).[28,90,140]

Gender
- male : 50
- female: 51

Mean age in years (range)
- male : 53.6 (17-86)
- female: 50.0 (16-82)

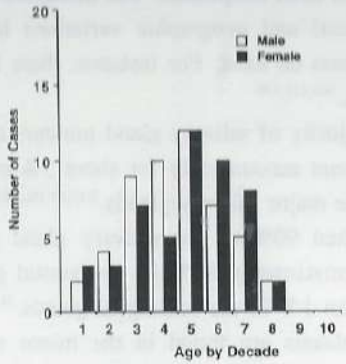

Fig. 1. Distribution of 101 patients with an intraoral salivary gland tumour by age and gender.

2.2. Etiology

The etiology of salivary gland neoplasms is still unknown.[159,162] In a few percent of patients with a salivary gland neoplasm there is a history of a previous low-dose irradiation of the head and neck area, sometimes even more than 20 years earlier.[98,138,150] An epidemiologic study has shown that the incidence of salivary gland tumours in Hiroshima A-bomb survivors was 2.0 times higher than among the non-exposed.[169] Findings from a study in Los Angeles demonstrated that tumours of the parotid gland are related to prior exposure of the gland to diagnostic medical and dental radiography; 28% of the malignant tumours were attributable to radiation.[130]

The association between salivary gland tumours and other malignancies has been often discussed in the literature.[19,93,128] In 1968, Berg, et al. reported a unique association between salivary gland cancer and breast cancer.[18] Abbey, et al. concluded from their study that women incurred a four-to-five fold increased risk of a second primary breast cancer subsequent to the first primary salivary gland tumour.[1] However, others reported no significant increase.[19,150]

Another suggestion that has been proposed is the association between salivary gland cancer and skin cancer, which is biologically and histogenetically plausible and could be

attributed to exposure to ultraviolet radiation.[160,161,163]

Besides breast cancer and skin cancer, lung cancer, prostate cancer and salivary gland neoplasms have been reported as second primary tumours after a first primary salivary gland tumour.[19,93,160]

It was not possible to get reliable information on previous primary tumours or previous irradiation from the files of the 101 patients with an intraoral salivary gland tumour, registered at the Free University Hospital.

2.3. Clinical aspects

Approximately 10%-15% of all salivary gland tumours are located in the accessory salivary glands. Most of these tumours are located in the oral cavity. The extraoral glandular tumours, e.g. tumours in the auditory canal,[36] the middle ear,[12] the nasal and paranasal sinuses,[178] the larynx[107,134] and the lacrimal glands[136] will not be discussed here.

Intraoral salivary gland tumours most often manifest as asymptomatic, slowly growing submucosal swellings. They seldom cause pain or ulcerate (Fig. 2, 3, 4, 5).[102] The duration of these tumours may vary from several months to many years.[28,158]

The junction of the hard and soft palate is the most favoured location for an intraoral salivary gland tumour, followed by the upper lip.[28,54,182] This distribution is also found in the group of 101 intraoral salivary gland tumours registered at the Free University Hospital (Table 2). In this study the seven sublingual tumours were somewhat arbitrarily designated as originating from the floor of the mouth, since it was often difficult to distinguish between the two.

Location of a tumour in the lower lip or tongue is rather rare.[69,120,126,185] Occurrence of a salivary gland tumour within the mandible is even more exceptional.[21,60,72,96,173] Despite many theories about the histogenesis of intraosseous salivary gland tumours, the source of salivary gland epithelium in the mandible remains uncertain.[94,174] Some of these tumours might have spread into the bone from the surrounding tissues instead of having their origin inside the bone.

Table 2. Distribution of 101 intraoral salivary gland tumours by site

Palate	61
Upper lip	11
Cheek	8
Floor of the mouth	7
Upper alveolar ridge	7
Retromolar area	3
Lower lip	2
Tongue	1
Mandible	1
Total	101

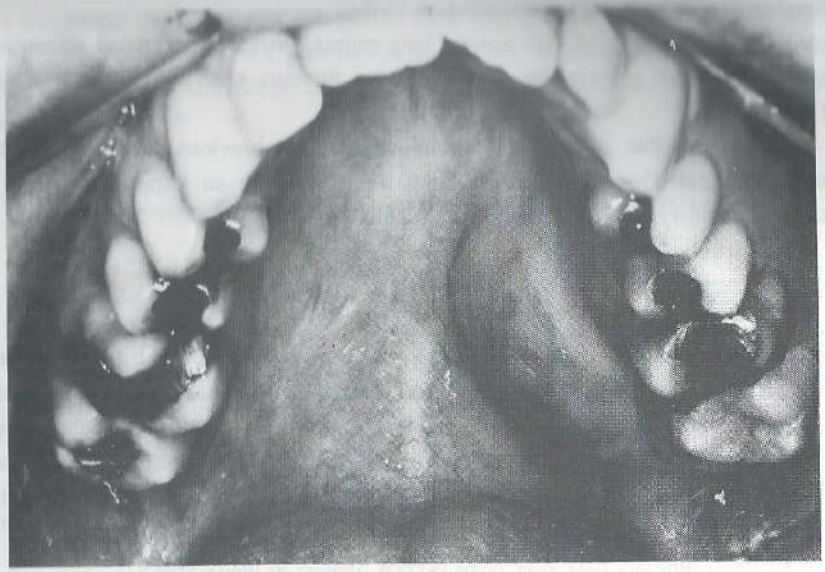

Fig. 2. A submucosal swelling of the palate, which existed for some months. The histological diagnosis was adenoid cystic carcinoma.

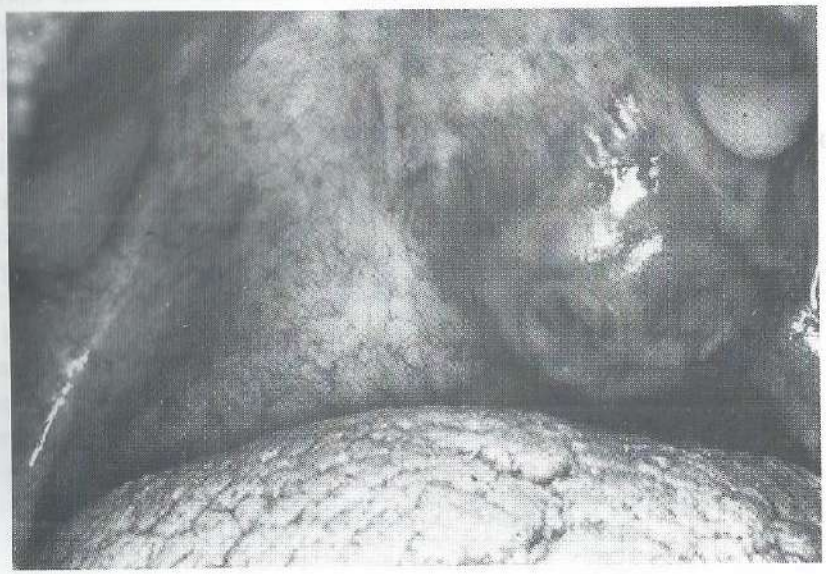

Fig. 3. A swelling of the palate with central ulceration. The histological diagnosis was adenoid cystic carcinoma.

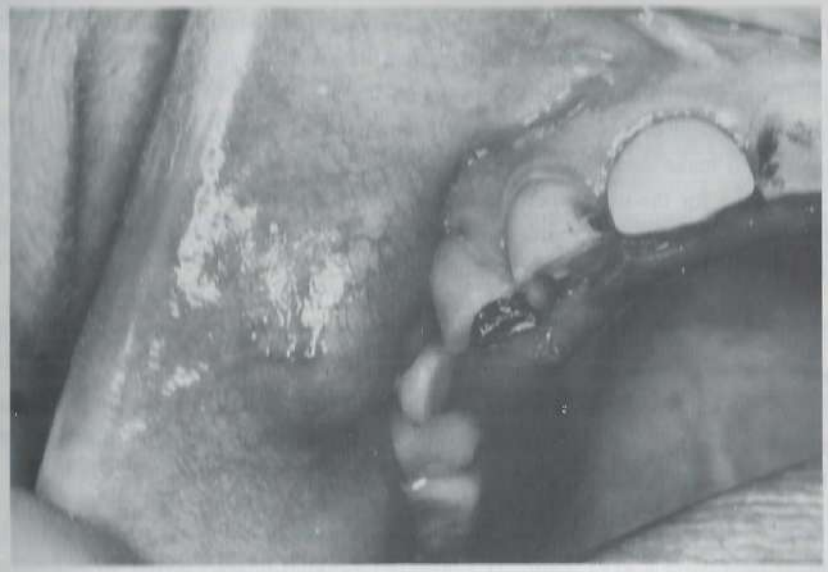

Fig. 4. A firm nodule in the upper lip, histologically compatible with the diagnosis of pleomorphic adenoma.

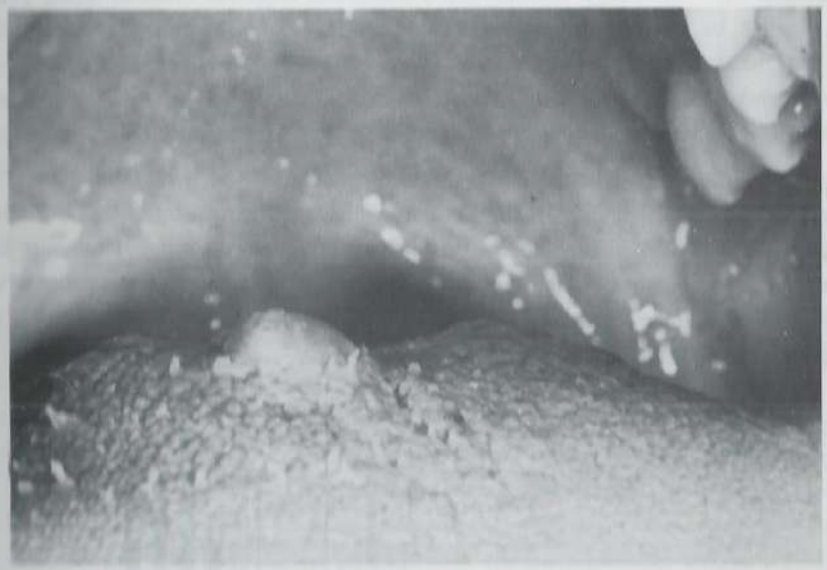

Fig. 5. A 37-year-old female patient with a firm swelling of the tongue near the foramen caecum. Histology of the tumour showed a mucoepidermoid carcinoma.

Fine-needle aspiration biopsy is one of the diagnostic tools when dealing with an intraoral (salivary gland) tumour to obtain a preoperative diagnosis. It is an economically valuable technique, but its reliability largely depends on the experience of the cytologist.[91,100,157] In a certain percentage of cases, the pleomorphic nature of salivary gland neoplasms makes it dangerous to make decisions on treatment on the basis of a cytological smear only. The same holds true for the use of peroperative frozen sections.[66,71,133] Since a biopsy is rather easy to perform when dealing with an intraoral (salivary gland) tumour, this should be the method of first choice to obtain a preoperative diagnosis.

A high percentage of the intraoral salivary gland tumours is malignant, varying from about 30% to 82%.[28,30,53,54,90,158,182] The differences reported probably depend on the source from which the material was drawn.

In the Free University study 56.4% of the 101 intraoral salivary gland tumours are malignant, including the mucoepidermoid tumours and acinic cell tumours (WHO-classification, 1972) (Table 3).[171]

Table 3. Distribution of 101 intraoral salivary gland tumours according to histological type (WHO-classification, 1972)

Pleomorphic adenoma	36
Monomorphic adenoma	8
Mucoepidermoid tumour	15
Acinic cell tumour	3
Adenoid cystic carcinoma	27
Adenocarcinoma	9
Carcinoma in pleomorphic adenoma	3
Total	101

The pleomorphic adenoma is the most common histological type, while the adenoid cystic carcinoma is the most common malignant one, which is in agreement with the findings in the literature.[54,90,179] In some papers a predominance of mucoepidermoid tumours instead of adenoid cystic carcinomas is described.[28,182] The peak incidence of the patients with a benign intraoral salivary gland tumour was in the third decade and for the patients with a malignant tumour in the fifth decade (Fig. 6).

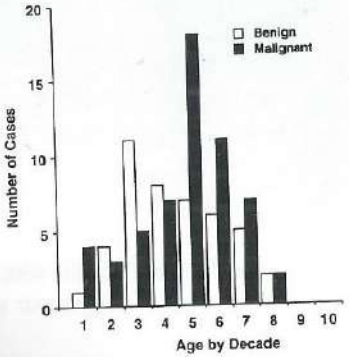

Fig. 6. Distribution of 101 patients with a benign or malignant intraoral salivary gland tumour by age.

2.4. Staging

In 1987 a revised unified formulation for the staging of malignant tumours, including major salivary gland tumours, has been published by the International Union Against Cancer (UICC) in collaboration with the American Joint Committee on Cancer (AJCC).[85] It does not apply to minor salivary gland tumours. However, sometimes the UICC-TNM-classification for malignant major salivary gland tumours is also used for the staging of minor salivary gland tumours.[2] Also the TNM-staging system for squamous cell carcinomas of the oral cavity has occasionally been applied to intraoral salivary gland neoplasms.[179] To permit comparison of studies a uniform staging system for minor salivary gland tumours is needed.

2.5. Histopathology and immunohistochemistry

Until recently the most widely used histological classification was the 1972-WHO-classification of salivary gland tumours (Appendix I). Since 1972 a great deal of information has been collected about new tumour entities and the behaviour and prognosis of the previously classified tumours. In 1991 a second edition of the WHO-classification for salivary gland tumours has been elaborated (Appendix II). This new WHO-classification contains more tumour entities and should improve the classification of salivary gland tumours. Furthermore, the introduction of immunohistochemical procedures, using monoclonal or polyclonal antibodies, has provided new possibilities for diagnostic refinements.[109] The selection of antibodies used in the present study has been based on data of the literature, and are shown in Table 4.

Table 4. Characterisation of cell types by different tumour markers

Antibody	Cell type
Keratin (CAM 5.2/AE1-AE3)	- duct cells, acinar cells, myoepithelial cells
Vimentin	- myoepithelial cells, stroma cells
S-100 protein	- duct cells, myoepithelial cells
EMA	- duct cells
CEA	- duct cells, acinar cells
GFAP	- periductal cells, stromal cells
laminin	- basement membrane structures
actin	- myoepithelial cells, smooth muscle cells
myosin	- myoepithelial cells
amylase	- acinar cells

EMA (epithelial membrane antigen) CEA (carcinoembryonic antigen)
GFAP (glial fibrillary acidic protein)

Another diagnostic aid in the histological classification of salivary gland tumours is the use of the AgNOR (Argyrophyl-Nucleolar Organizer Region) staining technique. AgNOR-dots can be detected in the nuclei of the salivary gland tumour cells. The number of dots within the nucleus can possibly be used to differentiate between the various histologic types, e.g. pleomorphic adenomas have a significant lower mean AgNOR-value than adenoid cystic carcinomas.[83,113]

The role of electron microscopy in the diagnosis of salivary gland tumours is limited.

ADENOMAS

Pleomorphic adenoma

"A tumour of variable capsulation characterized microscopically by architectural rather than cellular pleomorphism. Epithelial and modified myoepithelial elements intermingle with tissue of mucoid, myxoid or chondroid appearance. The epithelial and myoepithelial components form ducts, strands, sheets or structures resembling a swarm of bees. Squamous metaplasia is found in about 25% of pleomorphic adenomas" (WHO, 1991). (Figs. 7 - 11).

Pleomorphic adenomas result from the neoplastic transformation of the complete ductal-acinar unit, consisting of luminal, epithelial, and modified myoepithelial cells, rather than from one particular "reserve" cell.[42] The role of the myoepithelial cell in the histogenesis and differentiation of pleomorphic adenomas is often discussed in the literature.[7,44,95,127] Modified myoepithelial cells seem to be the principal cell type in the myxoid and chondromyxoid regions.[41,43]

The pleomorphic adenoma is the most commonly occurring tumour of both the major and minor salivary glands. Intraoral pleomorphic adenomas are well-circumscribed, but frequently do not have a well-defined capsule. The absence of a capsule must not be interpreted as infiltration but rather as a so called "pushing border effect".[182]

The main clinical problems associated with pleomorphic adenoma are the risk of recurrence and the tendency to show progression to malignancy, which will be discussed later. Major salivary gland pleomorphic adenomas are most often well-encapsulated, although they do have a tendency for intracapsular invasion, and may recur due to inadequate surgical excision. When arising from minor salivary glands, however, pleomorphic adenomas show a considerably lower recurrence rate in spite of being non-encapsulated.[9,29]

Some tumours are predominantly myxoid, other lesions are chiefly cellular. It has been suggested that cell-rich variants show a higher risk of malignant transformation and that cell-poor variants show a higher risk of recurrence. However, there may be a wide range of histological appearances within an individual tumour.

Many differentiations may be found in pleomorphic adenomas, which are responsible

for its alternative name of "mixed tumour". Besides the characteristic myxoid and chondroid areas, the tumour may consist of tubules and sheets of epithelial cells, squamous metaplasia, sebaceous differentiation, calcification and hyalinisation of the stroma. Epithelial islands with a cribriform structure are occasionally seen, giving rise to a cylindromatous pattern.[30,182] Some reports have been described on the occurrence of tyrosine-rich crystals in pleomorphic adenomas.[22,25,89] For unknown reasons such crystals only seem to occur in the parotid glands.

Immunohistochemical methods have been extensively applied to the study of pleomorphic adenomas, especially with regard to the role of the myoepithelial cell. They have been shown to be immunoreactive for keratin, S-100 protein, GFAP, (smooth muscle) actin, vimentin and myosin.[114,131,164,176] Lactoferrin and lysozyme (functional markers) are both found in pleomorphic adenoma.[144] However, lysozyme could not be detected in malignant tumours.[135]

Myoepithelioma (Myoepithelial adenoma)

"A rare tumour of myoepithelial cells; several growth patterns occur: solid, myxoid and reticular" (WHO, 1991). (Fig. 12).

Myoepitheliomas occur in both major and minor salivary glands. The myoepithelioma is most likely a variant of the pleomorphic adenoma.[8] It is composed exclusively of myoepithelial cells with a plasmacytoid (hyalin) appearance, a spindle-shaped appearance, or a combination of both.[48] Cytologic pleomorphism is a frequent histological feature, leading to a questionable diagnosis of malignancy.[172]

Neoplastic myoepithelial cells show immunoreactivity for cytokeratin, S-100 protein, GFAP, vimentin and (smooth muscle) actin. Lactoferrin is generally undetectable, just as lysozyme.[115] Spindle cell shaped lesions may be difficult to differentiate from mesenchymal lesions such as fibrous histiocytoma or Schwannoma. S-100 protein, cytokeratin and GFAP help to confirm the myoepithelial nature of the tumour.

Basal cell adenoma

"A tumour of isomorphic basaloid cells with a prominent basal cell layer, a distinct basement membrane-like structure and no mucoid stromal component as in pleomorphic adenomas. Four cellular patterns occur: solid, trabecular, tubular, membranous" (WHO, 1991). (Fig. 13).

In the oral cavity the basal cell adenoma has a preference for the upper lip and the older age groups.[129] They are often well-encapsulated.

Most authors state that myoepithelial cells are rarely seen in basal cell adenomas, but Dardick, et al. described the presence of myoepithelial cells in tubular-trabecular basal cell adenomas.[45] This population of cells stains strongly for S-100 protein. The stroma of the basal cell adenoma is typically fibrous with some blood vessels, which helps separate them from canalicular adenomas.[37]

Histologically the main differential diagnosis is between the basal cell adenoma and the adenoid cystic carcinoma since both are comprised of basaloid-type cells.[129] Membranous basal cell adenoma (dermal anlage type) seems to occur often in association with dermal cylindroma, trichoepithelioma or eccrine spiradenoma of the scalp.[17]

Warthin tumour (Adenolymphoma)

"A tumour composed of glandular and often cystic structures, sometimes with a papillary cystic arrangement, lined by characteristic eosinophilic epithelium. The stroma contains a variable amount of lymphoid tissue with follicles" (WHO, 1991). (Fig. 14).

The term Warthin tumour is preferred over the earlier designation "adenolymphoma" which could be confused with malignant lymphoma.[146] Warthin tumour is usually seen after the age of 40 and is more common in men than in women.[55] The tumour arises almost exclusively in the parotid gland.[146]

The histogenesis of Warthin tumour is still a source of controversy. The most widely accepted theory is that the tumour represents a neoplastic proliferation of salivary gland ducts entrapped in pre-existing lymph nodes. Extraparotid location is questionable, and much of these cases should rather be called "papillary cystadenoma" without the addition of "lymphomatosum" or even oncocytic hyperplasia with secondary chronic inflammation.[26,56,80] Malignant transformation in a Warthin tumour is exceedingly rare.[123]

Oncocytoma (Oncocytic adenoma)

"A rare tumour composed of a well demarcated mass of polyhedral eosinophilic cells with small, dark nuclei. It has a solid, trabecular or tubular pattern and frequently contains both light and dark cells" (WHO, 1991).

Oncocytomas rarely occur in the minor salivary glands.[27,39] Most of the so-called minor salivary gland oncocytomas probably represent oncocytic hyperplasia of ducts.

The granular eosinophilic appearance of the epithelial cells is due to an accumulation of mitochondria. Cytoplasmic staining with PTAH (phosphotungstic-acid-hematoxylin) might be helpful for the diagnosis of oncocytoma.[27,146] Some degree of increased cellular atypia and pleomorphism is accepted as compatible with benignancy and should not serve as a basis for a malignant interpretation.

Canalicular adenoma

"A tumour of columnar epithelial cells which are arranged in anastomosing bilayered strands that form a beading pattern. The stroma is loose, highly vascular and not fibrous" (WHO, 1991). (Figs. 15 and 16).

Canalicular adenomas usually occur in the upper lip of middle-aged or elderly people. Most lesions are well-circumscribed and encapsulated. However, a significant number of canalicular adenomas are multinodular or multifocal, in which the smaller nodules are often non-encapsulated.[37]

The canalicular adenoma should be separated from the basal cell adenomas, especially the trabecular type, since the clinical, histological and ultrastructural features are distinctly different, although their clinical behaviour is similar.[37] Immunohistochemical staining for S-100 protein shows significant immunoreactivity of only epithelial cells. In contrast, tubular-trabecular basal cell adenomas stain positive in both epithelial and mesenchymal cells.[187]

Sebaceous adenoma

"A rare tumour consisting of irregular nests of sebaceous cells without cellular atypia. The tumour is typically well circumscribed and cystic" (WHO, 1991).

Sebaceous differentiation in the salivary gland is an expected normal finding, especially in the major salivary glands. However, sebaceous neoplasms of the salivary glands are rare. Two types of sebaceous adenomas can be distinguished: sebaceous lymphadenomas characterized by islands of well-differentiated sebaceous cells and metaplastic salivary ducts diffusely distributed in lymphoid tissue, and sebaceous adenomas characterized by well-circumscribed nests of sebaceous cells, devoid of a lymphoid component.[13,65]

Ductal papilloma

a. Inverted ductal papilloma

"An extremely rare but distinct tumour that arises from the excretory ducts and resembles the inverted papilloma of the nasal and paranasal sinuses, both in growth pattern and cytologically" (WHO, 1991).

This tumour arises from the excretory ducts of the minor salivary glands which become lined by squamous epithelial cells extending into the surrounding connective tissue. Mucous cells and microcysts may be present.[186] Inverted ductal papilloma is an endophytic growing tumour, which helps separate them from the exophytic growing sialadenoma papilliferum.

b. Intraductal papilloma

"A very rare solitary tumour of the excretory ducts of minor salivary glands. The tumour consists of papillary intraductal projections with connective tissue cores that extend into widely dilated ducts or cystic spaces. The ingrowths are lined by one or two layers of benign, cuboidal or squamous epithelium" (WHO, 1991).

The differential diagnosis rests between the other types of ductal papillomas and papillary cystadenoma.[62] Intraductal papillomas are unicystic in contrast to the multicystic papillary cystadenomas.

c. Sialadenoma papilliferum

"An exophytic growth mainly in the palate with multiple papillary surface fronds and deeper duct-like structures which may be in continuity with the surface" (WHO, 1991).

This tumour entity will be discussed in Chapter 8.

Cystadenoma

a. Papillary cystadenoma

"A tumour that closely resembles Warthin tumour but without the lymphoid elements" (WHO, 1991).

Most cases have been described in the larynx. Occurrence in the major or minor salivary glands is rare.[145] The papillary cystadenoma of salivary gland origin appears to be derived from neoplastic proliferations of ductal epithelium.[99] It is a cystic adenoma, in which papillary (columnar) epithelial projections are found in the cyst lumen. Papillary cystadenomas are frequently well-circumscribed. However, they may show intracapsular growth or multifocal involvement which makes it difficult to separate them from, for instance, papillary cystic acinic cell carcinomas.

b. Mucinous cystadenoma

"A circumscribed tumour with cystic spaces lined by mucus-producing cells or goblet cells but no cellular atypia or invasive growth" (WHO, 1991).

The tumour must be differentiated from the malignant counterpart, the mucinous adenocarcinoma and from low-grade mucoepidermoid carcinoma. The circumscription and absence of cellular atypia must lead to a benign diagnosis.[145]

CARCINOMAS

Acinic cell carcinoma

"A malignant epithelial neoplasm that demonstrates some cytological differentiation toward acinar cells" (WHO, 1991). (Figs. 17 and 18).

In the first classification of the WHO (1972) this tumour was called acinic cell tumour. At present, in almost all countries the usual term is now acinic cell carcinoma, because of its clinical malignant behaviour.[145] Acinic cell carcinomas predominantly occur in the major salivary glands and are relatively uncommon in the minor salivary glands. It is considered to be a low-grade malignancy, capable of local recurrence as well as metastasis to regional lymph nodes and distant organs.[31]

The cell of origin is believed to be a pluripotential (reserve) intercalated duct cell, which, under neoplastic influences proliferates and undergoes histological differentiation along secretory cell lines.[31,46] This leads to the variety of cellular and tissue morphologic features observed in these tumours. Four growth patterns can be distinguished: solid,

microcystic, follicular and papillary-cystic.[108] They are composed of serous (granular) acinar cells and intercalated duct-type cells with frequent transitional forms, as vacuolated and clear cell variants. Even myoepithelial cell differentiation may occur.[46] Cellular atypia and mitoses are rare.

Calcospherites are more often present in acinic cell carcinomas than in any other salivary gland tumour.[15] One of the curious features of acinic cell carcinoma is their frequent association with a lymphoid infiltrate in the supporting stroma.[146]

Staining with periodic-acid-Schiff (PAS) stain for cytoplasmic granules may be helpful in the identification of well-differentiated acinar cells. Diastase digestion before staining with PAS shows that PAS-reactivity is not due to glycogen. Caution should be exercised when interpreting immunohistochemistry since reports are somewhat contradictory.[77,118,183,187] Acinic cell carcinomas have been shown to be immunoreactive for amylase, whereas other salivary gland tumours are usually negative for amylase.[23] As the other malignant salivary gland tumours, acinic cell carcinoma shows a clear destruction of the basal membrane as visualized by antibodies against type IV collagen and laminin.[24]

Histologically, the acinic cell carcinoma must be differentiated from the clear cell variant of a mucoepidermoid carcinoma or a metastasis of a renal cell carcinoma. Except for antiamylase, the use of immunohistochemistry is of little practical help in the diagnostic differentiation of acinic cell carcinomas from other salivary gland tumours.[77]

The value of grading of acinic cell carcinomas is still controversial.[15] None of the four growth patterns nor predominance of one of the cell types seems to be predictive for prognosis. The role of DNA-cytophotometry in providing prognostic information seems also of limited value.[78]

Mucoepidermoid carcinoma

"A tumour characterized by the presence of squamous cells, mucus-producing cells, and cells of intermediate type" (WHO, 1991). (Fig. 19).

As the acinic cell carcinomas, all mucoepidermoid tumours must be considered malignant and should, therefore, be classified as carcinomas. They occur in both major and minor salivary glands. Occasionally, central (intraosseous) mucoepidermoid carcinomas of the mandible and maxilla have been reported .[72,174] Mucoepidermoid carcinomas are non-encapsulated, but may be circumscribed.

Undifferentiated stem cells seem to serve as pluripotential reserve cells, which give rise to the various cell types seen in mucoepidermoid carcinomas.[33] Mucoepidermoid carcinomas are basically composed of three cell types: mucus-secreting, epidermoid (squamous-like), and intermediate cells. There is considerable variation in cell types, distribution of cells and their growth pattern in mucoepidermoid carcinomas. This leads to cystic or glandular structures, solid nests or cords, or combinations of these appearances.[14] Hydropic degeneration in the epidermoid cells may produce areas of clear cells, which may cause difficulties in the differential diagnosis with other clear cell tumours

such as acinic cell carcinomas or metastases.

The epithelial mucin produced by mucous and other cell types stains positively for mucicarmine and PAS and is resistant to diastase digestion. Immunohistochemistry is not very helpful in distinguishing mucoepidermoid carcinomas from other salivary gland tumours.[77,144]

Histological grading of mucoepidermoid carcinomas is based on the proportion of mucous cells, cellular differentiation, anaplasia, mitoses and growth pattern. A three-level grading had been generally accepted.[14] However, the 1991-WHO-classification elaborates a two-level system. The well-differentiated type, or low-grade tumour consists for more than 50% of mucus-producing cells and well-differentiated epidermoid cells; it tends to form cystic spaces and has minimal nuclear pleomorphism with occasional mitoses. The poorly-differentiated type, or high-grade tumour consists of less than 10% mucous cells; it tends to form a solid mass of either poorly-differentiated epidermoid or intermediate cells with nuclear pleomorphism, high mitotic frequency and infiltrative margins. Prognosis seems to correlate to the subtype.[119]

Single cell DNA assessment can be a useful supplementary tool in the clinicopathologic and prognostic evaluation of mucoepidermoid carcinomas.[75]

Adenoid cystic carcinoma

"An infiltrative malignant tumour having various histological features with three growth patterns: glandular (cribriform), tubular or solid. The tumour cells are of two types: duct-lining cells and cells of myoepithelial type. Perineural or perivascular spread without stromal reaction is very characteristic. All structural types of adenoid cystic carcinoma can be associated in the same tumour" (WHO, 1991). (Figs. 20 - 24).

Adenoid cystic carcinoma occurs more frequent in the minor salivary glands than in the major salivary glands. It is also found in the lacrimal glands, breast, uterine cervix, bronchi, sweat glands, prostate gland, skin and esophagus.[124] Occasionally intraosseous adenoid cystic carcinomas have been reported.[94,96]

The tumours are composed of four major cell types: intercalated duct, myoepithelial, secretory and pluripotential reserve/stem cells.[32] Ormos, et al. (1991) add a fifth cell type to these four, namely cells with squamous differentiation.[124] A dual origin of adenoid cystic carcinoma, partly from a population of acinar and ductal cells and partly from myoepithelium has been suggested and was confirmed by immunohistochemistry.[4,32,34] Luminal cells express CEA, EMA, keratin, and S-100, indicating their ductal character. Non-luminal cells express muscle specific actin (HHF-35) and low molecular weight cytokeratin (54KDa) as well as occasional expression of keratin and S-100 characteristic of myoepithelium. Just as in pleomorphic adenomas coexpression of keratin and vimentin may be seen.[116] In pseudocysts, replicated basal lamina react with antisera to laminin, fibronectin and type IV collagen.[34,144]

Besides the five different cell types two different types of cavities can be distinguished: true lumina and pseudocysts. The latter are filled with basement membrane-like material and mucosubstances, which together with collagenous fibers are responsible for the characteristic hyalin of adenoid cystic carcinoma.[124]

The combination of the different cell types gives rise to three different growth patterns: glandular (cribriform), tubular and solid (basaloid). Most adenoid cystic carcinomas do not occur in "pure" types. Rather, all three patterns can be observed in the majority of tumours. Generally, tumours are classified according to the histological pattern that predominates. In the 1991-WHO-classification tubular and cribriform growth patterns are combined in a single subtype, called glandular-tubular.

In the differential diagnosis the adenoid cystic carcinoma should be distinguished from benign tumours as a pleomorphic adenoma, in which cylindromatous areas may occur, or as a basal cell adenoma. Staining for GFAP could help differentiate between pleomorphic adenoma (positive for GFAP) and adenoid cystic carcinoma (negative for GFAP).[131] It may also be difficult to distinguish between the solid type of adenoid cystic carcinoma and a basal cell carcinoma.[145]

All adenoid cystic carcinomas are biologically aggressive and show a high rate of (distant) metastasis.[108] Tumours with predominantly solid patterns seem to have a worse prognosis than tumours with a more glandular or tubular appearance.[166] Adenoid cystic carcinomas have a marked tendency for endoneural and perineural invasion, which influences prognosis.[181] DNA-measurements of adenoid cystic carcinoma seem to give significant information regarding prognosis.[63]

Polymorphous low-grade adenocarcinoma (Terminal duct carcinoma)

"A malignant epithelial tumour characterized by cytological uniformity, morphological diversity and a low metastatic potential" (WHO, 1991). (Figs. 25 and 26).

Polymorphous low-grade adenocarcinoma (PLGA) is a relatively recent addition to the classification of salivary gland tumours. PLGA has previously been termed lobular carcinoma, terminal duct carcinoma, and low-grade papillary adenocarcinoma.[134] It almost exclusively arises in the intraoral salivary glands and is characterized by cytological uniformity, histological blandness, cellular organisation diversity and an infiltrative growth pattern. The growth pattern varies and includes solid islands, tubules, trabeculae, cribriform nests, cysts and papillary configurations. Perineural and perivascular invasion is often present.[57] Mitotic figures are rare and necrosis is not seen.

The cellular composition of PLGA is suggestive of an origin from the pluripotential reserve/stem cells that normally reside at the acinar intercalated junctions and which can differentiate along two cell lines, epithelial and myoepithelial.[132] The immunoprofile of PLGA includes consistent demonstration of cytokeratin, EMA, and S-100 protein. CEA and muscle specific actin are variably immunoreactive. No GFAP-staining can be detected.[67,132]

PLGA must be separated from adenoid cystic carcinoma, pleomorphic adenoma, carcinoma ex pleomorphic adenoma and papillary cyst adenocarcinoma.[131] The different staining patterns of EMA and CEA might be helpful in the differential diagnosis of adenoid cystic carcinoma and PLGA,[67] just as the different intensities of S-100 staining.[132]

PLGA is a biologically low-grade neoplasm, locally invasive with a low recurrence rate. Metastases are uncommon.[132]

Epithelial-myoepithelial carcinoma

"A tumour composed of variable proportions of two cell types which typically form duct-like structures. There is an inner layer of duct lining cells and an outer layer of clear cells" (WHO, 1991).

The epithelial-myoepithelial carcinoma predominantly occurs in the parotid glands of elderly patients with a peak incidence in the seventh and eighth decade.[38]

The tumour is multinodular and shows an invasive growth pattern with occasional perineural infiltration. Mitoses are infrequent. The growth pattern may vary from solid lobules that are separated by bands of hyalinized fibrous tissue to irregular, papillary cystic arrangements. The outer clear cells contain variable amounts of glycogen, which has led to earlier diagnoses of glycogen-rich tumours. Immunocytochemical staining for smooth muscle myosin and S-100 protein produce intense decoration of the outer clear cells, while the inner ductal cells show a strong reaction for keratin.[105]

Epithelial-myoepithelial carcinoma behaves as a low-grade malignancy with occasional recurrences or metastatic spread.[76] In the differential diagnosis epithelial-myoepithelial carcinoma must be separated from other clear cell tumours.[145]

Basal cell adenocarcinoma

"An epithelial neoplasm that has cytological characteristics of basal cell adenoma but morphological growth pattern indicative of malignancy" (WHO, 1991).

Basal cell adenocarcinoma predominantly occurs in the parotid gland and is extremely rare in the minor salivary glands. Basal cell adenocarcinomas are low-grade adenocarcinomas with a relatively good prognosis.

It may be difficult to separate a basal cell adenocarcinoma from a basal cell adenoma. However, two signs are important for the diagnosis of carcinoma: frequent mitoses and infiltrative growth including perineural and intravascular invasion. Basal cell adenocarcinoma is suggested to be the malignant counterpart of basal cell adenoma.[52,145] In accordance with the histological patterns described for basal cell adenomas, basal cell adenocarcinomas can be divided into four subtypes: solid, trabecular, tubular and membranous.[146]

Squamous eddies and palisading of peripheral tumour cells help differentiate basal cell adenocarcinoma from adenoid cystic carcinoma, especially the solid or basaloid types.

Sebaceous carcinoma

"A rare variety of carcinoma composed of sebaceous cells of varying degrees of maturity" (WHO, 1991).

Sebaceous carcinomas almost exclusively arise in the parotid glands. Only one case of intraoral sebaceous carcinoma has been reported in the literature.[40] They are similarly classified as sebaceous adenomas into a sebaceous carcinoma and a sebaceous lymphadenocarcinoma. They seem to arise from pluripotential duct cells, which can differentiate into sebaceous, ductal and mucous cells.[107] Sebaceous carcinoma and sebaceous lymphadenocarcinoma appear to be low-grade malignant tumours that recur locally and may develop late lymph node or distant metastases.[145]

Papillary cystadenocarcinoma

"A malignant tumour characterized by cysts and papillary endocystic projections" (WHO, 1991). (Fig. 27).

Papillary cystadenocarcinoma is a low-grade malignancy which demonstrates a predilection for the intraoral salivary glands of the palate. It only consists of papillary structures. There is some nuclear atypia with rare mitoses.[59] It was first described as a papillary subtype of polymorphous low-grade adenocarcinoma. But as the papillary variant shows a more aggressive behaviour than the non-papillary type, these two types have been segregated.[156]

The histological differential diagnosis should include tumours with possible papillary features such as acinic cell carcinoma, salivary duct carcinoma, polymorphous low-grade adenocarcinoma and intraductal papilloma.

Mucinous adenocarcinoma

"A rare tumour characterized by abundant mucus production" (WHO, 1991).

The tumour consists of mucus-secreting cuboidal or columnar cells, lining cysts filled with abundant mucous material (> 50%). The mucoid substance stains with mucicarmine, PAS and Alcian blue. It must be separated from mucoepidermoid carcinoma, in which besides mucous cells also epidermoid cells are present. Mucinous adenocarcinoma has not been reported in the minor salivary glands.[125,145]

Oncocytic carcinoma

"A very rare tumour composed of malignant oncocytic cells" (WHO, 1991).

The parotid gland is the principal site of occurrence. It is sometimes termed as "malignant oncocytoma". The diagnosis can be made on the following histological criteria: oncocytic features with dysplasia, perineural or vascular invasion and infiltration of the surrounding tissue.[70] As in benign oncocytoma, examination of special stains or use of electron microscopy is often necessary to confirm oncocytic differentiation.

Oncocytic carcinoma is believed to have a poor prognosis.

Salivary duct carcinoma

"An epithelial tumour of high malignancy with formation of relatively large cell aggregates resembling distended salivary ducts. The neoplastic epithelium presents a combination of cribriform, looping ("Roman bridging") and solid growth patterns, often with central necrosis both in the primary lesions and the lymph node metastasis" (WHO, 1991).

This uncommon high-grade malignancy occurs almost exclusively in the major salivary glands, usually the parotid. It is said to arise from the excretory and interlobular ducts, lacking myoepithelial cells.[153] The histopathological appearance resembles that of ductal carcinoma of the breast, with comedonecrosis and cribriform and papillary projections.

Salivary duct carcinoma has been found to be immunoreactive for keratin and variably reactive for S-100 protein and myosin.[105]

Adenocarcinoma

"A carcinoma with glandular, ductal or secretory differentiation that does not fit into the other categories of carcinoma" (WHO, 1991).

Malignant myoepithelioma

"A rare malignant epithelial tumour composed of atypical myoepithelial cells with increased mitotic activity and aggressive growth" (WHO, 1991).

Malignant myoepithelioma, also called myoepithelial carcinoma, may either arise de novo or develop in a pre-existing pleomorphic adenoma. The tumour may be quite cellular and more suggestive of sarcoma than carcinoma. The few cases described all occurred in the parotid gland.[49,155] Immunohistochemistry may help to identify the myoepithelial nature of these tumours, showing S-100, vimentin and actin positivity.[155]

Carcinoma in pleomorphic adenoma (Malignant mixed tumour)

"Tumours showing definitive evidence of malignancy, such as cytological and histological characteristics of anaplasia, abnormal mitoses, progressive course and infiltrative growth, and in which evidence of pleomorphic adenoma can still be found" (WHO, 1991).
(Figs. 28 and 29).

Findings suggestive of malignant change in pleomorphic adenoma are micronecrosis and hemorrhage, excessive hyalinisation, dystrophic calcification and even ossification. Four subtypes can be distinguished:

- non-invasive carcinoma in pleomorphic adenoma, showing circumscribed malignant areas in a pleomorphic adenoma without infiltration of the surrounding tissue, also called carcinoma-in-situ;
- invasive carcinoma in pleomorphic adenoma, in which the extent of invasion is a valuable guide to prognosis. Survival is also related to the histological type of the carcinoma arising in the pleomorphic adenoma, most often being an undifferentiated carcinoma, a ductal carcinoma or myoepithelial carcinoma;[175]

- carcinosarcoma or true malignant mixed tumour, made up of carcinomatous and sarcomatous features. In this type, an adenocarcinoma or squamous cell carcinoma co-exists with a sarcoma, which may be an undifferentiated tumour, a fibrosarcoma, a malignant fibrous histiocytoma, or more commonly, a chondrosarcoma. These tumours can occur with or without histological evidence of a pleomorphic adenoma in major and minor salivary glands.[47,168] They display a high degree of lethality;
- metastasizing pleomorphic adenoma, being a histological benign tumour that inexplicably manifests distant metastases. Both the primary tumour and the metastases show benign features. They predominantly occur in the parotid gland, with metastases in the bone, liver, lung and lymph nodes.[151] The vast majority of these tumours is of the second type, invasive carcinoma in pleomorphic adenoma.

Myoepithelial cells play a key role in the morphogenesis of "malignant mixed tumours", whether carcinoma in pleomorphic adenoma or true malignant mixed tumour.[47,84]

"Malignant mixed tumours" are immunoreactive for keratin, smooth muscle actin, vimentin, CEA, EMA and lactoferrin.[73] Atypical epithelial cells are generally negative for S-100 and GFAP, where spindle-shaped cells in the myxoid areas show intense immunoreactivity.[118] Lysozyme, positive in benign pleomorphic adenomas cannot be detected in its malignant counterpart.[135,144]

Squamous cell carcinoma

"A malignant epithelial tumour with cells forming keratin or having intercellular bridges. Mucus secretion is not present" (WHO, 1991).

Primary squamous cell carcinoma of the salivary glands is very rare. They almost exclusively arise in the parotid gland and may be confused with high-grade mucoepidermoid carcinoma, adenocarcinoma or metastatic squamous cell carcinoma of the skin of the head and neck region, external auditory canal or mucosal surface of the upper aerodigestive tract.[147,165] Cure rates are lower than almost all other histological types.

Small cell carcinoma

"A malignant tumour similar in histology, behaviour and histochemistry to the small cell carcinoma of the lung" (WHO, 1991).

A rare salivary gland neoplasm which predominantly occurs in the major salivary glands. It also has occasionally been reported in the minor salivary glands of the larynx, nose, paranasal sinuses, esophagus and oral cavity. A primary tumour in the lung should be excluded before making a diagnosis of small cell salivary gland carcinoma.

Virtually all salivary gland small cell carcinomas appear to have neuroendocrine characteristics by immunohistochemical evaluation, even in those lesions in which dense core granules cannot be demonstrated ultrastructurally.[68] The tumours are composed of infiltrating large sheets, ribbons, cords or nests of anaplastic cells. Mitoses are frequent, and tumour necrosis is prominent.

Undifferentiated carcinoma

"A malignant tumour of epithelial structure that is too poorly differentiated, i.e. is devoid of any phenotypic expression by light microscopy, to be placed in any of the other groups of carcinoma" (WHO, 1991).

Although this group of tumours accounts for only a small population of salivary gland tumours, it is an important entity because of its rapid progressive nature, in which prognosis is mostly dependent on the size of the primary neoplasm.[16] It can arise in both major and minor salivary glands.

Undifferentiated carcinomas may be large or small cell in type, grow in solid or trabecular patterns, and can evince ultrastructural evidence of differentiation not detectable by the light microscope. They ultrastructurally may show neuroendocrine, ductal, acinus-like or epidermoid features.[81,88] Undifferentiated carcinomas are generally negative for CEA, which underlines the statement that CEA reactivity is linked to the presence of better differentiation just as the reactivity for blood group substances.[74,144]

A special subtype is the undifferentiated carcinoma with lymphoid stroma, also known as malignant lymphoepithelial lesion or lymphoepithelial carcinoma. This tumour has a high incidence among North American Eskimos, native Greenlanders and Southern Chinese, exclusively arises in the major salivary glands, and seems to be associated with Epstein-Barr virus.[35]

Other carcinomas

Some very rare carcinomas, which cannot be classified as one of the forementioned histological types have been reported. Carcinoma in a Warthin tumour, embryonal carcinoma and adenosquamous carcinoma are examples of this category.

2.6. Treatment

Surgical resection with adequate margins has been demonstrated to be an effective modality in case of benign and malignant intraoral salivary gland tumours.[177] The surgical extent should be individualized based on anatomical site, size and histology.[179] Radical excision is often necessary in order to obtain an adequate margin, but this can result in significant functional and esthetic deficit. In palatal neoplasms the underlying bone should be included in the specimen, independent of the findings of the pre-operative CT-scans. The optimal management of minor salivary gland tumours must include consideration of neck treatment.

Irradicality of surgical margins is not uncommon, especially in case of adenoid cystic carcinoma. Postoperative radiotherapy should than be instituted. In some centres postoperative radiotherapy is even routinely applied irrespective of the histological status of the surgical margins to obtain local control. In case of tumours with a favourable prognosis as low-grade mucoepidermoid carcinoma or acinic cell carcinoma and tumours occurring in young people, it may be wiser to withhold radiotherapy because of potential long term complications.[58]

Primary radiotherapy is rarely used when dealing with a malignant salivary gland tumour. Long-term palliation, however, can be achieved with radiation therapy alone in patients with advanced-staged disease or medically inoperable patients.[51,92] The role of fast neutron therapy for the management of advanced, inoperable tumours seems promising and should be further investigated also as an adjuvant treatment after surgery in case of positive surgical margins.[179] Patients developing recurrent disease are best treated by subsequent surgery, with or without adjuvant radiotherapy.

The role of chemotherapy in the treatment of malignant salivary gland neoplasms is still controversial.[97,180] It seems that salivary gland cancer is definitively responsive to certain chemotherapeutic drugs and can be used in patients with recurrent, metastatic, or inoperable tumours which are not amenable to the usual treatment with surgery and postoperative irradiation.

The treatment of the 101 intraoral salivary gland tumours diagnosed at the Free University Hospital is shown in Table 5.

Table 5. Treatment regimens of 101 patients with an intraoral salivary gland tumour

Histological type (WHO, 1972)	Surgery	Surgery/ Radiotherapy	Chemotherapy/ Surgery	Chemotherapy/ Radiotherapy	No therapy	Total
Pleomorphic adenoma	35	1	-	-	-	36
Monomorphic adenoma	8	-	-	-	-	8
Mucoepidermoid tumour	13	1	1	-	-	15
Acinic cell tumour	2	-	-	-	1	3
Adenoid cystic carcinoma	6	16	-	-	5	27
Adenocarcinoma	5	3	-	1	-	9
Carcinoma in pleom. adenoma	-	3	-	-	-	3
Total	69	24	1	1	6	101

Ninety-three patients were initially treated by surgery. In seven of them a simultaneous radical neckdissection was performed because of suspicious lymph nodes or location of the tumour in the floor of the mouth. In 62 patients surgical margins were negative, in 20 patients positive and 11 patients had questionable surgical margins on account of clinical and histopathological findings. Seven patients were not treated surgically due to their age, general condition and/or size and extension of the tumour. Twenty-four of the 93 surgically treated patients received postoperative radiotherapy because of questionable or positive surgical margins.

2.7. Follow-up and prognosis

After treatment, patients require careful follow-up because of the tendency for late relapse. All patients with a salivary gland tumour registered at the Free University Hospital are, in general, routinely seen for follow-up for at least 10 years. Patients with a benign tumour are seen once a year, and patients with a malignant tumour the first year after treatment every month and thereafter with longer intervals. In Table 6 the follow-up of the 101 patients with an intraoral salivary gland tumour by histology is shown. The mean follow-up period was 6.5 years with a range from 2 to 18 years.

Table 6. Follow-up of 101 patients with an intraoral salivary gland tumour by histology (WHO, 1972)

Histological type	Number	Local recurrence	Neck node metastasis	Distant metastasis	2nd primary tumour	Death of disease	Other or unknown cause of death
Pleomorphic adenoma	36	-	-	-	-	-	1
Monomorphic adenoma	8	-	-	-	1	-	-
Acinic cell tumour	-	-	-	-	-	-	-
Mucoepidermoid tumour	15	4	1	1	2	1	1
Adenoid cystic carcinoma	27	-	4	10	1	9	4
Adenocarcinoma	9	-	1	2	1	1	1
Carcinoma in pleom. adenoma	-	-	-	-	-	-	-

Mean follow-up period: 6.5 years, range 2-18 years

The pleomorphic adenoma of the intraoral salivary glands hardly ever gives a local recurrence (Table 6). This is in contrast with the parotid gland in which local recurrences of pleomorphic adenoma, especially after inadequate surgery, are no exception.[184] These patients present with their primary tumour at a significantly younger age than those who remained disease-free.[86,110] In some cases of pleomorphic adenoma, often long-standing tumours, malignant changes may occur. Benign pleomorphic adenomas can even metastasize to distant organs.[151]

Control of local malignant disease is best achieved with combined surgery and radiation therapy, especially when dealing with an adenoid cystic carcinoma. The incidence of metastatic spread may not be affected by this regimen.[108,112] The occurrence of metastases seems to depend more on clinical stage and persistence of tumour than on histological grade.[6]

Spread to regional lymph nodes is rare other than by direct extension. Distant metastases, particularly to lungs and bone, are much more common. Lung metastases of an adenoid cystic carcinoma appear often more than 5 or even 10 years after diagnosis of the primary tumour and can be asymptomatic for months or even years. However, patients continue to die from metastatic disease.[112]

Patients with a primary salivary gland tumour tend to have an increased risk of second primary tumours, especially breast cancer and skin cancer.[19,93] In our study of 101 patients with a primary intraoral salivary gland tumour five patients (5%) developed a second primary tumour; one patient had a breast carcinoma, one patient a prostate carcinoma, one patient a thyroid carcinoma and two patients a benign salivary gland tumour. However, the number of patients may be too small to draw any firm conclusions from this study.

Prognosis varies with the location, clinical stage, histology of the tumour and treatment factors.[2,20] Gender seems to be another important prognostic factor, since a better survival rate for women has been reported.[86]

Malignant intraoral salivary gland tumours tend to have a better prognosis than major salivary gland tumours and tumours arising in the nasal and paranasal sinuses, probably because they are usually smaller and are earlier detected.[140,158,179]

Clinical stage at presentation proved to be a highly significant determinant of survival.[158] Histological grade of the tumour also significantly influences survival. A clear difference in predicted survival can be detected when tumours are separated into low, intermediate and high grades. This is best correlated in mucoepidermoid carcinomas in which low-grade tumours have the best prognosis.[119,122] Grading of acinic cell carcinoma and adenoid cystic carcinoma is still controversial.[15] The subdivision of adenocarcinomas in different subtypes seems valuable with regard to prognosis.[105]

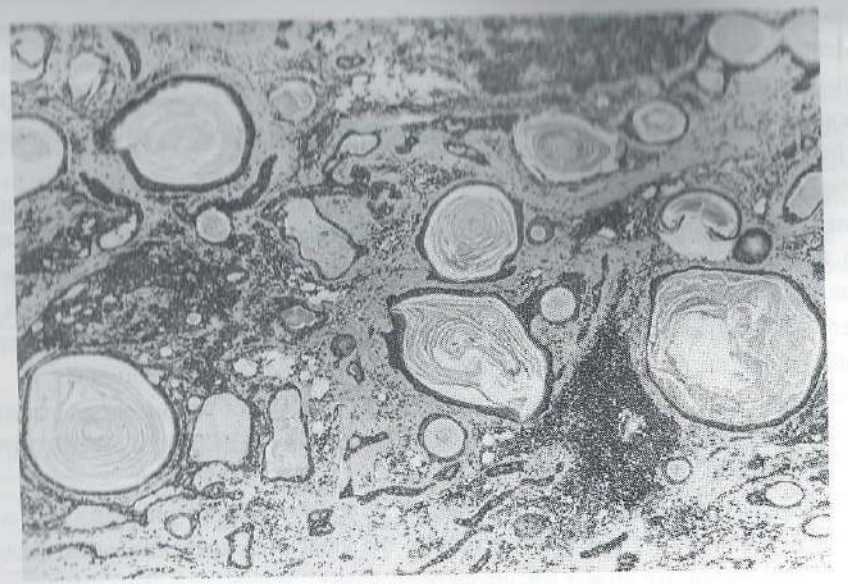

Fig. 7. Pleomorphic adenoma. Squamous epithelial islands with formation of multiple squamous epithelium-lined cysts (HE; x 45).

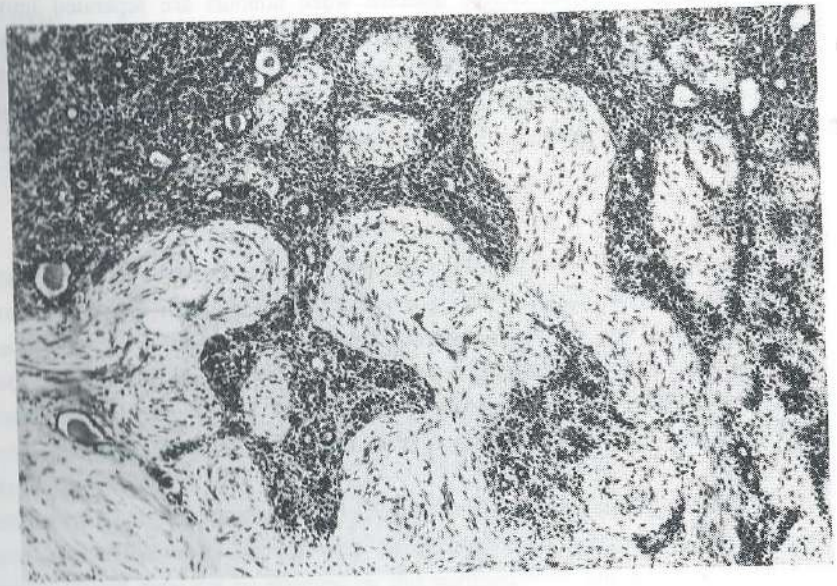

Fig. 8. Pleomorphic adenoma consisting of a cellular area with formation of occasional ductal structures and a spindle-shaped area (HE; x 90).

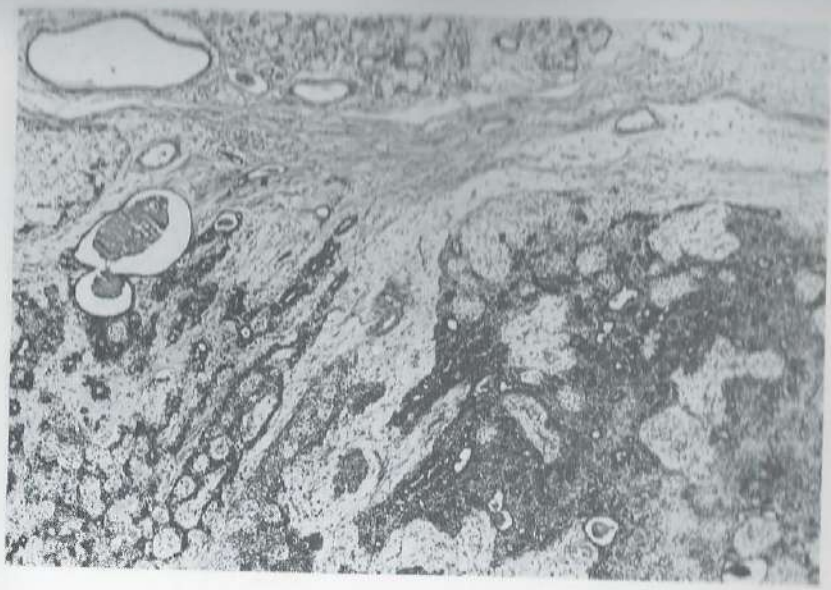

Fig. 9. Pleomorphic adenoma of the upper lip. A well-defined capsule is not present (HE; x 45).

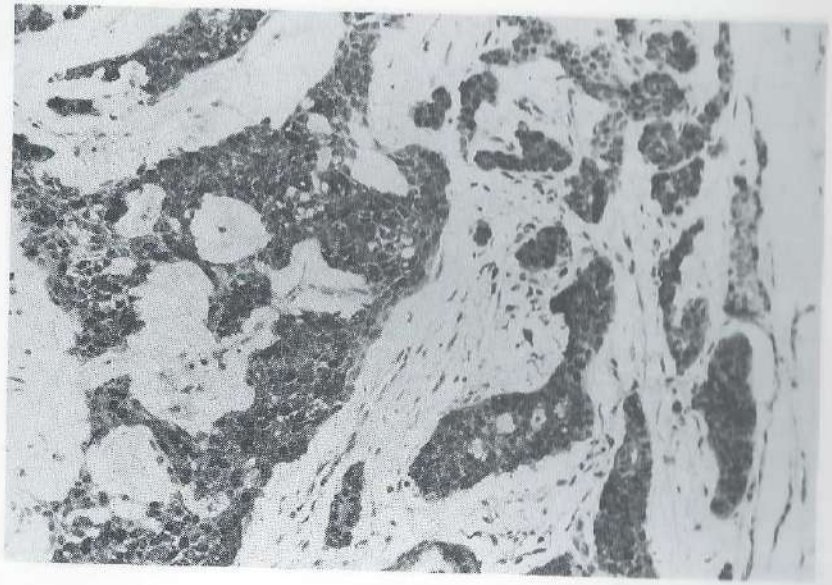

Fig. 10. S-100 staining in pleomorphic adenoma (x 180).

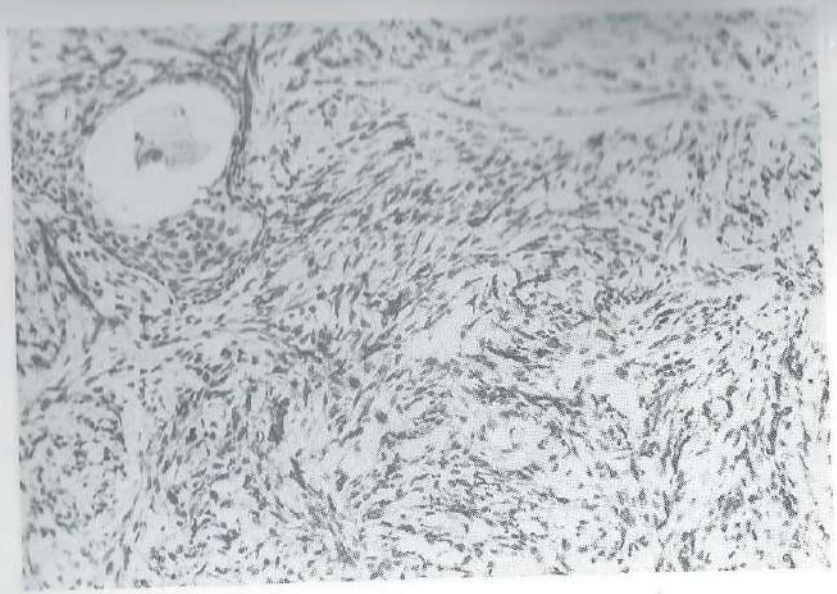

Fig. 11. Actin staining in spindle-shaped cells of pleomorphic adenoma (x 180).

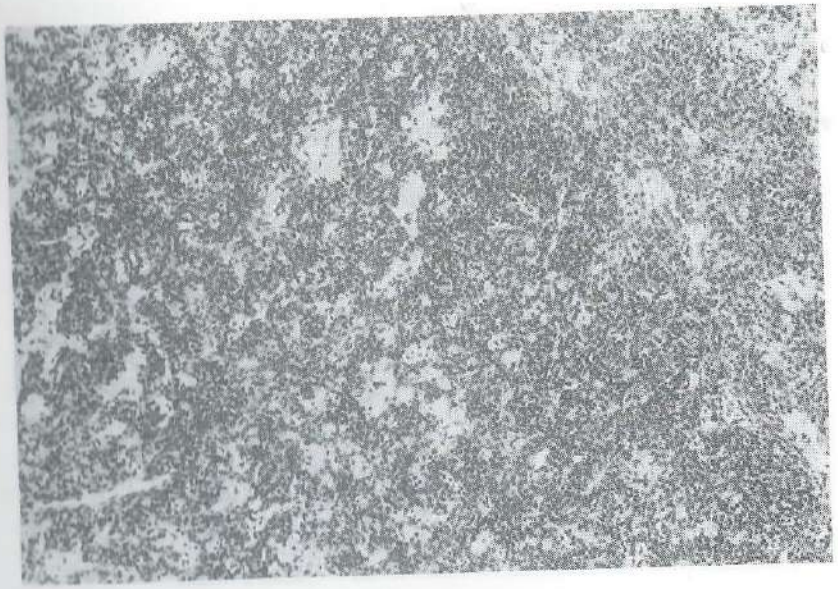

Fig. 12. Myoepithelioma of the cheek. No duct-like structures are present (HE; x 90).

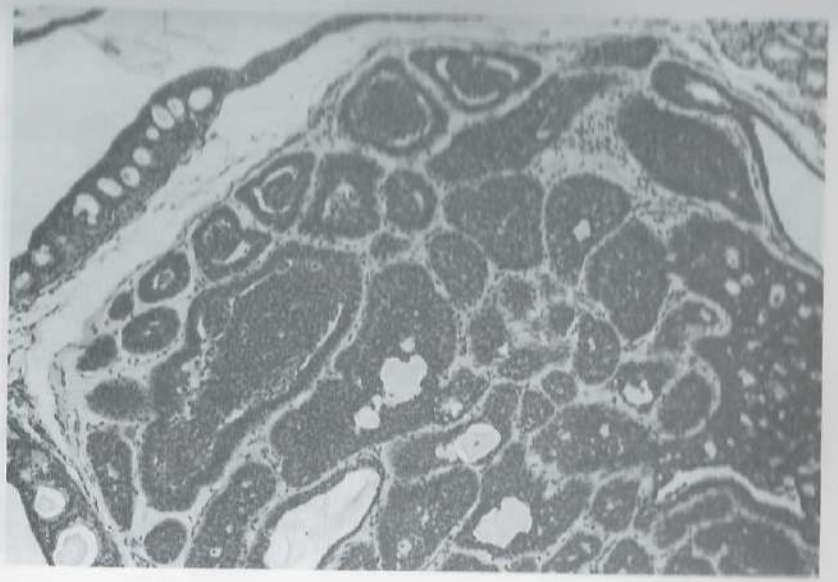

Fig. 13. Solid variant of basal cell adenoma, composed of islands of tumour cells with a hyperchromatic, palisaded peripheral cell layer (HE; x 90).

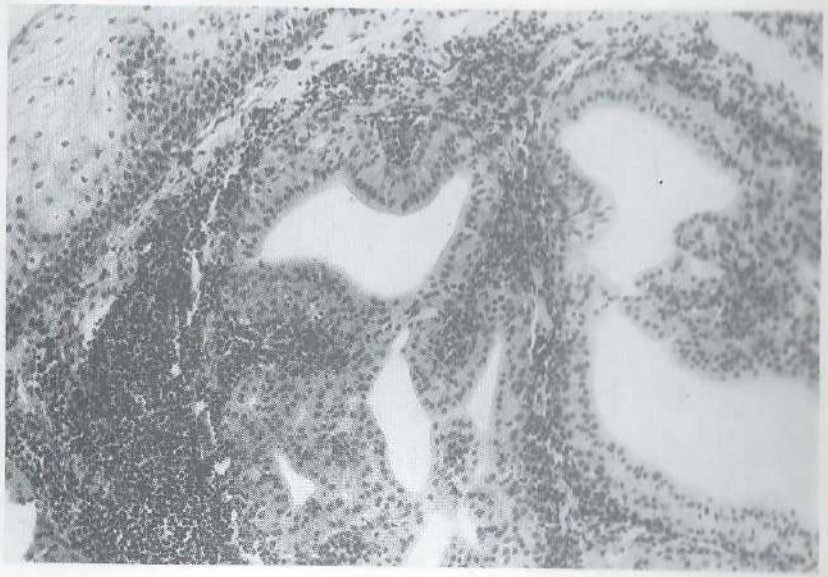

Fig. 14. Double-layered eosinophylic epithelium with papillary projections, surrounded by a lymphocytic infiltrate of the buccal fold resembling a Warthin tumour (HE; x 132).

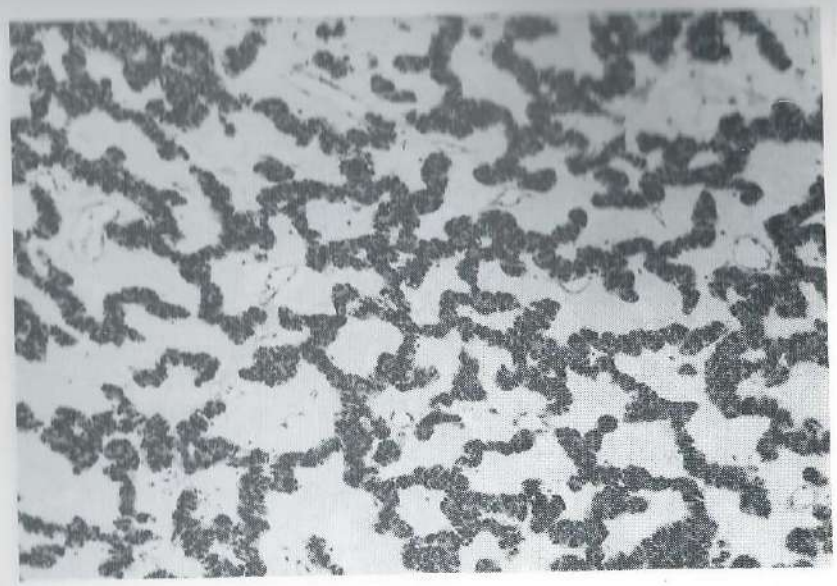

Fig. 15. Canalicular adenoma (HE; x 90).

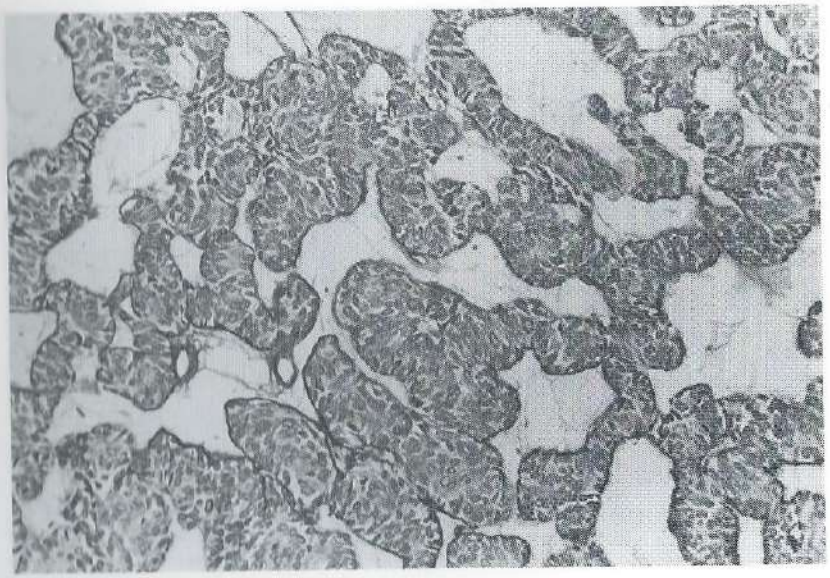

Fig. 16. Laminin staining in a canalicular adenoma (x 180).

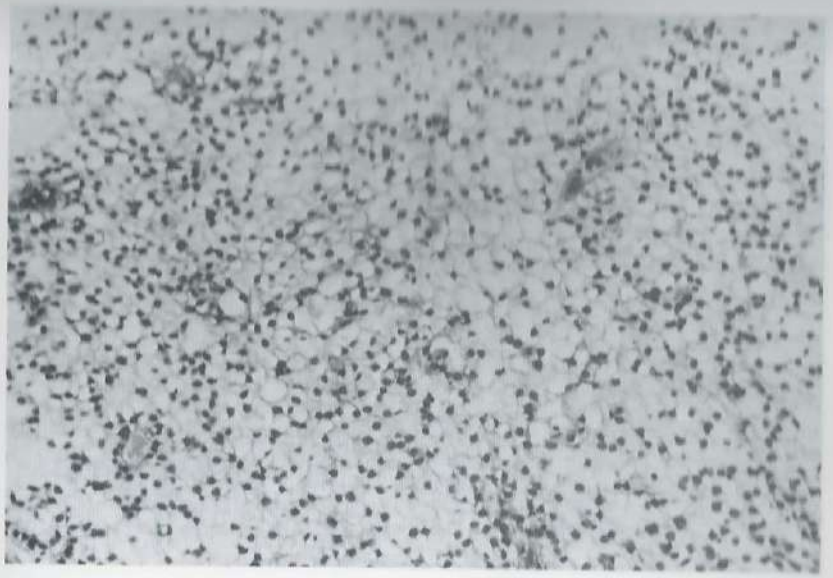

Fig. 17. A focus of clear cells in an acinic cell carcinoma (HE; x 180).

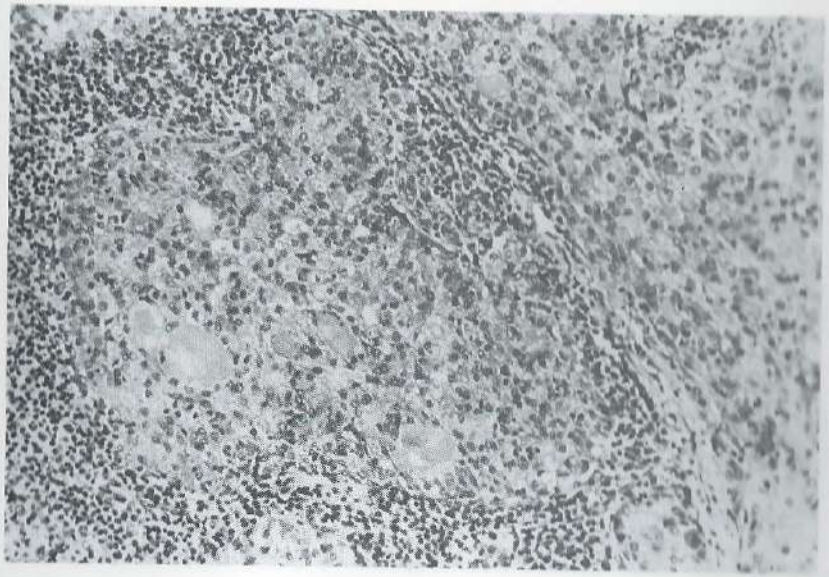

Fig. 18. Acinic cell carcinoma. Microcystic pattern with intercalated duct-like tumour cells surrounded by a variably dense lymphoid infiltrate (HE; x 180).

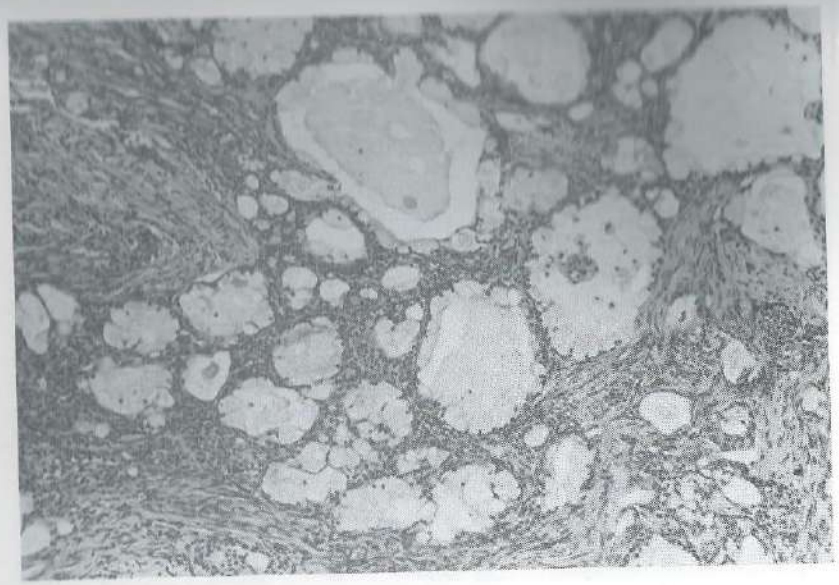

Fig. 19. Well-differentiated mucoepidermoid carcinoma with predominance of cystic spaces and mucus-producing cells (HE; x 90).

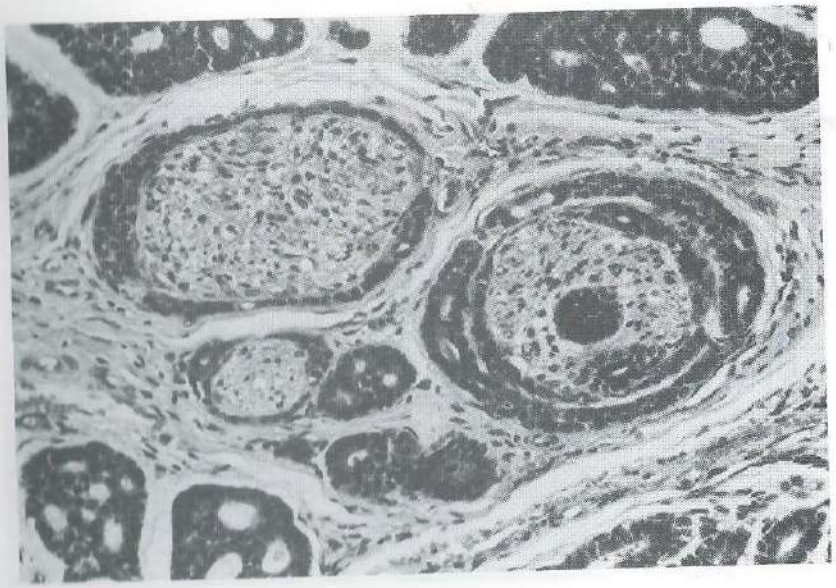

Fig. 20. Perineural and endoneural invasion in an adenoid cystic carcinoma (HE; x 180).

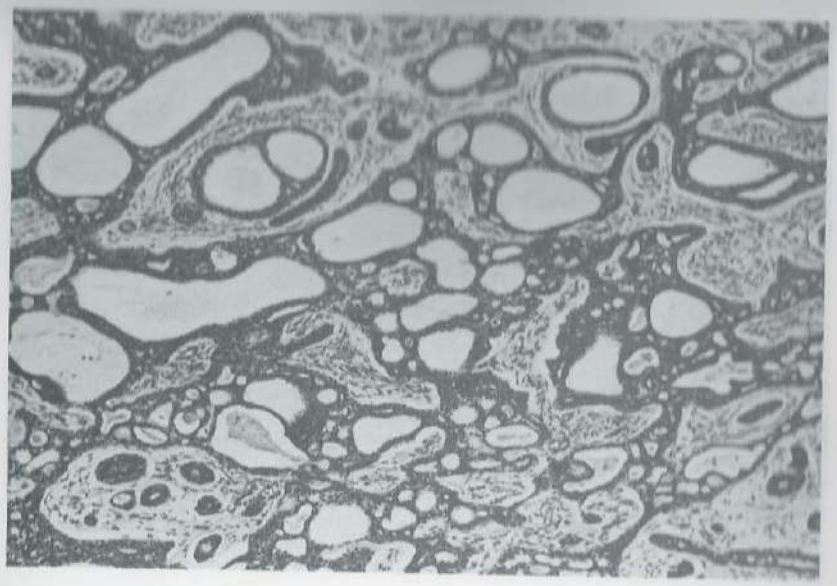

Fig. 21. Example of the cribriform pattern of adenoid cystic carcinoma (HE; x 90).

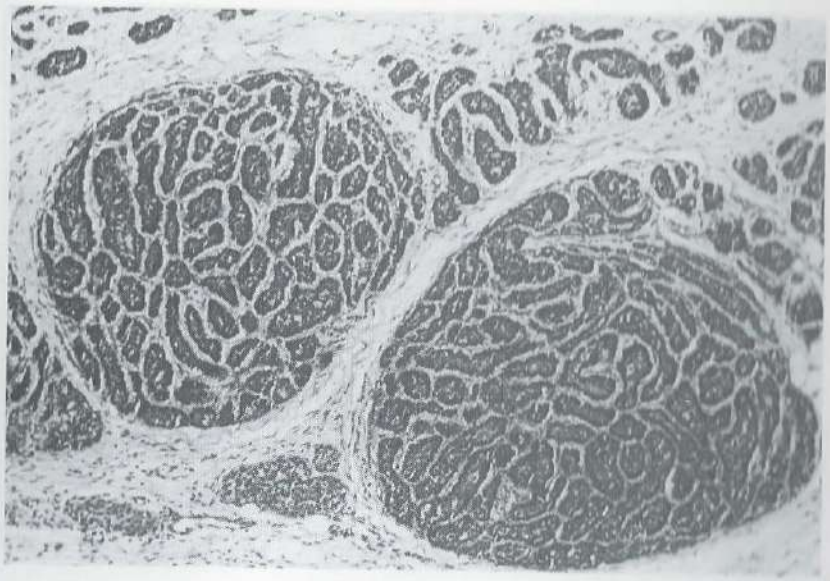

Fig. 22. Basaloid appearance in an adenoid cystic carcinoma of the floor of the mouth (HE; x 90).

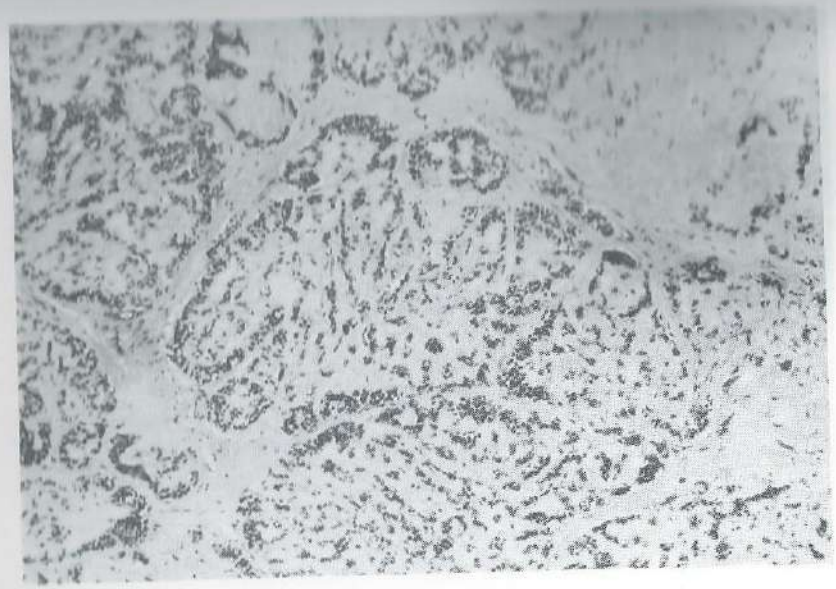

Fig. 23. Extensive hyalinisation in an adenoid cystic carcinoma of the floor of the mouth (HE; x 90).

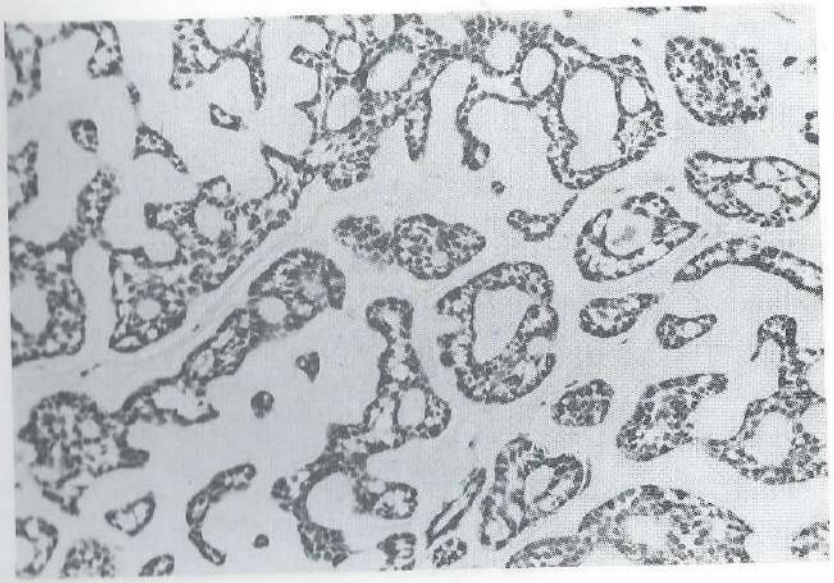

Fig. 24. Actin staining in an adenoid cystic carcinoma (x 180).

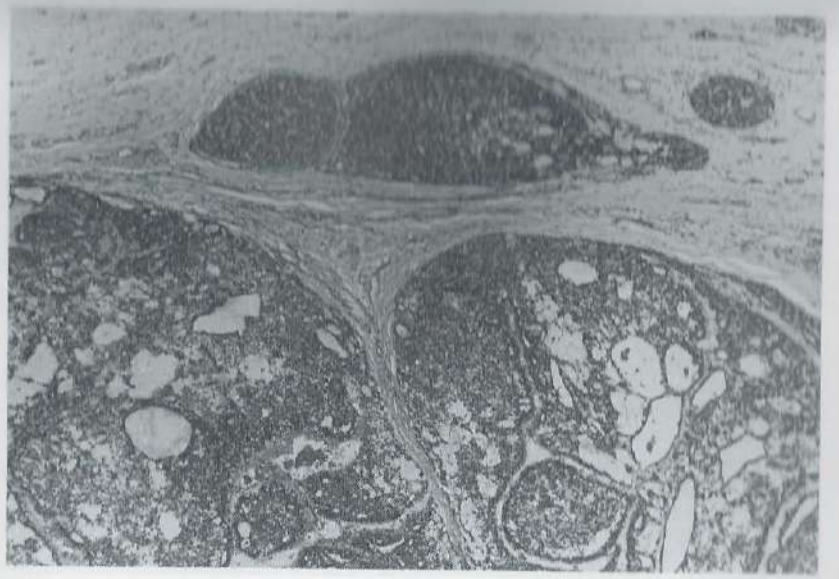

Fig. 25. Solid and cystic areas in a polymorphous low-grade adenocarcinoma. Note the capsular infiltration (HE; x 45).

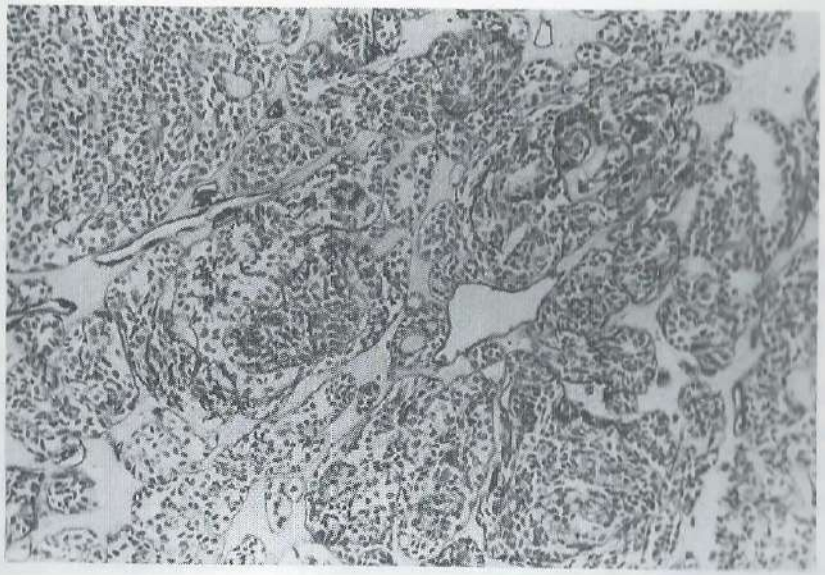

Fig. 26. Laminin staining in polymorphous low-grade adenocarcinoma. Focal staining of basal membrane material (x 180).

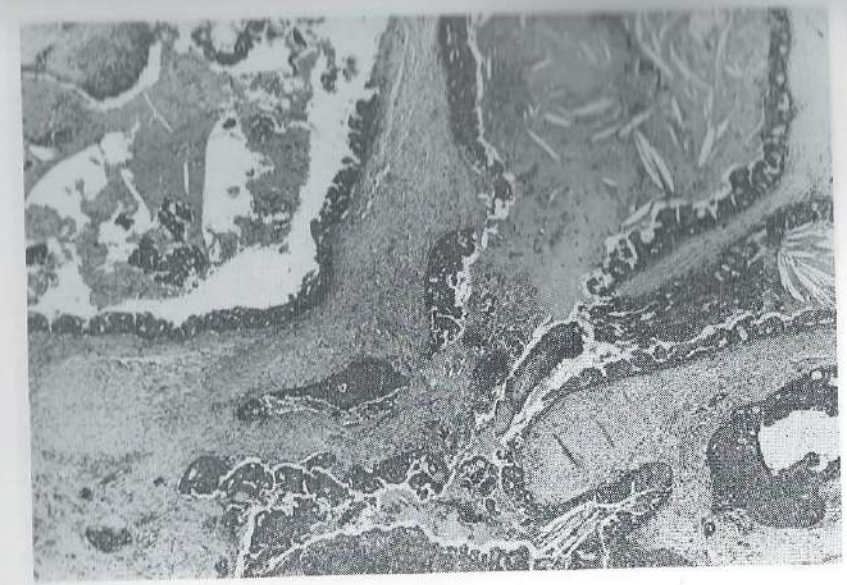

Fig. 27. Papillary cystadenocarcinoma with cysts and endocystic papillary projections (HE; x 45).

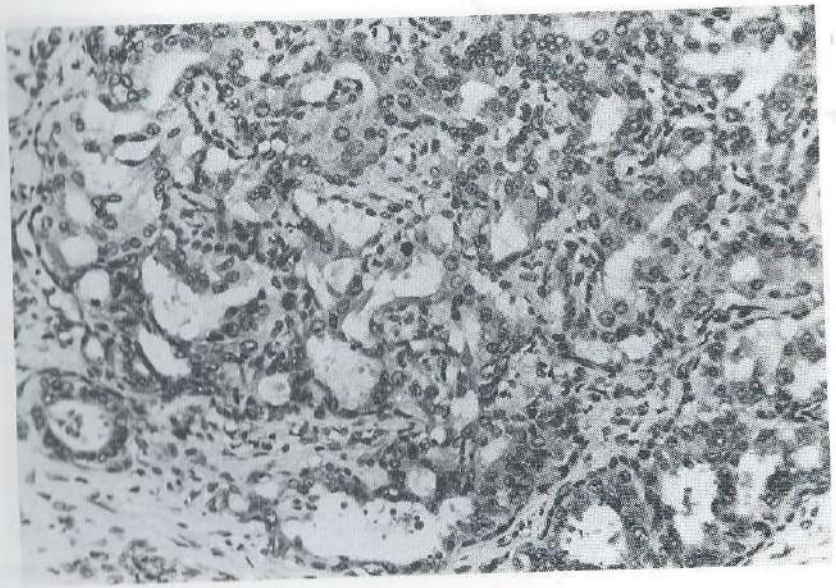

Fig. 28. Non-invasive carcinoma in pleomorphic adenoma. Irregular foci of adenocarcinoma with focal mitoses (HE; x 180).

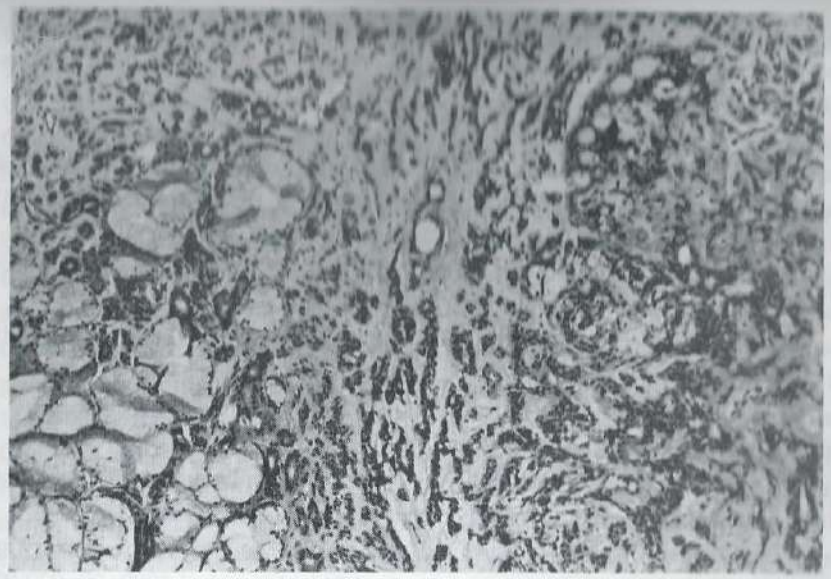

Fig. 29. Invasive carcinoma in pleomorphic adenoma. Note the infiltration in the adjacent salivary gland tissue (HE; x 90).

REFERENCES

1. Abbey LM, Schwab BH, Landau GC, Perkins ER. Incidence of second primary breast cancer among patients with a first primary salivary gland tumor. Cancer 1984; 54: 1439-1442.
2. Andersen LJ, Hamilton Therkildsen M, Ockelmann HH, Bentzen JD, Schiødt T, Hansen HS. Malignant epithelial tumors in the minor salivary glands, the submandibular gland, and the sublingual gland. Prognostic factors and treatment results. Cancer 1991; 68: 2431-2437.
3. Auclair PL, Langloss JM, Weiss SW, Corio RL. Sarcomas and sarcomatoid neoplasms of the major salivary gland regions. A clinicopathologic and immunohistochemical study of 67 cases and review of the literature. Cancer 1986; 58: 1305-1315.
4. Azumi N, Battifora H. The cellular composition of adenoid cystic carcinoma. An immunohistochemical study. Cancer 1987; 60: 1589-1598.
5. Baker SR, Malone B. Salivary gland malignancies in children. Cancer 1985; 55: 1730-1736.
6. Batsakis JG. Metastatic patterns of salivary gland neoplasms. Ann Otol Rhinol Laryngol 1982; 91: 465-466.

7. Batsakis JG, Kraemer B, Sciubba JJ. The pathology of head and neck tumors: The myoepithelial cell and its participation in salivary gland neoplasia, part 17. Head & Neck Surgery 1983; 5: 222-233.
8. Batsakis JG. Myoepithelioma. Ann Otol Rhinol Laryngol 1985; 94: 523-524.
9. Batsakis JG. Recurrent mixed tumor. Ann Otol Rhinol Laryngol 1986; 95: 543-544.
10. Batsakis JG. Vascular tumors of the salivary glands. Ann Otol Rhinol Laryngol 1986; 95: 649-650.
11. Batsakis JG, Luna MA. Low-grade and high-grade adenocarcinomas of the salivary duct system. Ann Otol Rhinol Laryngol 1989; 98: 162-163.
12. Batsakis JG. Adenomatous tumors of the middle ear. Ann Otol Rhinol Laryngol 1989; 98: 749-752.
13. Batsakis JG, El-Naggar AK. Sebaceous lesions of salivary glands and oral cavity. Ann Otol Rhinol Laryngol 1990; 99: 416-418.
14. Batsakis JG, Luna MA. Histopathologic grading of salivary gland neoplasms: I. Mucoepidermoid carcinomas. Ann Otol Rhinol Laryngol 1990; 99: 835-838.
15. Batsakis JG, Luna MA, El-Naggar AK. Histopathologic grading of salivary gland neoplasms: II. Acinic cell carcinomas. Ann Otol Rhinol Laryngol 1990; 99: 929-933.
16. Batsakis JG, Luna MA. Undifferentiated carcinomas of salivary glands. Ann Otol Rhinol Laryngol 1991; 100: 82-84.
17. Batsakis JG, Luna MA, El-Naggar AK. Basaloid monomorphic adenomas. Ann Otol Rhinol Laryngol 1991; 100: 687-690.
18. Berg JW, Hutter RVP, Foote FW. The unique association between salivary gland cancer and breast cancer. JAMA 1968; 204: 113-116.
19. Biggar RJ, Curtis RE, Hoffman DA, Flannery JT. Second primary malignancies following salivary gland cancers. Br J Cancer 1983; 47: 383-386.
20. Borthne A, Kjellevold K, Kaalhus O, Vermund H. Salivary gland malignant neoplasms: Treatment and prognosis. Int J Rad Oncol Biol Phys 1986; 12: 747-754.
21. Bruner JM, Batsakis JG. Salivary neoplasms of the jaw bones with particular reference to central mucoepidermoid carcinomas. Ann Otol Rhinol Laryngol 1991; 100: 954-955.
22. Campbell WG, Priest RE, Weathers DR. Characterization of two types of crystalloids in pleomorphic adenomas of minor salivary glands. A light-microscopic, electron-microscopic, and histochemical study. Am J Pathol 1985; 118: 194-202.
23. Caselitz J, Seifert G, Grenner G, Schmidtberger R. Amylase as an additional marker of salivary gland neoplasms. An immunoperoxidase study. Path Res Pract 1983; 176: 276-283.
24. Caselitz J, Schmitt P, Seifert G, Wustrow J, Schuppan D. Basal membrane associated substances in human salivary glands and salivary gland tumors. Path Res Pract 1988; 183: 386-394.

25. Chaplin AJ, Darke P, Patel S. Tyrosine-rich crystals in pleomorphic adenomas of parotid glands. J Oral Pathol 1983; 12: 342-346.
26. Chapnik JS. The controversy of Warthin's tumor. Laryngoscope 1983; 93: 695-716.
27. Chau MNY, Radden BG. Intraoral benign solid oncocytoma. Int J Oral Maxillofac Surg 1986; 15: 503-506.
28. Chau MNY, Radden BG. Intraoral salivary gland neoplasms: A retrospective study of 98 cases. J Oral Pathol 1986; 15: 339-342.
29. Chau MNY, Radden BG. A clinical-pathological study of 53 intraoral pleomorphic adenomas. Int J Oral Maxillofac Surg 1989; 18: 158-162.
30. Chaudhry AP, Labay GR, Yamane GM, Jacobs MS, Cutler LS, Watkins KV. Clinicopathologic and histogenetic study of 189 intraoral minor salivary gland tumors. J Oral Med 1984; 39: 58-78.
31. Chaudhry AP, Cutler LS, Leifer C, Satchidanand S, Labay GR, Yamane GM. Histogenesis of acinic cell carcinoma of the major and minor salivary glands. An ultrastructural study. J Pathol 1986; 148: 307-320.
32. Chaudhry AP, Leifer C, Cutler LS, Satchidanand S, Labay GR, Yamane GM. Histogenesis of adenoid cystic carcinoma of the salivary glands. Light and electron-microscopic study. Cancer 1986; 58: 72-82.
33. Chaudhry AP, Cutler LS, Leifer C, Labay GR, Satchidanand S, Yamane GM. Ultrastructural study of the histogenesis of salivary gland mucoepidermoid carcinoma. J Oral Pathol Med 1989; 18: 400-409.
34. Chen JC, Gnepp DR, Bedrossian CWM. Adenoid cystic carcinomas of the salivary glands: An immunohistochemical analysis. Oral Surg Oral Med Oral Pathol 1988; 65: 316-326.
35. Cleary KR, Batsakis JG. Undifferentiated carcinoma with lymphoid stroma of the major salivary glands. Ann Otol Rhinol Laryngol 1990; 99: 236-238.
36. Collins RJ, Yu HC. Pleomorphic adenoma of the external auditory canal. An immunohistochemical and ultrastructural study. Cancer 1989; 64: 870-875.
37. Daley TD, Gardner DG, Smout MS. Canalicular adenoma: Not a basal cell adenoma. Oral Surg Oral Med Oral Pathol 1984; 57: 181-188.
38. Daley TD, Wysocki GP, Smout MS, Slinger RP. Epithelial-myoepithelial carcinoma of salivary glands. Oral Surg Oral Med Oral Pathol 1984; 57: 512-519.
39. Damm DD, White DK, Geissler RH, Drummond JF, Henry BB. Benign solid oncocytoma of intraoral minor salivary glands. Oral Surg Oral Med Oral Pathol 1989; 67: 84-86.
40. Damm DD, O'Connor WN, White DK, Drummond JF, Morrow LW, Kenady DE. Intraoral sebaceous carcinoma. Oral Surg Oral Med Oral Pathol 1991; 72: 709-711.
41. Dardick I, van Nostrand AWP, Phillips MJ. Histogenesis of salivary gland pleomorphic adenoma (mixed tumor) with an evaluation of the role of the myoepithelial cell. Hum Pathol 1982; 13: 62-75.

42. Dardick I, van Nostrand AWP, Jeans MTD, Rippstein P, Edwards V. Pleomorphic adenoma, I: Ultrastructural organization of "epithelial" regions. Hum Pathol 1983; 14: 780-797.
43. Dardick I, van Nostrand AWP, Jeans MTD, Rippstein P, Edwards V. Pleomorphic adenoma, II: Ultrastructural organization of "stromal" regions. Hum Pathol 1983; 14: 798-809.
44. Dardick I, van Nostrand AWP. Myoepithelial cells in salivary gland tumors - revisited. Head & Neck Surgery 1985; 7: 395-408.
45. Dardick I, Daley TD, van Nostrand AWP. Basal cell adenoma with myoepithelial cell-derived "stroma": A new major salivary gland tumor entity. Head & Neck Surgery 1986; 8: 257-267.
46. Dardick I, George D, Jeans MTD, et al. Ultrastructural morphology and cellular differentiation in acinic cell carcinoma. Oral Surg Oral Med Oral Pathol 1987; 63: 325-334.
47. Dardick I, Hardie J, Thomas MJ, van Nostrand AWP. Ultrastructural contributions to the study of morphological differentiation in malignant mixed (pleomorphic) tumors of salivary gland. Head & Neck Surgery 1989; 11: 5-21.
48. Dardick I, Thomas MJ, van Nostrand AWP. Myoepithelioma - new concepts of histology and classification: A light and electron microscopic study. Ultrastructural Pathology 1989; 13: 187-224.
49. DiPalma S, Pilotti S, Rilke F. Malignant myo-epithelioma of the parotid gland arising in a pleomorphic adenoma. Histopathology 1991; 19: 273-275.
50. Donath K, Seifert G, Lentrodt J. The embryonal carcinoma of the parotid gland. A rare example of an embryonal tumor. Virchows Arch [A] Pathol Anat 1984; 403: 425-440.
51. Ellis ER, Million RR, Mendenhall WM, Parsons JT, Cassisi NJ. The use of radiation therapy in the management of minor salivary gland tumors. Int J Rad Oncol Biol Phys 1988; 15: 613-618.
52. Ellis GL, Wiscovitch JG. Basal cell adenocarcinomas of the major salivary glands. Oral Surg Oral Med Oral Pathol 1990; 69: 461-469.
53. Eveson JW, Cawson RA. Salivary gland tumours. A review of 2410 cases with particular reference to histological types, site, age and sex distribution. J Pathol 1985; 146: 51-58.
54. Eveson JW, Cawson RA. Tumours of the minor (oropharyngeal) salivary glands: A demographic study of 336 cases. J Oral Pathol 1985; 14: 500-509.
55. Eveson JW, Cawson RA. Warthin's tumor (cystadenolymphoma) of salivary glands. A clinicopathologic investigation of 278 cases. Oral Surg Oral Med Oral Pathol 1986; 61: 256-262.
56. Fantozzi RD, Bone RC, Fox R. Extraglandular Warthin's tumors. Laryngoscope 1985; 95: 682-688.

57. Fitzpatrick PJ, Black KM. Salivary gland tumors. J Otolaryngol 1985; 14: 296-300.
58. Fitzpatrick PJ, Theriault C. Malignant salivary gland tumors. Int J Rad Oncol Biol Phys 1986; 12: 1743-1747.
59. Fliss DM, Zirkin H, Puterman M, Tovi F. Low-grade papillary adenocarcinoma of buccal mucosa salivary gland origin. Head & Neck Surgery 1989; 11: 237-241.
60. Flood TR, Maharaja BB, MacDonald GD, Giri DD. Central acinic cell carcinoma of the mandible: Report of a case. Br J Oral Maxillofac Surg 1991; 29: 26-28.
61. Fonseca I, Martins AG, Soares J. Epithelial salivary gland tumors of children and adolescents in southern Portugal. A clinicopathologic study of twenty-four cases. Oral Surg Oral Med Oral Pathol 1991; 72: 696-701.
62. Franklin CD, Ong TK. Ductal papilloma of the minor salivary gland. Histopathology 1991; 19: 180-182.
63. Franzén G, Klausen OG, Grenko RT, Carstensen J, Nordenskjöld B. Adenoid cystic carcinoma: DNA as a prognostic indicator. Laryngoscope 1991; 101: 669-673.
64. Gleeson MJ, Bennett MH, Cawson RA. Lymphomas of salivary glands. Cancer 1986; 58: 699-704.
65. Gnepp DR, Brannon R. Sebaceous neoplasms of salivary gland origin. Report of 21 cases. Cancer 1984; 53: 2155-2170.
66. Gnepp DR, Rader WR, Cramer SF, Cook LL, Sciubba J. Accuracy of frozen section diagnosis of the salivary gland. Otolaryngol Head Neck Surg 1987; 96: 325-330.
67. Gnepp DR, Chen JC, Warren C. Polymorphous low-grade adenocarcinoma of minor salivary gland. An immunohistochemical and clinicopathologic study. Am J Surg Pathol 1988; 12: 461-468.
68. Gnepp DR, Wick MR. Small cell carcinoma of the major salivary glands. An immunohistochemical study. Cancer 1990; 66: 185-192.
69. Goldblatt LI, Ellis GL. Salivary gland tumors of the tongue. Analysis of 55 new cases and review of the literature. Cancer 1987; 60: 74-81.
70. Goode RK, Corio RL. Oncocytic adenocarcinoma of salivary glands. Oral Surg Oral Med Oral Pathol 1988; 65: 61-66.
71. Granick MS, Erickson ER, Hanna DC. Accuracy of frozen-section diagnosis in salivary gland lesions. Head & Neck Surgery 1985; 7: 465-467.
72. Grubka JM, Wesley RK, Monaco F. Primary intraosseous mucoepidermoid carcinoma of the anterior part of the mandible. J Oral Maxillofac Surg 1983; 41: 389-394.
73. Gustafsson H, Virtanen I, Thornell L-E. Glial fibrillary acidic protein and desmin in salivary neoplasms. Expression of four different types of intermediate filament proteins within the same cell type. Virchows Archiv [B] Cell Pathol 1989; 57: 303-313.
74. Hamper K, Caselitz J, Seifert G, Seitz R, Poschmann A. The occurrence of blood group substances (A, B, H, Le-a, Le-b) in salivary glands and salivary gland tumors. An immunohistochemical investigation. J Oral Pathol 1986; 15: 334-338.

75. Hamper K, Schimmelpenning H, Caselitz J, et al. Mucoepidermoid tumors of the salivary glands. Correlation of cytophotometrical data and prognosis. Cancer 1989; 63: 708-717.
76. Hamper K, Brügmann M, Koppermann R, et al. Epithelial-myoepithelial duct carcinoma of salivary glands: A follow-up and cytophotometric study of 21 cases. J Oral Pathol Med 1989; 18: 299-304.
77. Hamper K, Schmitz-Wätjen W, Mausch H-E, Caselitz J, Seifert G. Multiple expression of tissue markers in mucoepidermoid carcinomas and acinic cell carcinomas of the salivary glands. Virchows Arch [A] Pathol Anat 1989; 414: 407-413.
78. Hamper K, Mausch H-E, Caselitz J, et al. Acinic cell carcinoma of the salivary glands: The prognostic relevance of DNA cytophotometry in a retrospective study of long duration (1965-1987). Oral Surg Oral Med Oral Pathol 1990; 69: 68-75.
79. Harris MD, McKeever P, Robertson JM. Congenital tumours of the salivary gland: A case report and review. Histopathology 1990; 17: 155-157.
80. Hartwick RWJ, Batsakis JG. Non-Warthin's tumor oncocytic lesions. Ann Otol Rhinol Laryngol 1990; 99: 674-677.
81. Hayashi Y, Nagamine S, Yanagawa T, et al. Small cell undifferentiated carcinoma of the minor salivary gland containing exocrine, neuroendocrine, and squamous cells. Cancer 1987; 60: 1583-1588.
82. Heerden van WFP, Raubenheimer EJ. Intraoral salivary gland neoplasms: A retrospective study of seventy cases in an African population. Oral Surg Oral Med Oral Pathol 1991; 71: 579-582.
83. Heerden van WFP, Raubenheimer EJ. Evaluation of the nucleolar organizer region associated proteins in minor salivary gland tumors. J Oral Pathol Med 1991; 20: 291-295.
84. Hellquist H, Michaels L. Malignant mixed tumour. A salivary gland tumour showing both carcinomatous and sarcomatous features. Virchows Arch [A] Pathol Anat 1986; 409: 93-103.
85. Hermanek P, Sobin LH. TNM classification of malignant tumours, 4th edition, 1987. International Union Against Cancer. Springer-Verlag, Berlin-Heidelberg-New York.
86. Hickman RE, Cawson RA, Duffy SW. The prognosis of specific types of salivary gland tumors. Cancer 1984; 54: 1620-1624.
87. Horn-Ross PL, West DW, Brown SR. Recent trends in the incidence of salivary gland cancer. Int J Epidemiol 1991; 20: 628-633.
88. Hui KK, Luna MA, Batsakis JG, Ordóñez NG, Weber R. Undifferentiated carcinomas of the major salivary glands. Oral Surg Oral Med Oral Pathol 1990; 69: 76-83.
89. Humphrey PA, Ingram P, Tucker A, Shelburne JD. Crystalloids in salivary gland pleomorphic adenomas. Arch Pathol Lab Med 1989; 113: 390-393.
90. Isacsson G, Shear M. Intraoral salivary gland tumors: A retrospective study of 201 cases. J Oral Pathol 1983; 12: 57-62.

91. Jayaram N, Ashim D, Rajwanshi A, Radhika S, Banerjee CK. The value of fine-needle aspiration biopsy in the cytodiagnosis of salivary gland lesions. Diagn Cytopathol 1989; 5: 349-354.
92. Jenkins DW, Spaulding CA, Constable WC, Cantrell RW. Minor salivary gland tumors: The role of radiotherapy. Am J Otolaryngol 1989; 10: 250-256.
93. Johns ME, Shikhani AH, Kashima HK, Matanoski GM. Multiple primary neoplasms in patients with salivary gland or thyroid gland tumors. Laryngoscope 1986; 96: 718-721.
94. Johnson PA, Millar BG, Leopard PJ. Intraosseous adenoid cystic carcinomas of the mandible. Br J Oral Maxillofac Surg 1989; 27: 501-505.
95. Kahn HJ, Baumal R, Marks A, Dardick I, van Nostrand AWP. Myoepithelial cells in salivary gland tumors. Arch Pathol Lab Med 1985; 109: 190-195.
96. Kaneda T, Mizuno N, Takeuchi M, Yamashita T. Primary central adenoid cystic carcinoma of the mandible. J Oral Maxillofac Surg 1982; 40: 741-745.
97. Kaplan MJ, Johns ME, Cantrell RW. Chemotherapy for salivary gland cancer. Otolaryngol Head Neck Surg 1986; 95: 165-170.
98. Katz AD, Preston-Martin S. Salivary gland tumors and previous radiotherapy to the head or neck. Report of a clinical series. Am J Surg 1984; 147: 345-348.
99. Kerpel SM, Freedman PD, Lumerman H. The papillary cystadenoma of minor salivary gland origin. Oral Surg Oral Med Oral Pathol 1978; 46: 820-824.
100. Krishnamurthy S, Lanier AP, Dohan P, Lanier JF, Henle W. Salivary gland cancer in Alaskan natives, 1966-1980. Hum Pathol 1987; 18: 986-996.
101. Lack EE, Upton MP. Histopathologic review of salivary gland tumors in childhood. Arch Otolaryngol Head Neck Surg 1988; 114: 898-906.
102. Langdon JD. Tumors of the salivary glands: Clinical analysis of 68 cases. J Oral Maxillofac Surg 1985; 43: 688-692.
103. Lau T, Balle VH, Bretlau P. Fine needle aspiration biopsy in salivary gland tumours. Clin Otolaryngol 1986; 112: 75-77.
104. Lewis JE, Olsen KD, Weiland LH. Acinic cell carcinoma. Clinicopathologic review. Cancer 1991; 67: 172-179.
105. Luna MA, Batsakis JG, Ordóñez NG, Mackay B, Tortoledo ME. Salivary gland adenocarcinomas: A clinicopathologic analysis of three distinctive types. Sem Diagn Pathol 1987; 4: 117-135.
106. Luna MA, Batsakis JG, El-Naggar AK. Salivary gland tumors in children. Ann Otol Rhinol Laryngol 1991; 100: 869-871.
107. MacMillan III RH, Fechner RE. Pleomorphic adenoma of the larynx. Arch Pathol Lab Med 1986; 110: 245-247.
108. Matsuba HM, Spector GJ, Thawley SE, Simpson JR, Mauney M, Pikul FJ. Adenoid cystic salivary gland carcinoma. A histopathologic review of treatment failure patterns. Cancer 1986; 57: 519-524.

109. Matthews JB. Immunocytochemical methods: A technical overview. J Oral Pathol 1987; 16: 189-195.
110. McGregor AD, Burgoyne M, Tan KC. Recurrent pleomorphic salivary adenoma: The relevance of age at first presentation. Br J Plast Surg 1988; 41: 177-181.
111. Merrick Y, Albeck H, Højgaard Nielsen N, Hansen HS. Familial clustering of salivary gland carcinoma in Greenland. Cancer 1986; 57: 2097-2102.
112. Miglianico L, Eschwege F, Marandas P, Wibault P. Cervico-facial adenoid cystic carcinoma: Study of 102 cases. Influence of radiation therapy. Int J Rad Oncol Biol Phys 1987; 13: 673-678.
113. Morgan DW, Crocker J, Watts A, Shenoi PM. Salivary gland tumours studied by means of the AgNOR technique. Histopathology 1988; 13: 553-559.
114. Mori M, Tsukitani T, Ninomiya T, Okada Y. Various expressions of modified myoepithelial cells in salivary pleomorphic adenoma. Immunohistochemical studies. Path Res Pract 1987; 182: 632-646.
115. Mori M, Ninomiya T, Okada Y, Tsukitani K. Myoepitheliomas and myoepithelial adenomas of salivary gland origin. Immunohistochemical evaluation of filament proteins, S-100 α and ß, glial fibrillary acidic proteins, neuron-specific enolase, and lactoferrin. Path Res Pract 1989; 184: 168-178.
116. Morinaga S, Nakajima T, Shimosato Y. Normal and neoplastic myoepithelial cells in salivary glands: An immunohistochemical study. Hum Pathol 1987; 18: 1218-1226.
117. Nagao K, Matsuzaki O, Shigematsu H, Kaneko T, Katoh T, Kitamura T. Histopathologic studies of benign infantile hemangioendothelioma of the parotid gland. Cancer 1980; 46: 2250-2256.
118. Nakazato Y, Ishida Y, Takahashi K, Suzuki K. Immunohistochemical distribution of S-100 protein and glial fibrillary acidic protein in normal and neoplastic salivary glands. Virchows Arch [A] Pathol Anat 1985; 405: 299-310.
119. Nascimento AG, Amaral ALP, Prado LAF, Kligerman J, Silveira TRP. Mucoepidermoid carcinoma of salivary glands: A clinicopathologic study of 46 cases. Head & Neck Surgery 1986; 8: 409-417.
120. Neville BW, Damm DD, Weir JC, Fantasia JE. Labial salivary gland tumors. Cancer 1988; 61: 2113-2116.
121. Norberg LE, Burford-Mason AP, Dardick I. Cellular differentiation and morphologic heterogeneity in polymorphous low-grade adenocarcinoma of minor salivary gland. J Oral Pathol Med 1991; 20: 373-379.
122. O'Brien CJ, Soong S-J, Herrera GA, Urist MM, Maddox WA. Malignant salivary tumors: Analysis of prognostic factors and survival. Head & Neck Surgery 1986; 9: 82-92.

123. Önder T, Tiwari RM, Waal van der I, Snow GB. Malignant adenolymphomas of the parotid gland: Report of carcinomatous transformation. J Laryngol Otol 1990; 104: 656-661.
124. Ormos J, Halász A. Electron microscopic study of adenoid cystic carcinoma. Ultrastructural Pathology 1991; 15: 149-157.
125. Osaki T, Hirota J, Ohno A, Tatemoto Y. Mucinous adenocarcinoma of the submandibular gland. Cancer 1990; 66: 1796-1801.
126. Owens OT, Calcaterra TC. Salivary gland tumors of the lip. Arch Otolaryngol 1982; 108: 45-47.
127. Palmer RM, Lucas RB, Knight J, Gusterson B. Immunocytochemical identification of cell types in pleomorphic adenoma, with particular reference to myoepithelial cells. J Pathol 1985; 146: 213-220.
128. Pogrel MA, Hansen LS. Second primary tumor associated with salivary gland cancer. Oral Surg Oral Med Oral Pathol 1984; 58: 71-75.
129. Pogrel MA. The intraoral basal cell adenoma. J Cranio-Max.-Fac Surg 1987; 15: 372-375.
130. Preston-Martin S, Thomas DC, White SC, Cohen D. Prior exposure to medical and dental X-rays related to tumors of the parotid gland. J Natl Cancer Inst 1988; 80: 943-949.
131. Regezi JA, Lloyd RV, Zarbo RJ, McClatchey KD. Minor salivary gland tumors. A histopathologic and immunohistochemical study. Cancer 1985; 55: 108-115.
132. Regezi JA, Zarbo RJ, Stewart JCB, Courtney RM. Polymorphous low-grade adenocarcinoma of minor salivary gland. A comparative histologic and immunohistochemical study. Oral Surg Oral Med Oral Pathol 1991; 71: 469-475.
133. Rigual NR, Milley P, Loré JM, Kaufman S. Accuracy of frozen-section diagnosis in salivary gland neoplasms. Head & Neck Surgery 1986; 8: 442-446.
134. Robinson AC, Kaberos A, Cox PM, Stearns MP. Oncocytoma of the larynx. J Laryngol Otol 1990; 104: 346-349.
135. Rognum TO, Thrane PS, Korsrud FR, Brandtzaeg P. Epithelial tumor markers: Special markers of glandular differentiation. Cur Top Pathol 1987; 77: 133-153.
136. Rosa de G, Zeppa P, Tranfa F, Bonavolonta G. Acinic cell carcinoma arising in a lacrimal gland. First case report. Cancer 1986; 57: 1988-1991.
137. Roth A, Micheau C. Embryoma (or embryonal tumor) of the parotid gland: Report of two cases. Pediatric Pathology 1986; 5: 9-15.
138. Scanlon EF, Sener SF. Head and neck neoplasia following irradiation for benign conditions. Head & Neck Surgery 1981; 4: 139-145.
139. Sehested M, Hainau B, Albeck H, Nielsen NH, Hansen JPH. Ultrastructural investigation of anaplastic salivary gland carcinomas in Eskimos. Cancer 1985; 55: 2732-2736.

140. Seifert G, Rieb H, Donath K. Klassifikation der Tumoren der kleinen Speicheldrüsen. Pathohistologische Analyse von 160 Tumoren. Laryng Rhinol 1980; 59: 379-400.
141. Seifert G, Oehne H. Die mesenchymalen (nicht-epithelialen) Speicheldrüsentumoren. Analyse von 167 Tumorfällen des Speicheldrüsen-Registers. Laryng Rhinol Otol 1986; 65: 485-491.
142. Seifert G, Okabe H, Caselitz J. Epithelial salivary gland tumors in children and adolescents. Analysis of 80 cases (Salivary Gland Register 1965-1984). ORL 1986; 48: 137-149.
143. Seifert G. Klassifikation der mesenchymalen Tumoren der grossen Speicheldrüsen. Dtsch Z Mund Kiefer GesichtsChir 1988; 12: 64-73.
144. Seifert G, Caselitz J. Epithelial salivary gland tumors: Tumor markers. Progress in Surgical Pathology, 1989; Chapter 8, pg. 157-187.
145. Seifert G, Brocheriou C, Cardesa A, Eveson JW. WHO International Histological Classification of Tumours. Tentative Histologic Classification of Salivary Gland Tumours. Path Res Pract 1990; 186: 555-581.
146. Seifert G, Sobin LH. WHO International Histological Classification of Tumours. Histological Typing of Salivary Gland Tumours. Second Edition. Springer-Verlag, Heidelberg, 1991.
147. Shemen LJ, Huvos AG, Spiro RH. Squamous cell carcinoma of salivary gland origin. Head & Neck Surgery 1987; 9: 235-240.
148. Shikhani A, Samara M, Allam C, Salem P, Lenhard R. Primary lymphoma in the salivary glands: Report of five cases and review of the literature. Laryngoscope 1987; 97: 1438-1442.
149. Shikhani A, Johns ME. Tumors of the major salivary glands in children. Head & Neck Surgery 1988; 10: 257-263.
150. Shore-Freedman E, Abrahams C, Recant W, Schneider AB. Neurilemomas and salivary gland tumors of the head and neck following childhood irradiation. Cancer 1983; 51: 2159-2163.
151. Sim DW, Maran AGD, Harris D. Metastatic salivary pleomorphic adenoma. J Laryngol Otol 1990; 104: 45-47.
152. Simpson PR, Rutledge JC, Schaefer SD, Anderson RC. Congenital hybrid basal cell adenoma - adenoid cystic carcinoma of the salivary gland. Pediatric Pathology 1986; 6: 199-208.
153. Simpson RHW, Clarke TJ, Sarsfield PTL, Babajews AV. Salivary duct adenocarcinoma. Histopathology 1991; 18: 229-235.
154. Simpson RHW, Clarke TJ, Sarsfield PTL, Gluckman PGC, Babajews AV. Polymorphous low-grade adenocarcinoma of the salivary glands: A clinicopathological comparison with adenoid cystic carcinoma. Histopathology 1991; 19: 121-129.

155. Singh R, Cawson RA. Malignant myoepithelial carcinoma (myoepithelioma) arising in a pleomorphic adenoma of the parotid glands. An immunohistochemical study and review of the literature. Oral Surg Oral Med Oral Pathol 1988; 66: 65-70.
156. Slootweg PJ, Müller H. Low-grade adenocarcinoma of the oral cavity. A comparison between the terminal duct and the papillary type. J Cranio-Max.-Fac Surg 1987; 15: 359-364.
157. Smith Frable MA, Frable WJ. Fine-needle aspiration biopsy of salivary glands. Laryngoscope 1991; 101: 245-249.
158. Spiro RH. Salivary neoplasms: Overview of a 35-year experience with 2,807 patients. Head & Neck Surgery 1986; 8: 177-184.
159. Spitz MR, Tilley BC, Batsakis JG, Gibeau JM, Newell GR. Risk factors for major salivary gland carcinoma. A case-comparison study. Cancer 1984; 54: 1854-1859.
160. Spitz MR, Newell GR, Gibeau JM, Byers RM, Batsakis JG. Multiple primary cancer risk in patients with major salivary gland carcinoma. Ann Otol Rhinol Laryngol 1985; 94: 129-132.
161. Spitz MR, Sider JG, Newell GR, Batsakis JG. Incidence of salivary gland cancer in the United States relative to ultraviolet radiation exposure. Head & Neck Surgery 1988; 10: 305-308.
162. Spitz MR, Fueger JJ, Goepfert H, Newell GR. Salivary gland cancer. A case-control investigation of risk factors. Arch Otolaryngol Head Neck Surg 1990; 116: 1163-1166.
163. Spitz MR, Sider JG, Newell GR. Salivary gland cancer and risk of subsequent skin cancer. Head & Neck Surgery 1990; 12: 254-256.
164. Stead RH, Qizilbash AH, Kontozoglou T, Daya AD, Riddell RH. An immunohistochemical study of pleomorphic adenomas of the salivary gland: Glial fibrillary acidic protein-like immunoreactivity identifies a major myoepithelial component. Hum Pathol 1988; 19: 32-40.
165. Sterman BM, Kraus DH, Sebek BA, Tucker HM. Primary squamous cell carcinoma of the parotid gland. Laryngoscope 1990; 100: 146-148.
166. Szanto PA, Luna MA, Tortoledo ME, White RA. Histologic grading of adenoid cystic carcinoma of the salivary glands. Cancer 1984; 54: 1062-1069.
167. Takata T, Ogawa I, Nikai H. Sebaceous carcinoma of the parotid gland. An immunohistochemical and ultrastructural study. Virchows Arch [A] Pathol Anat 1989; 414: 459-464.
168. Takata T, Nikai H, Ogawa I, Ijuhin N. Ultrastructural and immunohistochemical observations of a true malignant mixed tumor (carcinosarcoma) of the tongue. J Oral Pathol Med 1990; 19: 261-265.
169. Takeichi N, Hirose F, Yamamoto H, Ezaki H, Fujikura T. Salivary gland tumors in atomic bomb survivors, Hiroshima, Japan. II. Pathologic study and supplementary epidemiologic observations. Cancer 1983; 52: 377-385.

170. Taylor GP. Case 6. Congenital epithelial tumor of the parotid: Sialoblastoma. Pediatric Pathology 1988; 8: 447-452.
171. Thackray AC, Sobin LH. WHO International Histological Classification of Tumours. Histological Typing of Salivary Gland Tumours. World Health Organization, Geneva, 1972.
172. Thompson SH, Bender S, Richards A. Plasmacytoid myoepithelioma of a minor salivary gland. J Oral Maxillofac Surg 1985; 43: 285-288.
173. To EWH, Chan FFY. Intramandibular salivary monomorphic adenoma. J Cranio-Max-Fac Surg 1990; 18: 122-124.
174. Tornes K, Bang G, Møller P. Central mucoepidermoid tumour of the mandible. Report of 2 cases. J Cranio-Max-Fac Surg 1987; 15: 38-41.
175. Tortoledo ME, Luna MA, Batsakis JG. Carcinomas ex pleomorphic adenoma and malignant mixed tumors. Arch Otolaryngol 1984; 110: 172-176.
176. Toto PD, Hsu DJ. Product definition of pleomorphic adenoma of minor salivary glands. J Oral Pathol 1985; 14: 818-832.
177. Tran L, Sadeghi A, Hanson D, Ellerbroek N, Calcaterra TC, Parker RG. Salivary gland tumors of the palate: The UCLA experience. Laryngoscope 1987; 97: 1343-1345.
178. Tran L, Sidrys J, Horton D, Sadeghi A, Parker RG. Malignant salivary gland tumors of the paranasal sinuses and nasal cavity. The UCLA experience. Am J Clin Oncol 1989; 12: 387-392.
179. Tran L, Sidrys J, Sadeghi A, Ellerbroek N, Hanson D, Parker RG. Salivary gland tumors of the oral cavity. Int J Rad Oncol 1990; 18: 413-417.
180. Venook AP, Tseng A, Meyers FJ, et al. Cisplatin, doxorubicin, and 5-fluorouracil chemotherapy for salivary gland malignancies: A pilot study of the Northern California Oncology Group. J Clin Oncol 1987; 5: 951-955.
181. Vrielinck LJG, Ostyn F, Van Damme B, Van den Bogaert W, Fossion E. The significance of perineural spread in adenoid cystic carcinoma of the major and minor salivary glands. Int J Oral Maxillofac Surg 1988; 17: 190-193.
182. Waldron CA, El-Mofty SK, Gnepp DR. Tumors of the intraoral minor salivary glands: A demographic and histologic study of 426 cases. Oral Surg Oral Med Oral Pathol 1988; 66: 323-333.
183. Warner TFCS, Seo IS, Azen EA, Hafez GR, Zarling TA. Immunocytochemistry of acinic cell carcinomas and mixed tumors of salivary glands. Cancer 1985; 56: 2221-2227.
184. Watkin GT, Hobsley M. Influence of local surgery and radiotherapy on the natural history of pleomorphic adenomas. Br J Surg 1986; 73: 74-76.
185. Weber RS, Palmer JM, El-Naggar A, McNeese MD, Guillamondegui OM, Byers RM. Minor salivary gland tumors of the lip and buccal mucosa. Laryngoscope 1989; 99: 6-9.

186. White DK, Miller AS, McDaniel RK, Rothman BN. Inverted ductal papilloma: A distinctive lesion of minor salivary gland. Cancer 1982; 49: 519-524.
187. Zarbo RJ, Regezi JA, Batsakis JG. S-100 protein in salivary gland tumors: An immunohistochemical study of 129 cases. Head & Neck Surgery 1986; 8: 268-275.

CHAPTER 3

HISTOLOGICAL RE-EVALUATION OF 101 INTRAORAL SALIVARY GLAND TUMOURS BY AN EORTC-STUDY GROUP

J.E. van der Wal[1], R.L. Carter[2], J. Klijanienko[3], C. Micheau[3], F. Rilke[4], G. Seifert[5], I. van der Waal[1]

[1]Department of Oral & Maxillofacial Surgery and Oral Pathology, Free University Hospital, Academic Centre for Dentistry Amsterdam (ACTA), Amsterdam, The Netherlands

[2]Department of Histopathology, Royal Marsden Hospital, Sutton, United Kingdom

[3]Institut Gustave Roussy Histopathologie "A", Villejuif Cedex, France

[4]Division of Pathology, Istituto Nazionale Tumori, Milano, Italy

[5]Institut für Pathologie der Universität Hamburg, Hamburg, Germany

Submitted for publication

ABSTRACT

Tumours of the salivary glands constitute a heterogeneous group of lesions of great morphologic variation and, for this reason, present many difficulties in histologic classification.

The histologic slides of 101 consecutive intraoral salivary gland tumours of the Department of Oral Pathology of the Free University in Amsterdam were reviewed retrospectively by an EORTC-study group on salivary gland tumours. Complete concurrence of diagnosis was reached in 54 cases. In 33 cases there were minor disagreements, mostly related to subclassification. Major disagreements, relating to benign versus malignant, occurred in eight cases (7.9 per cent).

INTRODUCTION

Salivary gland tumours account for about 3% of all head and neck neoplasms.[1] The majority of these tumours is of epithelial origin. More than 90% of the salivary gland neoplasms are localized in the major salivary glands. The remaining 10% of the salivary gland tumours are found in the minor salivary glands.[2]

Tumours of the salivary glands constitute a group of lesions of great morphologic variation and, for this reason, may present difficulties in histologic classification. The histologic slides of 101 intraoral salivary gland tumours were re-evaluated by an EORTC (European Organization on Research and Treatment of Cancer)-study group on salivary gland tumours.

MATERIALS AND METHODS

In the period January 1970 - January 1988 101 consecutive patients with a tumour of the intraoral salivary glands have been registered at the Free University Hospital in Amsterdam. There were 50 male patients and 51 female patients, with a mean age of 52.6 and 50.0 years, respectively. The distribution of the 101 tumours according to site and original histologic diagnosis based on the 1972-WHO-classification, is shown in Table 1.[3] The pleomorphic adenoma was the most common histologic type, followed by the adenoid cystic carcinoma. Most of these tumours were located on the palate.

Treatment of benign tumours consisted of enucleation. In case of malignant salivary gland tumours a more aggressive surgical approach has been applied. Postoperative irradiation has been used in cases of adenoid cystic carcinoma irrespective of the histologic findings of the surgical margins. The mean follow-up period was 6.5 years (range 2-18 years).

The histologic slides of the 101 patients with a primary intraoral salivary gland tumour have been re-evaluated by all 5 members of an EORTC-study group on salivary gland tumours. A

modified WHO-classification was used, acinic cell tumours and mucoepidermoid tumours being referred to as carcinomas. Furthermore, the entities of polymorphous low-grade adenocarcinoma and myoepithelioma were recognized.[4] Unavoidably, some of the more recent terminology has been used during the re-evaluation of the histologic slides.

Table 1. Distribution of 101 intraoral salivary gland tumours according to site and histologic type (original diagnosis) according to the 1972-WHO-classification[3]

	Palate	Upper lip	Lower lip	Cheek	Floor of the mouth	Retro-molar area	Upper alv. ridge	Mandible	Tongue	Total
Pleomorphic adenoma	27	4	1	4	-	-	-	-	-	36
Monomorphic adenoma	3	4	-	1	-	-	-	-	-	8
Mucoepidermoid tumour	8	-	1	2	1	1	1	-	1	15
Acinic cell tumour	2	-	-	-	-	1	-	-	-	3
Adenoid cystic carcinoma	15	2	-	1	4	1	3	1	-	27
Adenocarcinoma	5	1	-	-	1	-	2	-	-	9
Ca. in pleom. adenoma	1	-	-	-	1	-	1	-	-	3
Total	61	11	2	8	7	3	7	1	1	101

The slides were reviewed independently by each member. Only hematoxylin and eosin stained slides were available for review in every case. No special stains were used. The reviewers have not been informed about the original diagnosis and the further clinical course.

Three categories of re-evaluation were instituted: one category contained all cases in which complete concurrence of diagnoses was reached, the second category was the group of minor disagreement in diagnosis, related to different diagnoses within the benign or malignant tumourgroup, and a third category of major disagreement in diagnosis related to a benign versus malignant diagnosis. The cases with major disagreement in diagnosis have been reviewed for a second time. The members revised the same slides with the same clinical information, without knowing that they had seen the slides before. Only the Paris group did not review these slides again.

RESULTS

Complete concurrence of diagnosis was reached in 54 cases (53%) (Table 2). In 33 cases (33%) there was minor disagreement, related to subclassification both within the benign and malignant tumourgroup, such as for instance pleomorphic versus monomorphic adenoma, or adenoid cystic carcinoma versus adenocarcinoma (Table 3). Major disagreement, related to benign versus malignant, occurred in 14 cases (14%). In 50% of these cases one out of five diagnoses was different and in the other 50% of the cases two out of five diagnoses were different.

Table 2. Distribution of 54 cases with complete concurrence of diagnosis

	Number of cases	Total no. in group of 101 tumours
Pleomorphic adenoma	25	36
Monomorphic adenoma	2	7
Mucoepidermoid carcinoma	7	15
Adenocarcinoma	1	8
Adenoid cystic carcinoma	19	27
Total	54	93

Table 3. Distribution of 33 cases with minor disagreement in diagnosis

Monomorphic adenoma	- Pleomorphic adenoma	11
Acinic cell carcinoma	- Mucoepidermoid carcinoma	2
Mucoepidermoid carcinoma	- Adenocarcinoma	3
Adenocarcinoma	- Adenoid cystic carcinoma	11
Acinic cell carcinoma	- Adenocarcinoma	1
Adenocarcinoma	- Sebaceous carcinoma	1
Mucoepidermoid carcinoma	- Acinic cell carcinoma	1
Adenocarcinoma	- Sebaceous carcinoma	1
Adenoid cystic carcinoma	- Squamous cell carcinoma	1
Adenocarcinoma	- Myoepithelial carcinoma	1
Total		33

The results of the second revision of the 14 cases with major disagreement in diagnosis is shown in Table 4.

In eight cases there was still a major disagreement in diagnosis. In three cases only a minor disagreement remained after second revision and in the other three cases a complete concurrence of diagnosis was reached.

Table 4. Distribution of the 8 cases with major disagreement in diagnosis after two re-evaluations

Original diagnosis	Revised EORTC diagnosis			
Amsterdam	Pathologist 1	Pathologist 2	Pathologist 3	Pathologist 4
1. CPA	MEC	CPA	CPA	PA
2. MA	MEC	AC	MA	CA, NOS
3. PA	reactive?	AC	MEC	Adenitis
4. PA	CPA	PA	CPA	PLGA
5. PA	BSC	MA	Sialometaplasia	?
6. ACC	PLGA	MA	ACC	MA
7. AC	PLGA	PLGA	CPA	PA
8. AC	ME	AC	PLGA	MA

AC = adenocarcinoma
ACC = adenoid cystic carcinoma
BSC = basaloid squamous carcinoma
CA, NOS = carcinoma, not otherwise specified
CPA = carcinoma in pleomorphic adenoma
MA = monomorphic adenoma
ME = myoepithelioma
MEC = mucoepidermoid carcinoma
PA = pleomorphic adenoma
PLGA = polymorphous low-grade adenocarcinoma

DISCUSSION

The distribution of the histologic types and localisation in our study is somewhat similar to other studies on intraoral salivary gland tumours, with the pleomorphic adenoma being the most common histologic type and the palate the most common localisation.[5] To the best of our knowledge, no earlier studies have been reported in which a re-evaluation of the histologic slides of salivary gland tumours was described, that also included the follow-up data.

The typing of salivary gland tumours and especially of minor salivary gland tumours is apparently rather difficult. As shown in Table 2 some histologic types seem more easy to characterize than others, for instance adenoid cystic carcinomas (complete concurrence of diagnosis in 19 out of 27 cases).

The second revision of the 14 cases with major disagreement in diagnosis shows that in some of these cases a concurrence of diagnosis has been reached. However, there are still tumours in which a major disagreement in diagnosis remains. In some of these cases the examiners even changed their first diagnosis from benign to malignant or vice versa which further illustrates the difficulty of the histologic classification of minor salivary gland tumours.

Although the terminology of the various histologic types of salivary gland tumours has apparently somewhat changed even since the 1972-WHO monograph, this development has not really influenced the results of the present study.

In none of the cases of complete concurrence of diagnosis nor of the group of minor disagreements events have occurred during the follow-up period which seriously questioned the original diagnoses and results of the re-evaluation.

In none of the eight cases in which major disagreements were recorded, local recurrence or metastatic spread has taken place. Nor has any other event that would have shed new light on the correctness of the diagnoses.

From the data obtained there are no reasons to change the original diagnosis of the four benign neoplasms which had one or more malignant diagnoses in the re-evaluation. With regard to the four cases in which an original malignant diagnosis was made the possibility of an overdiagnosis and, therefore, of an overtreatment remains.

Because of the great variety of tumour types and the now known differences in behaviour and prognosis a new WHO Histological Classification of Salivary Gland Tumours is elaborated.[4] This new classification contains more entities in the adenoma and carcinoma group, which should be helpful to surgical pathologists to more accurately - and perhaps also more reproducibly - classify a tumour.

REFERENCES

1. Eveson JW, Cawson RA. Salivary gland tumours. A review of 2410 cases with particular reference to histological types, site, age and sex distribution. J Oral Pathol 1985; 14: 51-58.
2. Fitzpatrick PJ, Black KM. Salivary gland tumors. J Otolaryngol 1985; 14: 296-300.
3. Thackray AC, Sobin LH. WHO International Histological Classification of Tumours. Nr. 7. Histological Typing of Salivary Gland Tumours. Geneva, World Health Organization, 1972.
4. Seifert G, Sobin LH. WHO International Histological Classification of Tumours. Histological Typing of Salivary Gland Tumours. Springer Verlag Heidelberg, 1991.
5. Waldron CA, El-Mofty SK, Gnepp DR. Tumors of the intraoral minor salivary glands: A demographic and histologic study of 426 cases. Oral Surg Oral Med Oral Pathol 1988; 66: 323-333.

CHAPTER 4

HISTOLOGICAL RECLASSIFICATION OF 101 INTRAORAL SALIVARY GLAND TUMOURS ACCORDING TO THE NEW WHO-CLASSIFICATION

J.E. van der Wal[1], G.B. Snow[2], I. van der Waal[1]

[1]Department of Oral & Maxillofacial Surgery and Oral Pathology,

[2]Department of Otolaryngology/Head and Neck Surgery, Free University Hospital,

Academic Centre for Dentistry Amsterdam (ACTA), Amsterdam, The Netherlands

J Clin Pathol (in press)

ABSTRACT

The epithelial salivary gland tumours have for many years been categorized according to the 1972-WHO-classification. In 1990 a proposed revision of this classification was elaborated. In the present study 101 intraoral salivary gland tumours are reclassified according to this new classification.

In 29% of the cases the original histological diagnosis was changed. In the majority of these cases it concerned a change of diagnosis within the benign or malignant tumour-group. In seven cases there was a change in diagnosis from the benign to the malignant tumourgroup or vice versa.

As shown by the results of this study the histological classification of intraoral salivary gland tumours remains difficult, also when applying the new WHO-classification.

INTRODUCTION

Salivary gland tumours account for about 3% of all head and neck neoplasms, the majority being of epithelial origin.[1] About 90% of these neoplasms are localized in the major salivary glands, the other 10% in the minor salivary glands.[2,3] The epithelial salivary gland tumours consist of a great variety of histological types and have until recently been classified according to the 1972-WHO-classification.[4] Since 1972 a number of new tumour entities has been reported in the literature. Therefore, a proposed revision of the WHO Histological Classification of Salivary Gland Tumours was elaborated.[5] In this study 101 intraoral salivary gland tumours are reclassified according to this new classification.

MATERIALS AND METHODS

In the period January 1970 - January 1988 101 patients with a tumour of the intraoral salivary glands were registered at the Free University Hospital in Amsterdam. There were 50 male and 51 female patients with a mean age of 53.6 (range 17-86) years and 50.0 (range 16-82) years respectively. The distribution of the 101 tumours according to the localisation and original histological diagnosis (WHO, 1972) is shown in Table 1.

Table 1. Distribution of 101 intraoral salivary gland tumours according to site and histological type (original diagnosis) according to the 1972-WHO-classification[4]

	Palate	Upper lip	Lower lip	Cheek	Floor of the mouth	Retro-molar area	Upper alv. ridge	Mandible	Tongue	Total
Pleomorphic adenoma	27	4	1	4	-	-	-	-	-	36
Monomorphic adenoma	3	4	-	1	-	-	-	-	-	8
Mucoepidermoid tumour	8	-	1	2	1	1	1	-	1	15
Acinic cell tumour	2	-	-	-	-	1	-	-	-	3
Adenoid cystic carcinoma	15	2	-	1	4	1	3	1	-	27
Adenocarcinoma	5	1	-	-	1	-	2	-	-	9
Ca. in pleom. adenoma	1	-	-	-	1	-	1	-	-	3
Total	61	11	2	8	7	3	7	1	1	101

The majority of the patients had a malignant tumour (57%) on first diagnosis, which included the mucoepidermoid tumour and the acinic cell tumour. The pleomorphic adenoma was the most common histological type.

The majority of the 101 patients was initially treated by surgery. Eight patients were not treated surgically due to their age, general condition and/or size and extension of the tumour. In case of questionable or positive surgical margins postoperative radiotherapy has been instituted.

All patients with a salivary gland tumour are routinely seen for follow-up for at least 10 years. The mean follow-up period was 6.5 (range 2-18) years.

Slides stained with hematoxylin and eosin were available for reclassification in every case. No special stains were used. The tumours were reclassified according to the Tentative Histological Classification of Salivary Gland Tumours.[5]

RESULTS

The outcome of the reclassification is shown in Table 2. In 29 cases (29%) the original histological diagnosis was changed.

Table 2. Distribution of 101 histological types according to the 1972-WHO-classification and the tentative WHO-classification (1990) for salivary gland tumours

WHO, 1972 (Thackray, et al.)		WHO, 1990 (Seifert, et al.)	
Pleomorphic adenoma	36	Pleomorphic adenoma	33
Monomorphic adenoma	8	Myoepithelioma	4
		Basal cell adenoma	1
		Canalicular adenoma	3
		Intraductal papilloma	1
Mucoepidermoid tumour	15	Mucoepidermoid carcinoma, low-grade	11
		high grade	2
Acinic cell tumour	3	Acinic cell carcinoma	4
Adenoid cystic carcinoma	27	Adenoid cystic carcinoma glandular/tubular	22
		solid	5
Adenocarcinoma	9	Polymorphous low-grade adenocarcinoma	8
		Papillary cystadenocarcinoma	1
		Adenocarcinoma, NOS	3
Carcinoma in pleomorphic adenoma	3	Carcinoma in pleomorphic adenoma invasive	1
		non-invasive	1
		Salivary duct cyst	1

In 15 of these cases it concerned a subclassification within a histological tumour type either being benign or malignant:

1. the subdivision of adenocarcinomas in polymorphous low-grade adenocarcinoma, papillary cystadenocarcinoma and adenocarcinoma, NOS;
2. the subdivision of monomorphic adenomas in canalicular adenoma and basal cell adenoma;
3. the reclassification of two monomorphic adenomas and two pleomorphic adenomas as myoepitheliomas.

In 7 cases there was a change of diagnosis within the malignant tumour group, e.g. from adenocarcinoma to adenoid cystic carcinoma or carcinoma in pleomorphic adenoma. Of the remaining 7 cases 4 benign diagnoses were changed into a malignant diagnosis and 3 malignant diagnoses were changed into a benign diagnosis (Table 3).

Table 3. Seven cases with a change in diagnosis from benign to malignant or vice versa in the reclassification

Original diagnosis	Reclassification
Pleomorphic adenoma	Polymorphous low-grade adenocarcinoma
Pleomorphic adenoma	Polymorphous low-grade adenocarcinoma
Monomorphic adenoma	Mucoepidermoid carcinoma
Monomorphic adenoma	Adenoid cystic carcinoma, glandular type
Mucoepidermoid tumour	Pleomorphic adenoma
Mucoepidermoid tumour	Salivary duct cyst
Adenoid cystic carcinoma	Intraductal papilloma

DISCUSSION

The distribution of the histological types and tumour sites in this study are somewhat similar to other studies on intraoral salivary gland tumours, the palate being the most common location and the pleomorphic adenoma being the most common histological type.[6]

As shown by the results of this study the histological classification of intraoral salivary gland tumours remains difficult, also when applying the new WHO-classification.[7] In 29% of the cases the original histological diagnosis was changed. In the majority of these cases the change of diagnosis occurred either within the benign or within the malignant tumour-group. In case of adenocarcinomas the more detailed histological typing may lead to a better prediction of the prognosis. This seems especially true with regard to the polymorphous low-grade adenocarcinoma. However, the clinical relevance of the new subtyping of adenomas seems somewhat questionable, although it has been claimed that the myoepithelioma is a potentially more aggressive neoplasm.[5]

In seven cases there was a change in diagnosis from the benign to the malignant tumour-group or vice versa. Benign tumours of the minor salivary glands tend to be non-encapsulated which can make the differentiation between adenomas and carcinomas difficult, e.g. the differential diagnosis pleomorphic adenoma versus polymorphous low-grade adenocarcinoma.

The follow-up data of this study did not provide further support for the correctness of the reclassified diagnoses.

REFERENCES

1. Eveson JW, Cawson RA. Salivary gland tumours. A review of 2410 cases with particular reference to histologic types, site, age and sex distribution. J Oral Pathol 1985; 146: 51-58.
2. Spiro RH. Salivary neoplasms: Overview of a 35-year experience with 2807 patients. Head & Neck Surgery 1986; 8: 177-184.
3. Waldron CA, El-Mofty SK, Gnepp DR. Tumors of the intraoral minor salivary glands: A demographic and histologic study of 426 cases. Oral Surg Oral Med Oral Pathol 1988; 66: 323-333.
4. Thackray AC, Sobin LH. WHO International Histological Classification of Tumours. Histological Typing of Salivary Gland Tumours. Nr. 7. Geneva, World Health Organization, 1972.
5. Seifert G, Brocheriou C, Cardesa A, Eveson JW. WHO International Histological Classification of Tumours. Tentative Histological Classification of Salivary Gland Tumours. Path Res Pract 1990; 186: 555-581.
6. Chau MNY, Radden BG. Intraoral salivary gland neoplasms: A retrospective study of 98 cases. J Oral Pathol 1986; 15: 339-342.
7. Tischendorf L, Herrmann PK, Luttermann Th. Konsequenzen aus Studien zur Reklassifizierung von Geschwülsten der Kopfspeicheldrüsen. Dtsch Z Mund Kiefer Gesichts-Chir 1991; 15: 35-37.

CHAPTER 5

INTRAORAL ADENOID CYSTIC CARCINOMA

The role of postoperative radiotherapy in local control

J.E. van der Wal[1], G.B. Snow[2], A.B.M.F. Karim[3], I. van der Waal[1]

[1]Department of Oral & Maxillofacial Surgery and Oral Pathology,

[2]Department of Otolaryngology/Head & Neck Surgery,

[3]Department of Radiotherapy, Free University Hospital,

Academic Centre for Dentistry Amsterdam (ACTA), Amsterdam, The Netherlands

Head & Neck Surgery 1989; 11: 497-499

ABSTRACT

Fourteen cases of adenoid cystic carcinoma (ACC) of the intraoral salivary glands with positive surgical margins have been reviewed in order to determine the role of postoperative radiotherapy in local control.

Since local control was obtained in all patients, postoperative radiotherapy seems an adequate treatment to deal with the problem of positive surgical margins at the microscopic level in cases of intraoral adenoid cystic carcinoma, making additional surgical treatment redundant.

INTRODUCTION

Adenoid cystic carcinoma (ACC) of the salivary glands accounts for less than 1% of all head and neck malignancies and for approximately 10% of all salivary gland neoplasms.[1] It is the most common malignancy in the minor salivary glands.

ACC is a biologically aggressive tumor characterized by slow growth, insiduous infiltration into adjacent soft tissue and bone, and perineural invasion. Regional metastases are rather uncommon in contrast to distant metastases.[2]

Surgery is the treatment of choice for ACC of the intraoral salivary glands.[3] Postoperative radiotherapy has been advocated to improve the rate of local control. Combined treatment seems to result in a better local control than surgery or radiotherapy alone.[3-6]

In this study the experience of 20 patients with an ACC of the intraoral salivary glands is reported, especially focusing on the role of postoperative radiotherapy in obtaining local control when dealing with positive surgical margins.

MATERIALS AND METHODS

In the period January 1, 1970, to January 1, 1988, a total number of 33 patients with an adenoid cystic carcinoma of the intraoral salivary glands were registered at the Free University Hospital in Amsterdam. Tumors of the sublingual salivary glands which present in the floor of the mouth have been registered as being of intraoral salivary gland origin. Six patients were excluded on the basis of prior treatment at another institution. Five patients had no treatment for their primary tumors because of their age or general condition and were also excluded. Two other patients were excluded because of an initial misdiagnosis of the tumor as a pleomorphic adenoma which resulted in a different therapeutic approach. In the first patient the diagnosis of ACC was made after a routine revision of the histologic slides, and in the other patient the diagnosis was made when a neck node metastasis developed 9 years after the initial treatment.

The remaining 20 patients were initially treated by surgery. A margin of clinically (and radiographically) normal tissue was included in the excision. The width of the margin varied depending on the site of the tumor. For instance, in tumors of the palate a margin of approximately 1 cm was included, while in other sites (e.g. the upper lip) a more conservative excision was performed.

In four cases there were negative surgical margins at histologic examination. In one of these patients postoperative radiotherapy was instituted.

In 16 cases there were positive margins at histologic examination. Fourteen of these patients received postoperative radiotherapy. The other two patients did not receive postoperative radiotherapy because of the following reasons: one patient underwent re-excision with negative histopathologic findings in the specimen; the other patient could not be radiated postoperatively because of a poor general condition postoperatively. Among the remaining 14 patients there were nine men and five women; the mean age was 51.4 years with a range of 32 - 71 years. The distribution by primary site is shown in Table 1.

Table 1. Location of primary tumor

Location	No. of patients
Palate	8
Upper alveolar ridge	2
Retromolar area	1
Upper lip	1
Floor of the mouth	1
Cheek	1
Total	14

Postoperative radiotherapy was used in this group of patients, using individualized shell-masks, simulator planning, and computer dosimetry. Relatively wide fields and custom-made cerro-blocks were routinely used along with shrinking field techniques. Dosages, with conventional tumor dose fractions of 2 Gy, five fractions a week, ranged from 66 to 70 Gy. Follow-up information was available of all 14 patients for periods that varied from 2.0 to 15.0 years, the average being 6.0 years. In this study short- and long-term local control were defined as the absence of clinical signs or symptoms of residual or recurrent tumor for at least 2 and 5 years, respectively.

RESULTS

The distribution of the 14 postoperatively irradiated patients by local control is shown in Table 2. In all 14 patients short-term (2-years) local control was obtained.

Table 2. Short-term (2-years) and long-term (5-years) local control of 14 patients with positive surgical margins, treated by postoperative radiotherapy

Follow-up period	No. of patients	Too short follow-up period	Dead of distant disease	Local control
Short-term (> 2 years)	14	-	-	14
Long-term (> 5 years)	14	6	3	5

In six patients the follow-up period was less than 5 years which does not permit long-term local control evaluation. Three of the remaining eight patients died within 5 years, without local disease. The other five patients are still alive without evidence of local disease.

One patient of the group of 14 developed regional neck node metastases, 28 months after initial treatment. A total number of six patients of the group of 14 developed distant metastases: five to the lungs alone (7, 16, 31, 63, 106 months after initial treatment); and one to the lungs and bone (32 months after initial treatment).

Adenoid cystic carcinoma was responsible for five deaths in this series (26, 50, 78, 85 and 119 months after primary treatment), the average being 72 months. All five patients had distant metastases, and one patient also had neck node metastases.

The two non-irradiated patients with positive surgical margins did not develop a local recurrence or metastatic disease. One patient died 6 years after initial treatment without evidence of local or distant disease, and the other patient had been alive for 15 years now.

Finally, of the four patients with negative surgical margins, two patients are alive without evidence of disease, 43 and 188 months after initial treatment, and the third patient died without evidence of disease, 147 months after initial treatment. The fourth patient developed neck node and distant metastasis 2 years after initial treatment and died 58 months later.

DISCUSSION

In this study only patients with an intraoral ACC were included. This site selection was made to get a group of patients with a uniform treatment. In most studies, patients with both major and minor salivary gland tumors are examined, making comparison with our results difficult.[3-5,7]

Sixteen out of 20 resection specimens of intraoral ACC had positive surgical margins, which is in accordance with the reported incidence in the literature.[3] The extensive infiltrative spread in surrounding tissues makes radical resection extremely difficult. One can only aim at the widest local excision permitted anatomically. Actually, irradical surgical margins were preoperatively expected in a number of cases.

In this study, local control, short- (2-years) and long-term (5-years), was achieved in all patients with positive surgical margins who underwent postoperative irradiation, making

additional surgical treatment perhaps redundant. However, the follow-up periods may be considered too short and the number of patients too small to draw any firm conclusions from this study. The same holds true for the possible influence of postoperative radiotherapy on the occurrence of lymph node metastasis, distant metastasis, and the survival rate.[5,9] The high local control rate in this study might be the result of the high dose of radiotherapy, ranging from 66 - 70 Gy.[5,9] In most reported cases of local failure doses less than 66 Gy have been applied.[6,8]

Our material does not permit comment on the possible value of postoperative radiotherapy in case of negative surgical margins.

REFERENCES

1. Matsuba HM, Spector GJ, Thawley SE, Simpson JR, Mauney M, Pikul FJ. Adenoid cystic salivary gland carcinoma. A histopathologic review of treatment patterns. Cancer 1986; 57: 519-524.
2. Dal Maso M, Lippi L. Adenoid cystic carcinoma of the head and neck: A clinical study of 37 cases. Laryngoscope 1985; 95: 177-181.
3. Cowie VJ, Pointon RCS. Adenoid cystic carcinoma of the salivary glands. Clin Radiol 1984; 35: 331-333.
4. Nascimento AG, Amaral ALP, Prado LAF, Kligerman J, Silveira TRP. Adenoid cystic carcinoma of salivary glands: A study of 61 cases with clinicopathologic correlation. Cancer 1986; 57: 312-319.
5. Simpson JR, Thawley SE, Matsuba HM. Adenoid cystic salivary gland carcinoma: Treatment with irradiation and surgery. Radiology 1984; 151: 509-512.
6. Matsuba HM, Thawley SE, Simpson JR, Levine LA, Mauney M. Adenoid cystic carcinoma of major and minor salivary gland origin. Laryngoscope 1984; 94: 1316-1318.
7. Schans vd EJ, Knegt P, Jong d PC, Andel v JG, Boer d MF, Eykenboom W. Adenoid cystic carcinoma of the upper digestive and respiratory tracts. A retrospective study of 59 cases. Clin Otolaryngol 1985; 10: 63-67.
8. Ampil FL, Misra RP. Factors influencing survival of patients with adenoid cystic carcinoma of the salivary glands. J Oral Maxillofac Surg 1987; 45: 1005-1010.
9. Miglianico L, Eschwege F, Marandas P, Wibault P. Cervico-facial adenoid cystic carcinoma: Study of 102 cases. Influence of radiotherapy. Int J Rad Oncol Biol Phys 1987; 13: 673-678.

INTRAORAL ADENOID CYSTIC CARCINOMA

The presence of perineural spread in relation to site, size, local extension and metastatic spread in 22 cases

J.E. van der Wal[1], G.B. Snow[2], I. van der Waal[1]

[1]Department of Oral & Maxillofacial Surgery and Oral Pathology,

[2]Department of Otolaryngology/Head and Neck Surgery, Free University Hospital, Academic Centre for Dentistry Amsterdam (ACTA), Amsterdam, The Netherlands

Cancer 1990; 66: 2031-2033

ABSTRACT

Twenty-two patients with an intraoral adenoid cystic carcinoma (ACC), initially treated by surgery with or without postoperative radiotherapy, were examined for the presence of perineural spread in relation to primary site, size, local extension, histologic status of the surgical margins, and metastatic spread of the tumor.

There seems to be no correlation between perineural spread and the primary site or size of the tumor. However, perineural spread occurred more often in tumors with local extension and in cases with surgical margins with positive results. There seems to be no statistically significant correlation between perineural invasion and distant metastatic disease.

INTRODUCTION

Adenoid cystic carinoma (ACC) is the most common malignant tumor of the minor salivary glands. It is an aggressive tumor characterized by slow growth and insiduous destruction of surrounding tissues. Perineural invasion is a prominent feature.[1,2] Spread to regional lymph nodes is rare, other than by direct extension. Distant metastases are much more common.

In this study the presence of perineural spread in relation to primary site, size, local extension, histologic status of the surgical margins, and metastatic spread of the tumor in 22 ACC of the intraoral salivary glands is examined.

MATERIALS AND METHODS

Twenty-seven patients with an ACC of the intraoral salivary glands were registered at the Free Universiy Hospital in Amsterdam between 1970 and 1988. Five patients had no treatment for their primary tumor because of their age and/or general condition. These patients are excluded for additional examination. The remaining group of 22 patients consisted of 13 male and nine female patients. The mean age was 50.3 years with a range from 20 to 72 years.

The distribution of patients by primary site of the tumor is shown in Table 1.
Tumors of the sublingual salivary glands that presented themselves in the floor of the mouth have been registered as being of intraoral salivary gland origin. Data about the size of the tumor were based on clinical findings and macroscopic examination of the resection specimen.

Table 1. Location of primary tumor

Site	No. of patients
Palate	13
Upper alveolar ridge	2
Retromolar area	1
Upper lip	2
Floor of the mouth	3
Cheek	1
Total	22

Because there is no universal classification for the staging of tumors of the minor salivary glands, in this study tumors are staged according to the UICC TNM classification for malignant major salivary gland tumors (Table 2).[3]

Table 2. T-classification of primary tumor

T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension
Note:	All categories are subdivided: a. no local extension* b. local extension

* Local extension is clinical or macroscopic evidence of invasion of skin, soft tissues, bone or nerve. Microscopic evidence alone is not local extension for classification purposes.

Additional information on local extension was provided by the radiologic investigations (conventional tomography and/or computed tomography (CT)scan).

The histologic diagnosis was based on the definition provided by the World Health Organization,[4] being "an infiltrative malignant tumor having a very characteristic cribriform appearance. The tumor cells are arranged as small duct-like structures or larger masses of myoepithelial cells disposed around cystic spaces to give a cribriform or lacelike pattern." The presence of perineural and/or endoneural invasion was based on re-examination of the histologic slides of the resection specimens. Perineural invasion was defined as "tumor cells filling the perineural spaces and infiltrating along them, encircling the nerves in a continuous concentric sheath" (Fig. 1).[5]

All patients were initially treated by surgery. In 17 cases there were surgical margins with positive results at histologic examination. Fourteen of these patients received postoperative radiation therapy. The other three patients did not receive postoperative radiation therapy for various reasons. The remaining five patients had surgical margins

with negative results. Follow-up information was available for all 22 patients for periods that varied from 1 year to 15.6 years, the average being 7.0 years.

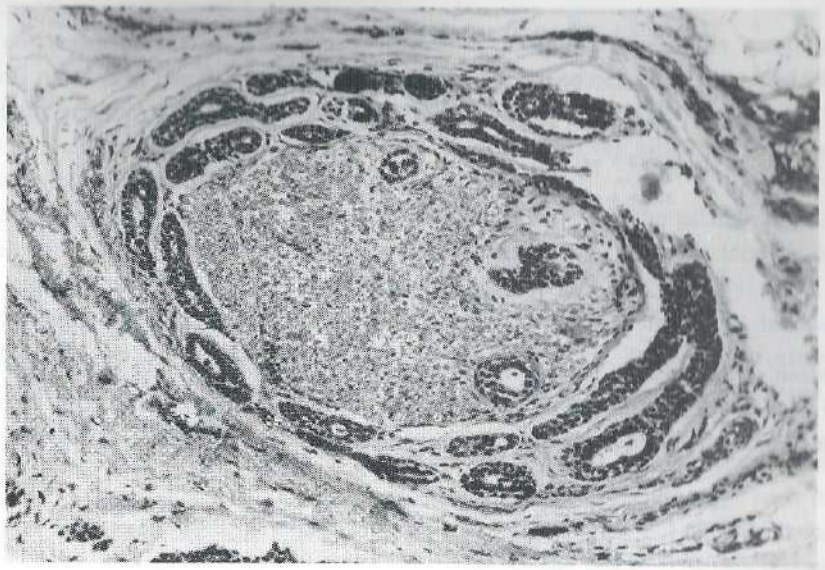

Fig. 1. Perineural invasion in ACC (HE; x132).

RESULTS

In 17 of the 22 resection specimens (72%) perineural invasion was present. The relation between the presence of perineural invasion and primary site of the tumor is shown in Table 3. There seems to be no relation between primary site and perineural invasion.

Table 3. Relation between location of primary tumor and perineural spread

Location	Perineural invasion	No perineural invasion	Total
Palate	10	3	13
Upper alveolar ridge	2	-	2
Retromolar area	2	-	2
Upper lip	1	2	3
Floor of the mouth	1	-	1
Cheek	1	-	1
Total	17	5	22

The relation between perineural spread and the size and local extension of the tumor is shown in Table 4. There might be a relation between the size of the tumor and the presence of perineural invasion. Perineural invasion is more often present in tumors with local extension than in tumors without local extension.

Table 4. Perineural spread in relation to tumor size

Size		Perineural invasion	No perineural invasion	Total
T1 (< 2 cm)	a*	3	2	5
	b	4	-	4
T2 (2-4 cm)	a	5	2	7
	b	2	1	3
T3 (> 4 cm)	a	1	-	1
	b	2	-	2
Total		17	5	22

* a. no local extension b. local extension

Seventeen of 22 resection specimens had surgical margins with positive results (Table 5). In 15 of these 17 resection specimens perineural invasion was present, which is suggestive of a relation between surgical margins with positive results and perineural invasion.

Table 5. Relation between perineural invasion and surgical margins

Surgical margins	Perineural invasion	No perineural invasion	Total
Positive	15	2	17
Negative	2	3	5
Total	17	5	22

The relation between perineural invasion and metastatic spread is shown in Table 6. Distant metastases occurred more often in patients with perineural invasion. However, the mean follow-up period for patients with metastatic disease was slightly longer (8 years, 5 months) than for patients without metastatic disease (6 year, 4 months).

Table 6. Relation between perineural invasion and metastatic spread

Metastases	Perineural invasion	No perineural invasion
Lymph node metastasis	2*	1*
Distant metastasis	6	1
No metastasis	10	4

* One patient developed both lymph node and distant metastasis

DISCUSSION

In this study, and also in earlier reports of intraoral ACC the palate was the most commonly affected site.[1,2] Because of the local extension of the tumor, it is sometimes difficult to decide whether the tumor primarily arose on the oral or on the (para)nasal side of the palate.

In our series perineural invasion was present in 72% of the resection specimens of intraoral ACC. The reported incidence in the literature varies between 15% and 55% and the difference probably depends to a large extent on the number of sections studied.[6,7] In this study the presence of perineural invasion was based on the histologic slides of the resection specimen and not only on biopsy material.

Because of the small number of patients with a tumor outside the palatal region, it is difficult to make a statement about the possible correlation between the location of the tumor and the occurrence of perineural invasion.

There seems to be a correlation between the local extension of the tumor, the state of the surgical margins, and the occurrence of perineural invasion. Perineural invasion was encountered more often in tumors with local extension and in resection specimens with surgical margins with positive results.

It is well recognized that spread to regional lymph nodes is rare. Distant metastases, particularly to lungs and bone, are much more common.[8] The incidence of such distant metastases was higher when perineural invasion was present; seven out of 17 patients with perineural invasion developed metastatic disease against one out of five patients without perineural invasion, which is not statistically significant (chi-square test).

REFERENCES

1. Nascimento AG, Amaral ALP, Prado LAF, Kligerman J, Silveira TRP. Adenoid cystic carcinoma of salivary glands: A study of 61 cases with clinicopathologic correlation. Cancer 1986; 57: 312-319.
2. Matsuba HM, Spector GJ, Thawley SE, Simpson JR, Mauney M, Pikul FJ. Adenoid cystic salivary gland carcinoma. A histopathologic review of treatment failure patterns. Cancer 1986; 57: 519-524.
3. TNM classification of malignant tumors, UICC. Fourth fully revised edition. Springer-Verlag, Heidelberg, 1987.
4. Thackray AC, Sobin LH. WHO International Histological Classification of Tumours. Histological Typing of Salivary Gland Tumours. Nr. 7. Geneva, World Health Organization, 1972.

5. Carter RL, Tanner NSB, Clifford P, Shaw HJ. Perineural spread in squamous cell carcinoma of the head and neck: A clinicopathologic study. Clin Otolaryngol 1979; 4: 271-281.
6. Howard DJ, Lund VJ. Reflections on the management of adenoid cystic carcinoma of the nasal cavity and paranasal sinuses. Otolaryngol Head Neck Surg 1985; 93: 338-341.
7. Vrielinck LJG, Ostyn F, Damme BV van, Bogaert W vd, Fossion E. The significance of perineural spread in adenoid cystic carcinoma of the major and minor salivary glands. Int J Oral Maxillofac Surg 1988; 17: 190-193.
8. Matsuba HM, Thawley SE, Simpson JR, Levine LA, Mauney M. Adenoid cystic carcinoma of major and minor salivary gland origin. Laryngoscope 1984; 94: 1316-1318.

ADENOID CYSTIC CARCINOMA OF THE PALATE WITH SQUAMOUS METAPLASIA

Report of a case

J.E. van der Wal[1], G.B. Snow[2], A.B.M.F. Karim[3], I. van der Waal[1]

[1]Department of Oral & Maxillofacial Surgery and Oral Pathology,

[2]Department of Otolaryngology/Head and Neck Surgery,

[3]Department of Radiotherapy, Free University Hospital,

Academic Centre for Dentistry Amsterdam (ACTA), Amsterdam, The Netherlands

Submitted for publication

ABSTRACT

A case of an adenoid cystic carcinoma of the palate with squamous metaplasia is presented. The differential diagnosis between an adenoid cystic carcinoma and a basaloid squamous carcinoma is discussed.

INTRODUCTION

Adenoid cystic carcinoma (ACC) is a malignant salivary gland tumor, most commonly arising in the minor salivary glands, especially of the palate.[1] Three different histological types are commonly described: glandular (cribriform), tubular and solid (basaloid).[2] A relation of the solid/basaloid ACC with the overlying epithelium makes the differential diagnosis with a basaloid squamous carcinoma, as described by Wain et al. in 1986, very difficult,[3] as will be shown in the present case report.

CASE REPORT

A 57-year-old-male otherwise healthy patient was admitted to the Department of Oral and Maxillofacial Surgery of the Free University Hospital in Amsterdam for a swelling of the right maxilla with an ulceration of the palatal mucosa (Fig. 1). The lesion existed for about three months and slowly increased in size. On palpation the tumor measured approximately 3 cm. in diameter, was painful and not fixed to the buccal mucosa.

CT-scanning showed a polypoid mass in the right maxillary sinus with destruction of the palatal bone. A biopsy resulted in a diagnosis of squamous cell carcinoma with basaloid differentiation, although the possibility of a salivary gland tumor i.c. an adenoid cystic carcinoma could not be excluded.

Treatment consisted of a partial maxillectomy followed by postoperative radiotherapy. The tumor seemed to be removed radically. Half-way through the course of radiotherapy (3780 cGy of the planned 6300 cGy) the patient refused further treatment.

Seven years postoperatively there are no signs of local recurrence or regional or distant metastases.

Histopathology

The tumor of the surgical specimen was composed of solid lobules and cords of cells with scant cytoplasm and dark hyperchromatic nuclei intermingled with cribriform areas (Fig. 2). Few mitotic figures and hardly any pleomorphism were present. Small cystic gland like spaces containing Alcian blue positive material were seen. Between the cells there were thin septae of connective tissue which were PAS and Alcian blue positive. At

several sites the tumor cells appeared to fuse with the overlying surface epithelium (Figs. 3 and 4). Furthermore, squamous metaplasia of tumor cells was observed in several areas (Figs. 5 and 6). There was no evidence of perineural spread.

Semithin plastic sections showed basal lamina-lined "pseudocysts" and small duct lumens along the more numerous and angular basaloid cells.

Keratin markers were positive. Vimentin was focally positive in spindle shaped cells. Amylase, CEA, GFAP, actin and laminin were not detected. Foci of tumor cells were positive for EMA. Only some diffuse cells surrounding "pseudocysts" were positive for S-100.

The previous features along with the characteristic cribriform growth pattern were felt to support the diagnosis of an adenoid cystic carcinoma. Variously sized duct lumens are also evident in the H & E sections further indicating that the tumor is an adenocarcinoma rather than a squamous cell carcinoma.

DISCUSSION

Adenoid cystic carcinomas are the most common malignancies of the minor salivary glands with the palate being the most favorite location.[4] According to the new WHO-classification (1991) there are two distinctive histologic types, a glandular/tubular type and a solid type.[2] The solid type is also described as a basal cell tumor in which foci of squamous metaplasia can be present.

The histopathologic features of the solid type of ACC are similar, if not identical, to those of the basaloid component of basaloid-squamous carcinoma.[3,5] Since the basaloid-squamous carcinoma is a variably differentiated squamous cell carcinoma, that recognizable phenotype should be present.[6] Despite the squamous metaplasia, epithelial dysplasia and the intimate relation with the overlying squamous epithelium in this case, the ultrastructural findings of the basal lamina-lined "pseudo-cysts" and the small duct lumens among the angular basaloid cells together with the focally somewhat cribriform growth pattern, seems to sufficiently support the diagnosis of ACC, indeed.

There are no reports on the immunohistochemistry of basaloid-squamous carcinomas. The immunohistochemical findings in this study seem to be compatible with the diagnosis solid (basaloid) ACC.[7]

ACC with squamous cell carcinoma either in situ or invasive, showing a tendency to form solid or basaloid areas have been reported in the esophagus.[8,9] Gnepp and Heffner described that the majority of sinonasal tract adenomatous neoplasms originate from the mucosal lining of the sinonasal tract.[10] The most acceptable concept for the genesis of coexistence of adenoid cystic and squamous elements is suggested to be a "field effect" situation wherein both mucosal and submucosal epithelial structures were similarly affected during the process of carcinogenesis.[9]

Both basaloid squamous carcinoma and solid adenoid cystic carcinoma are found to be very aggressive and are associated with poor prognosis.[3,11] The patient of this report, however, is still alive without disease seven years after primary treatment. The possibility remains that we have been dealing with a basaloid squamous carcinoma. Most likely, the treatment would have been similar, including the advice for postoperative irradiation.

Acknowledgement

We thank Dr. I. Dardick (Toronto, Canada) for his valuable criticism in this case.

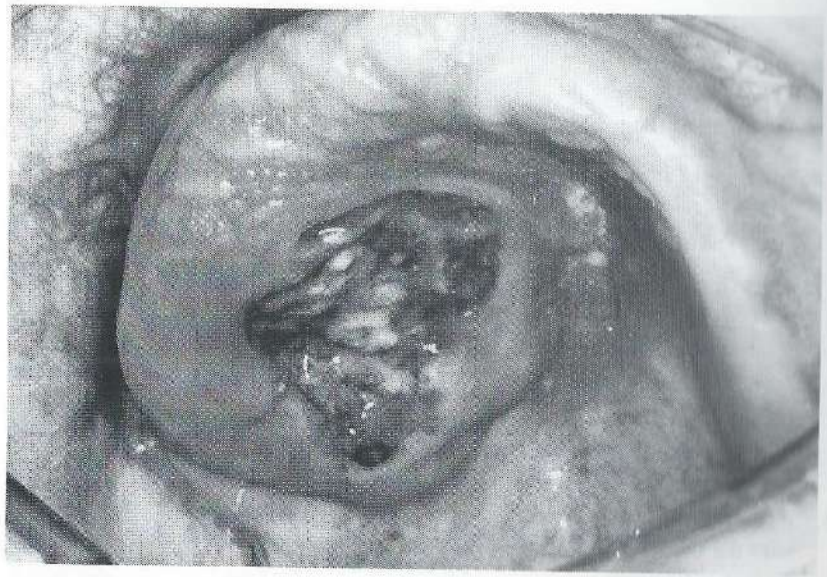

Fig. 1. Clinical view of the lesion of the palate.

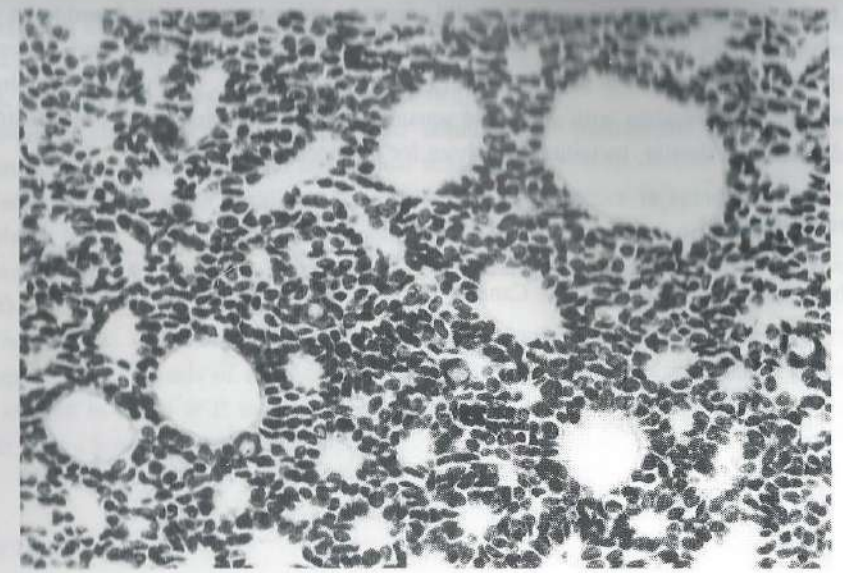

Fig. 2. Solid sheets of tumor cells with scant cytoplasm and hyperchromatic nuclei. Pseudocysts are present (HE; x 360).

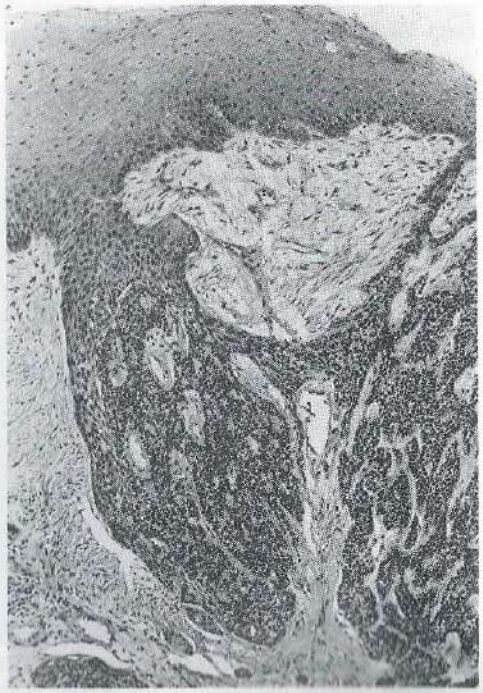

Fig. 3. Fusion of the tumor with the overlying surface epithelium (HE; x 90).

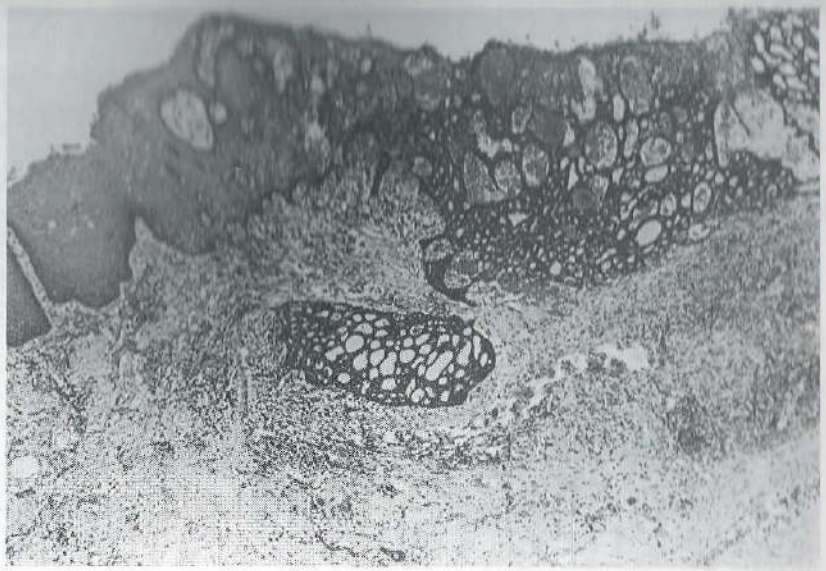

Fig. 4. Junction of the tumor and the overlying squamous epithelium (HE; x 45).

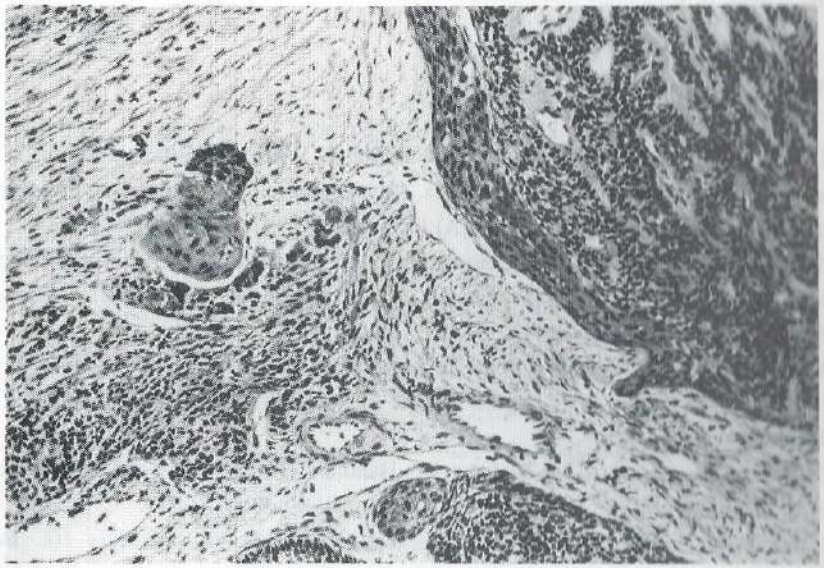

Fig. 5. Squamous metaplasia in several tumor areas (HE; x 132).

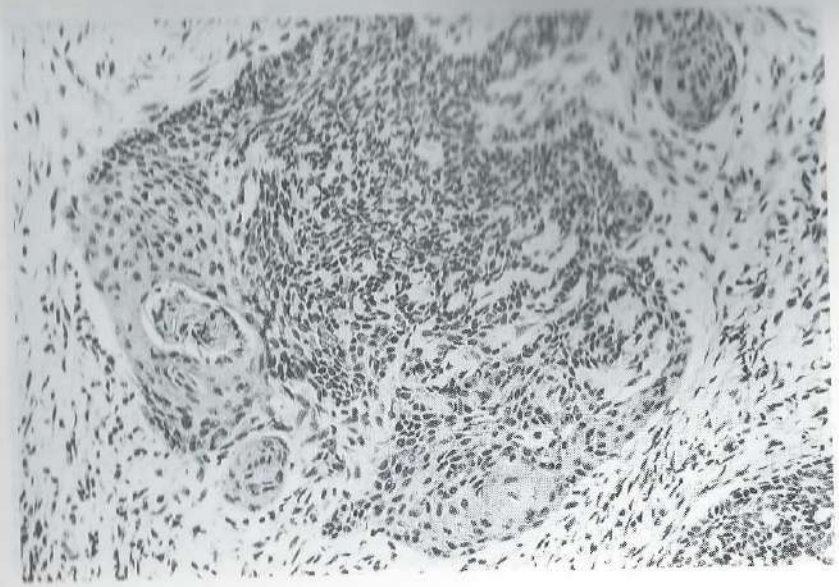

Fig. 6. Detail of squamous metaplasia in relation to the tumor (HE; x 180).

REFERENCES

1. Chomette G, Auriol M, Tranbaloc P, Vaillant JM. Adenoid cystic carcinoma of minor salivary glands. Analysis of 86 cases. Clinico-pathological, histoenzymological and ultrastructural studies. Virch Arch [A] Pathol Anat 1982; 395: 289-307.
2. Seifert G, Sobin LH. WHO International Histological Classification of Tumours. Histological Typing of Salivary Gland Tumours. Springer Verlag, Berlin, Heidelberg, New York, 2nd edition, 1991.
3. Wain SL, Kier R, Vollmer RT, Bossen EH. Basaloid-squamous carcinoma of the tongue, hypopharynx, and larynx: Report of 10 cases. Hum Pathol 1986; 17: 1158-1166.
4. Cleveland D, Abrams AM, Melrose RJ, Handlers JP. Solid adenoid cystic carcinoma of the maxilla. Oral Surg Oral Med Oral Pathol 1990; 69: 470-478.
5. Luna MA, El-Naggar A, Parichatikanond P, Weber RS, Batsakis JG. Basaloid squamous carcinoma of the upper aerodigestive tract. Clinicopathologic and DNA flow cytometric analysis. Cancer 1990; 66: 537-542.
6. Batsakis JG, El-Naggar A. Basaloid-squamous carcinomas of the upper aerodigestive tracts. Ann Otol Rhinol Laryngol 1989; 98: 919-920.

7. Caselitz J, Schulze I, Seifert G. Adenoid cystic carcinoma of the salivary glands: An immunohistochemical study. J Oral Pathol 1986; 15: 308-318.
8. Cerar A, Jutersek AJ, Vidmar S. Adenoid cystic carcinoma of the esophagus. A clinicopathologic study of three cases. Cancer 1991; 67: 2159-2164.
9. Epstein JI, Sears DL, Tucker RS, Eagan JW. Carcinoma of the esophagus with adenoid cystic differentiation. Cancer 1984; 53: 1131-1136.
10. Gnepp DR, Heffner DK. Mucosal origin of sinonasal tract adenomatous neoplasms. Modern Pathology 1989; 2: 365-371.
11. Szanto PA, Luna MA, Tortoledo E, White RA. Histologic grading of adenoid cystic carcinoma of the salivary glands. Cancer 1984; 54: 1062-1069.

CHAPTER 8

THE RARE SIALADENOMA PAPILLIFERUM

Report of a case and review of the literature

J.E. van der Wal, I. van der Waal

Department of Oral & Maxillofacial Surgery and Oral Pathology,

Free University Hospital, Academic Centre for Dentistry Amsterdam (ACTA),

Amsterdam, The Netherlands

Int J Oral Maxillofac Surg (in press)

ABSTRACT

Sialadenoma papilliferum is a rare benign tumor of salivary gland origin. A case, occurring at the junction of the hard and soft palate is described. It concerned a 46-year-old male with an exophytic lesion on the junction of the hard and soft palate. The literature is briefly discussed.

INTRODUCTION

Sialadenoma papilliferum is a rare, benign exophytic tumor of salivary gland origin, first described by Abrams and Finck in 1969 as an analogue of the cutaneous syringocystadenoma papilliferum.[1] Since their description of the lesion less than 30 cases have been reported in the English literature (Table 1).

Table 1. Previously reported cases of sialadenoma papilliferum

	YEAR	AGE	SEX	LOCATION
Abrams and Finck[1]	1969	71	M	parotid gland
		57	M	hard palate
Crocker, et al.[3]	1972	71	M	buccal mucosa
Jensen and Reingold[8]	1973	48	M	hard palate
Whittaker and Turner[22]	1976	65	M	junction of hard and soft palate
		50	M	junction of hard and soft palate
Drummond, et al.[4]	1978	71	M	floor of the mouth
Freedman and Lumerman[6]	1978	68	M	hard palate
		68	M	hard palate
Solomon, et al.[19]	1978	62	M	soft palate
McCoy and Eckert[9]	1980	77	F	buccal mucosa
Nasu, et al.[12]	1981	61	M	hard palate
Wertheimer, et al.[21]	1983	43	M	soft palate
		32	F	hard palate
Grushka, et al.[7]	1984	35	F	parotid gland
Puts, et al.[14]	1984	71	M	hard palate
Rennie, et al.[16]	1984	78	F	junction of hard and soft palate
Shirasuna, et al.[18]	1984	56	M	hard palate
Bass and Cosentino[2]	1985	76	F	faucial pillar
Regezi, et al.[15]	1985	63	M	hard palate
		79	F	hard palate
Fantasia, et al.[5]	1986	87	F	hard palate
		77	M	buccal mucosa
		48	F	hard palate
		45	M	hard palate
		60	F	mucosa upper lip
Mitre[11]	1986	42	F	junction of hard and soft palate
Papanicolaou and Triantafyllou[13]	1987	46	M	hard palate
Present study	1991	46	M	junction of hard and soft palate

The lesion has not been mentioned in the 1972-WHO-classification.[20] In the Tentative Histological Classification of Salivary Gland Tumours the sialadenoma papilliferum is listed in the group of the adenomas, subgroup ductal papilloma.[17]

The purpose of this report is to add one more case of sialadenoma papilliferum to the literature and to review the previously reported cases.

CASE REPORT

A 46-year-old Caucasian male was admitted to the Department of Oral and Maxillofacial Surgery of the Free University in Amsterdam for evaluation of an exophytic growth at the right junction of the hard and soft palate which was first noticed 10 years before (Fig. 1). The tumor had a diameter of 5 mm. and its consistency was firm. The somewhat pedunculated lesion was removed under local anaesthesia with a provisional diagnosis of a fibroepithelial polyp. The differential diagnosis included the possibility of a salivary gland neoplasm. The tissue was submitted for histologic evaluation.

The gross specimen consisted of a wedge-shaped segment of mucosa with a papillary lesion projecting from the center. Microscopic examination revealed a broad-based exophytic lesion with an overlying orthokeratotic squamous epithelium in continuity with elongated and dilated excretory salivary ducts (Fig. 2). The luminal surface of the ducts exhibited numerous papillary folds which were lined with a double layer of basilar cuboidal cells, surfaced by tall columnar cells (Fig. 3). At the base of the tumor some mucous salivary gland tissue was present. The supporting fibrous connective tissue was well-vascularized and contained an infiltrate of chronic inflammatory cells of variable density. A diagnosis of benign sialadenoma papilliferum was made. The lesion was considered to be completely removed, therefore no additional treatment was instituted.

Postoperative healing was uneventful. The patient has been followed at regular intervals and there has been no evidence of recurrence 12 months after excision.

DISCUSSION

Sialadenoma papilliferum is an exophytic, papillary lesion of salivary gland origin.[10,15] Analysis of the clinical data of 28 previously described patients and the patient presented reveals an age range from 32 to 87 years, with a mean age of 62 years. Sixty-five percent of the patients described were male. The palate is the most common location with 21 of 29 cases occurring in this location. There are only two reports of major salivary gland involvement.[1,7]

The tumors are well-circumscribed, slow-growing and often asymptomatic. Clinically, the lesion has to be differentiated from squamous cell papilloma, early verrucous carcinoma and Warty dyskeratoma.[8]

Histologically, the lesion is composed of two distinct components: the superficial squamous epithelium making up the exophytic papillomatous part of the lesion and the

tortuous, widely dilated duct-like structures with the typical double-layering.[1] Squamous metaplasia and oncocytic differentiation may be present. The differential diagnosis of sialadenoma papilliferum may include oncocytoma, papillary cystadenoma lymphomatosum, inverted papilloma, intraductal papilloma and papillary-cystadenoma-like hyperplasia.[10] Immunohistochemistry and electronmicroscopic examination are not helpful to arrive at a correct histologic diagnosis.

The exact nature of sialadenoma papilliferum has not been fully clarified. Both a hyperplastic and neoplastic origin have been considered.[1,22] The double-layered ductal epithelium, the inward ductal proliferation, and the cytologic differences between tumor cells and hyperplastic duct cells are in favor of a neoplastic origin. Electronmicroscopic findings suggest that the tumor might be of intercalated duct cell origin.[18] However, a recent report by Nakahata et al.,[11] has shown the coexpression of different types of intermediate-sized filaments in sialadenoma papilliferum. Their findings suggest a primitive precursor cell of the duct apparatus capable of multidirectional differentiation to account for the different components of the sialadenoma papilliferum.

Clinical course and follow-up of the reported cases point to the benign nature of the tumor. Apparently, local recurrence is exceptional.[16] One case of a possibly malignant analogue of sialadenoma papilliferum has been presented.[19]

Conservative local excision seems to be the treatment of choice but follow-up at regular intervals is required.

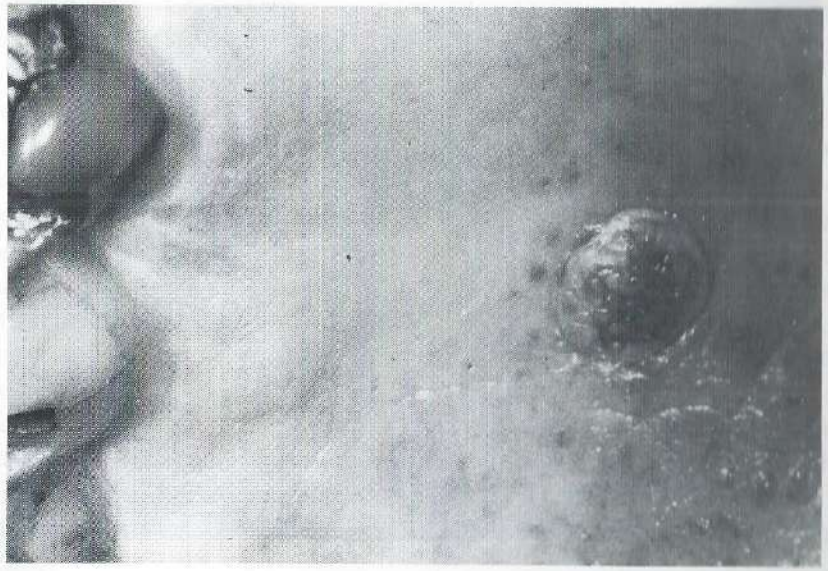

Fig. 1. Clinical view of the lesion at the junction of the hard and soft palate.

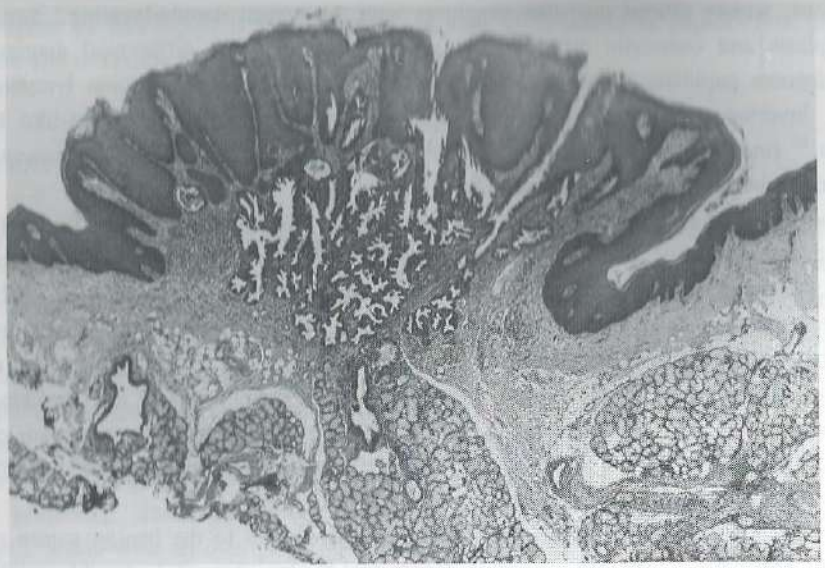

Fig. 2. Low power view of sialadenoma papilliferum showing its exophytic growth pattern and the dilated salivary ducts in the submucosa (HE; x 22.5).

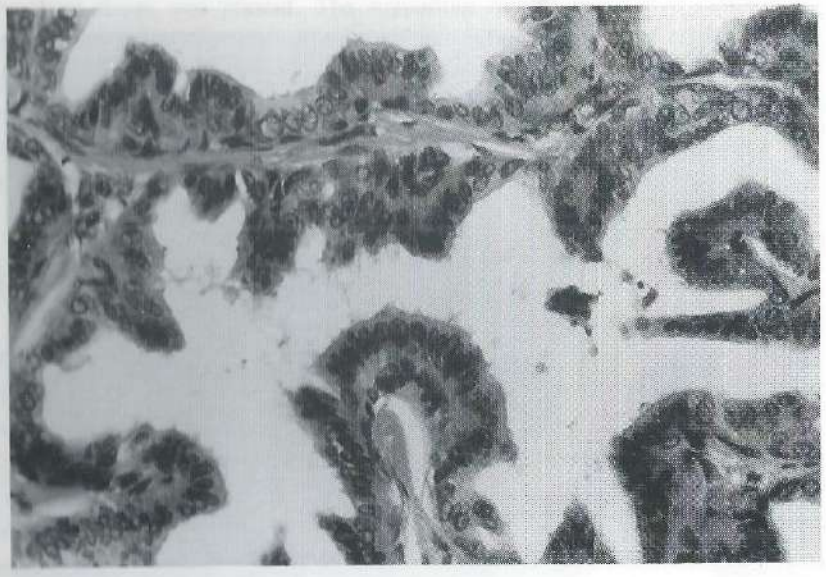

Fig. 3. High power view of the lesion showing ducts with papillary projections and double cell layer lining (HE; x 360).

REFERENCES

1. Abrams AM, Finck FM. Sialadenoma papilliferum. Cancer 1969: 24: 1057-1063.
2. Bass KD, Cosentino BJ. Sialadenoma papilliferum. J Oral Maxillofac Surg 1985: 43: 302-304.
3. Crocker DJ, Christ TF, Cavalaris CJ. Sialadenoma papilliferum: Report of case. J Oral Surg 1972: 30: 520-521.
4. Drummond JF, Giansanti JS, Sabes WR, Smith CR. Sialadenoma papilliferum of the oral cavity. Oral Surg 1978: 45:72-75.
5. Fantasia JE, Nocco CE, Lally ET. Ultrastructure of sialadenoma papilliferum. Arch Pathol Lab Med 1986: 110: 523-527.
6. Freedman PD, Lumerman H. Sialadenoma papilliferum. Oral Surg 1978: 45: 88-94.
7. Grushka, M, Podoshin L, Boss JH, Fradis M. Sialadenoma papilliferum of the parotid gland. Laryngoscope 1984: 94: 231-233.
8. Jensen JL, Reingold IM. Sialadenoma papilliferum of the oral cavity. Report of a case. Oral Surg 1973: 35: 521-525.
9. McCoy JM, Eckert EF. Sialadenoma papilliferum. J Oral Surg 1980: 38: 691-693.
10. Mitre BK. Sialadenoma papilliferum. Report of case and review of literature. J Oral Maxillofac Surg 1986: 44: 469-474.
11. Nakahata A, Deguchi H, Yanagawa T, Yoshida H, Sato M, Hayashi Y. Coexpression of intermediate-sized filaments in sialadenoma papilliferum and other salivary gland neoplasms. J Oral Pathol Med 1990: 19: 313-318.
12. Nasu M, Takagi M, Ishikawa G. Sialadenoma papilliferum: Report of case. J Oral Surg 1981: 39: 367-369.
13. Papanicolaou SJ, Triantafyllou AG. Sialadenoma papilliferum of the oral cavity. A case report and review of the literature. J Oral Med 1987: 42: 57-60.
14. Puts JJG, Voorsmit RACA, Van Haelst UJGM. Sialocystadenoma papilliferum of the palate. J Max-fac Surg 1984: 12: 90-94.
15. Regezi JA, Lloyd RV, Zarbo RJ, McClatchey KD. Minor salivary gland tumors. A histologic and immunohistochemical study. Cancer 1985: 55: 108-115.
16. Rennie JS, MacDonald DG, Critchlow HA. Sialadenoma papilliferum. A case report and review of the literature. Int J Oral Surg 1984: 13: 452-454.
17. Seifert G, Brocheriou C, Cardesa A, Eveson JW. WHO International Classification of Tumours. Tentative Histologcal Classification of Salivary Gland Tumours. Path Res Pract 1990: 186: 555-581.
18. Shirasuna K, Watatani K, Miyazaki T. Ultrastructure of a sialadenoma papilliferum. Cancer 1984: 53: 468-474.
19. Solomon MP, Rosen Y, Alfonso A. Intraoral papillary squamous cell tumor of the soft palate with features of sialadenoma papilliferum-? Malignant sialadenoma papilliferum. Cancer 1978: 42: 1859-1869.

20. Thackray AC, Sobin CH. WHO International Histological Classification of Tumours. Histological Typing of Salivary Gland Tumours. Nr. 7. Geneva, World Health Organization, 1972.
21. Wertheimer FW, Bonk K, Ruskin WJ. Sialoadenoma papilliferum. Int J Oral Surg 1983; 12: 190-193.
22. Whittaker JS, Tumer EP. Papillary tumors of the minor salivary glands. J Clin Pathol 1976; 29: 795-805.

CHAPTER 9

NECROTIZING SIALOMETAPLASIA

Report of 12 new cases

J.E. van der Wal, I. van der Waal

Department of Oral & Maxillofacial Surgery and Oral Pathology,

Free University Hospital, Academic Centre for Dentistry Amsterdam (ACTA),

Amsterdam, The Netherlands

Br J Oral Maxillofac Surg 1990; 28: 326-328

ABSTRACT

The clinical and histopathological findings of 12 new cases of necrotizing sialometaplasia are described.

INTRODUCTION

Since the introduction of the term necrotizing sialometaplasia (NS) in 1973 by Abrams, et al.,[1] more than 80 cases have been reported in the literature. NS is a self-limiting, variably ulcerated, benign process. It most frequently occurs on the palate but it has also been reported in other locations such as the lip, major salivary glands and nasopharynx.[2-7]

The cause of NS is still questionable, although most authors consider the lesion a secondary reaction to ischaemic injury.[8,9] The importance of NS rests in the fact that it may be confused clinically and histologically with malignancy.[10]

Clinical and histopathological findings of 12 new cases of NS will be discussed.

Clinicalpathologic findings

In the period January 1977 to June 1989, 12 cases of NS have been registered at the Free University Hospital of Amsterdam. In all cases the diagnosis was based on the histologic criteria for NS as given by Abrams, et al. (1973)[1]:

1. ischaemic lobular necrosis of seromucinous glands,
2. maintenance of intact lobular architecture despite necrosis and inflammation,
3. squamous metaplasia of ducts and acini with adjacent lobules containing mucous or necrotic debris,
4. histologically benign (non-anaplastic) nuclear morphology, although normal mitoses may occur,
5. prominent acute and chronic inflammatory reaction and granulation tissue in or around the glands.

The clinical data of the 12 patients are listed in Table 1. The male:female ratio was 2:1 and the mean age for male and female patients was 44 (28 - 67) years and 51 (18-80) years, respectively. The palate was the most common location.

The lesion presented clinically as ulceration (five cases), swelling (three cases) or was accidentally found in a re-excision specimen of a neoplasm (four cases) (Figs. 1 and 2).

In nine out of the 12 cases the lesion occurred after some sort of injury (Table 1). Figures 3, 4 and 5 from cases 3 and 9 are representative and typical of the histologic findings of the necrotizing sialometaplasia in all 12 cases.

Table 1. Summary of cases

No.	Age	Sex	Location	Clinical appearance	History
1	18	f	Upper lip	Swelling	Trauma
2	60	f	Palate	Swelling	Unknown
3	33	f	Palate	Ulceration	Intubation
4	28	m	Palate	Ulceration	Unknown
5	29	m	Palate	Ulceration	Anaesthesia
6	67	m	Maxillary sinus	Re-excision	Surgery
7	40	m	Lower lip	Re-excision	Surgery
8	67	f	Floor of mouth	Re-excision	Surgery
9	36	m	Palate	Ulceration	Unknown
10	80	f	Palate	Ulceration	Dentures
11	57	m	Palate	Swelling	Dentures
12	50	m	Tongue	Re-excision	Surgery

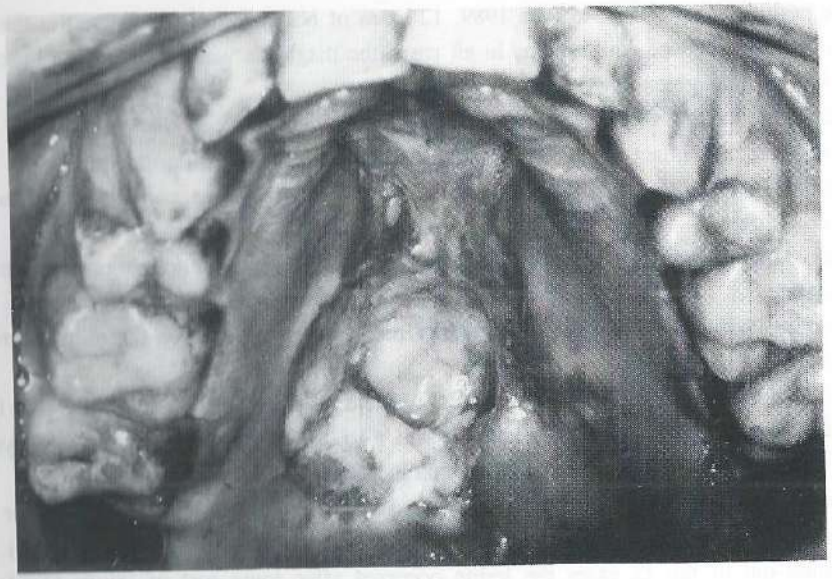

Fig. 1. Palatal ulceration in a 29-year-old man with necrotizing sialometaplasia 3 weeks after bilateral local anaesthesia.

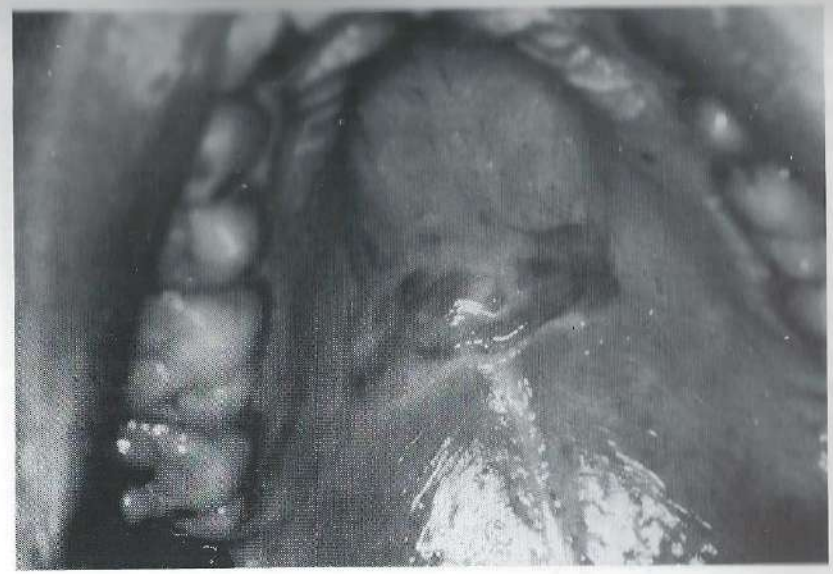

Fig. 2. Same lesion as in Figure 1, six weeks later. The ulcer has healed almost to the level of the surrounding mucosa.

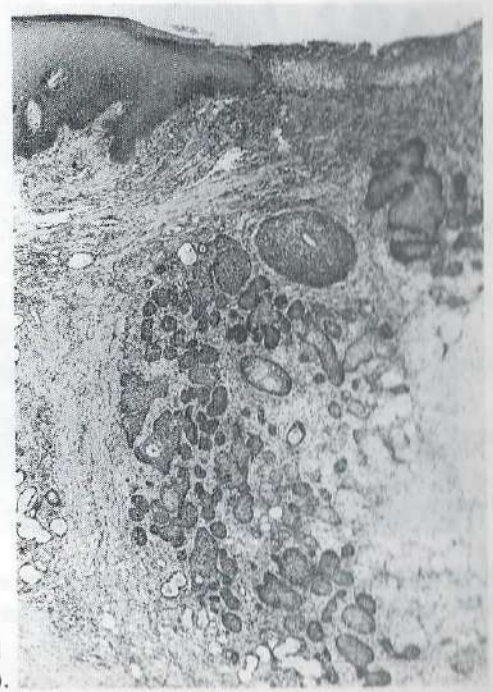

Fig. 3. Necrotizing sialometaplasia. The surface epithelium is ulcerated. Beneath the lamina propria, masses of necrotic and metaplastic salivary gland structures are seen (HE; x 45).

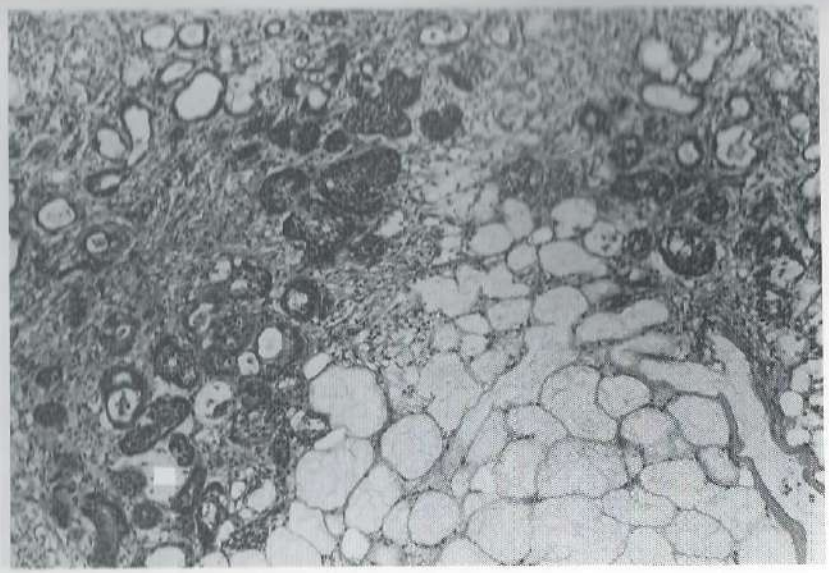

Fig. 4. Necrotizing sialometaplasia. Necrosis of the acini, lobular preservation and squamous metaplasia of acini and ducts (HE; x 90).

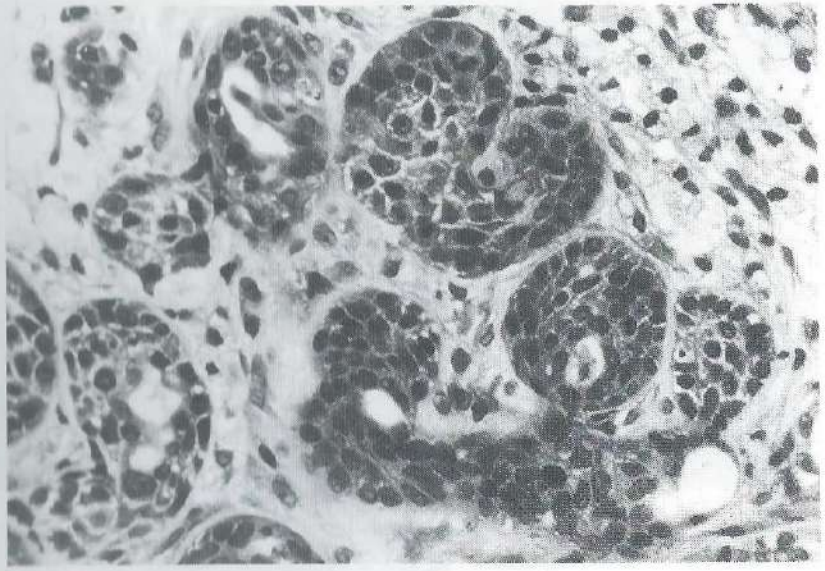

Fig. 5. Necrotizing sialometaplasia. Squamous metaplasia of the ducts with partial or total obliteration of the lumen of the ducts. Benign nuclear morphology, although normal mitoses may occur (HE x 360).

DISCUSSION

Necrotizing sialometaplasia (NS) is a disease of the salivary glands, occurring chiefly in the palatine glands.[1] However, NS can be found in any site where salivary gland tissue is present and is not restricted to the palate only. It can occur as an ulcer or swelling or as an incidental histological finding.

Infarction of the salivary gland is suggested as the main aetiological factor which is caused by a compromised blood supply (ischaemia) due to vascular injury of different kinds: anaesthesia, denture trauma or surgery.[8] Histologically, this is characterized by lobular necrosis, squamous metaplasia of the excretory ducts and preservation of the lobular architecture of the involved gland.

In the majority of the cases in our study there was a history of trauma, which supports the view that NS is a histopathological phenomenon occurring a few days or weeks after trauma, rather than being an entity in itself.

Since NS heals spontaneously in some weeks the "disease" does not require treatment other than follow-up. If no evidence of healing is noted in 2 to 3 weeks, a biopsy, large enough to show the preservation of the lobular salivary gland pattern, is necessary to confirm the diagnosis of NS and to exclude malignancy.[11-13]

Purely from a histological point of view NS can be mistaken for a squamous cell carcinoma or a salivary gland neoplasm. It is, therefore, important that the clinician and pathologist are aware of this not so uncommon phenomenon.

REFERENCES

1. Abrams AM, Melrose RJ, Howell FV. Necrotizing sialometaplasia. A disease simulating malignancy. Cancer 1973; 32: 130-135.
2. Batsakis JG, Manning JT. Necrotizing sialometaplasia of major salivary glands. J Laryngol Otol 1987; 101: 962-966.
3. Birkholz H, Brownd CL. Necrotizing sialometaplasia: Report of an ulcerative case. J Am Dent Ass 1981; 103: 48-50.
4. Gad A, Willen H, Willen R, Thortensson S, Ekman L. Necrotizing sialometaplasia of the lip simulating squamous cell carcinoma. Histopathology 1981; 4: 111-121.
5. Gahhos F, Enriquez RE, Bahn SL, Ariyan S. Necrotizing sialometaplasia: Report of five cases. Plastic Reconstr Surg 1983; 71: 650-657.
6. Gavron JP, Ardito JA, Curtis AW. Necrotizing sialometaplasia. Laryngoscope 1981; 9: 1176-1180.
7. Granick MS, Solomon MP, Benedetto AV, Hannegan MW, Sohn M. Necrotizing sialometaplasia masquerading as residual cancer of the lip. Ann Plastic Surg 1988; 21: 152-154.

8. Anneroth G, Hansen LS. Necrotizing sialometaplasia. The relationship of its pathogenesis to its clinical characteristics. Int J Oral Surg 1982; 11: 283-291.
9. Grillon GL, Lally ET. Necrotizing sialometaplasia: Literature review and presentation of five cases. J Oral Surg 1981; 39: 747-753.
10. Poulson TC, Greer Jr RO, Ryser RW. Necrotizing sialometaplasia obscuring an underlying malignancy: Report of a case. J Oral Maxillofac Surg 1984; 44: 570-574.
11. Kinney RB, Burton CS, Vollmer RT. Necrotizing sialometaplasia: A sheep in wolf's clothing: Healing as a diagnostic test. Arch Dermatol 1986; 122: 208-210.
12. Mesa ML, Gertler RS, Schneider LC. Necrotizing sialometaplasia: Frequency of histologic misdiagnosis. Oral Surg Oral Med Oral Pathol 1984; 57: 71-73.
13. Santis HR, Kabani SP, Roderiques A, Roderiques A, Driscoll JM. Necrotizing sialometaplasia: An early, nonulcerative presentation. Oral Surg Oral Med Oral Pathol 1982; 53: 387-390.

CHAPTER 10

SUMMARY AND GENERAL DISCUSSION

10. SUMMARY AND GENERAL DISCUSSION

In this thesis a clinicopathologic study of neoplasms and allied lesions of the intraoral salivary glands is described. A general introduction on the study and an outline of the aims of the study is presented in *chapter 1*. Since this study was performed in a transition period between two classifications in some parts the old WHO-classification (1972) was used and in others the new WHO-classification (1991).

In *chapter 2* an overview of the clinicopathologic aspects of intraoral salivary gland tumours together with a discussion of 101 patients with an intraoral salivary gland tumour, registered in the Department of Oral Pathology of the Free University Hospital in Amsterdam, is given. Based on the new 1991-WHO-classification for salivary gland tumours the different histological types are discussed together with the results of immunohistochemistry.

Approximately 10%-15% of all salivary gland tumours occur in the minor salivary glands of the oral cavity and upper aerodigestive tract. In our study a higher percentage is found (35%), probably due to the fact that the Free University Hospital is a referring Centre for Head and Neck Oncology.

The majority of the tumours occur in the fourth to seventh decades, with an equal sex distribution. The etiology of salivary gland neoplasms is unknown. However, some patients are known with a previous history of low-dose irradiation of the head and neck area. The junction of the hard and soft palate is the most favoured location for an intraoral salivary gland tumour. Pleomorphic adenomas are the most common benign tumours and adenoid cystic carcinomas the most common malignant ones. Treatment of intraoral salivary gland tumours consists of (radical) surgery eventually followed by postoperative radiotherapy in case of malignancy. Prognosis varies with the location, clinical stage, histology of the tumour and treatment factors. Spread to regional lymph nodes is rare in case of malignancy, but distant metastases are much more common.

The value of tumour markers in the diagnosis of salivary gland tumours seems limited (Table 1). However, some useful remarks can be made:

- amylase demonstration characterizes the clear cell variant of acinic cell carcinoma;
- S-100 protein, actin or myosin staining and keratin-vimentin coexpression indicate a myoepithelial differentiation;
- GFAP can be useful for the differentiation between pleomorphic adenoma (positive) and adenoid cystic carcinoma (negative);
- a degradation of basal-membrane substances and a loss of blood group substances is found in malignant transformation. Lysozym is not detected in malignant tumours;
- the different staining pattern of EMA in adenoid cystic carcinoma and polymorphous low-grade adenocarcinoma might be useful in separating these two tumours;

- the use of tumour markers can give insights to the cytologic differentiation and histogenetic development of salivary gland tumours.

Table 1. Expression of markers in epithelial salivary gland tumours

		PA	MA	MET	ACT	ACC	AC	CPA	UC
COMPONENTS OF THE CYTOSKELETON									
	actin	+	(+)	-	-	+	-	+	-
	myosin	+	-	-	-	(+)	-	-	-
	keratin	+	+	+	+	+	+	+	+
	vimentin	(+)	-	-	-	(+)	-	(+)	-
	desmin	-	-	-	-	-	-	-	-
	GFAP	+	-	-	-	-	-	(+)	-
CELL MEMBRANE ANTIGENS									
	CEA	+	(+)	+	-	+	+	+	-
	EMA	+	+	+	(+)	(+)	+	+	+
	S-100	+	(+)	-	-	+	(+)	(+)	-
CELL PRODUCTS									
	amylase	-	-	-	+	-	-	-	-
	lactoferrin	+	+	(+)	+	+	+	+	-
	lysozym	(+)	(+)	-	-	-	-	-	-
	SC/IgA	+	+	(+)	-	+	(-)	(-)	-
BM-ASSOCIATED SUBSTANCES									
	laminin	+	+	+	-	+	-	-	-
	type IV collagen	+	+	+	-	+	-	-	-
	fibronectin	+	+	-	-	+	-	-	-
	elastin	+	+	+	-	+	+	-	-
BLOODGROUP SUBSTANCES		+	+	+	-	+	+	-	-

(+) focally positive + positive - negative

PA pleomorphic adenoma MET mucoepidermoid tumour ACC adenoid cystic carcinoma
MA monomorphic adenoma CPA carcinoma in pleomorphic adenoma AC adenocarcinoma
ACT acinic cell tumour UC undifferentiated carcinoma

The histological slides of the 101 intraoral salivary gland tumours have been re-evaluated by an EORTC (European Organization on Research and Treatment of Cancer)-study group on salivary gland tumours *(chapter 3)*. A modification of the 1972-WHO-classification was used. Complete concurrence of diagnosis was reached in 53% of the cases. In 33% of the cases there was minor disagreement, related to subclassification both within the benign and malignant tumour group. Major disagreement in diagnosis, related to benign versus malignant occurred in 14 cases. These cases with major disagreement in diagnosis were reviewed by the same panel for a second time. After the second revision major disagreement remained in eight cases, and a minor disagreement in three cases, which illustrates the difficulty of the histological classification of intraoral salivary gland tumours.

In 1990 a proposed revision of the WHO histological classification of salivary gland tumours was elaborated. This classification contains more entities and should be helpful in better classifying salivary gland tumours. The 101 intraoral salivary gland tumours were reclassified according to the proposed revision of the WHO-classification *(chapter 4)*. In 29% of the cases the original histological diagnosis was changed. In the majority of these cases it concerned a change of diagnosis within the benign or malignant tumour group. In case of an adenoma the subclassification seems somewhat superfluous since the clinical behaviour of the subtypes is more or less similar. In case of a carcinoma the subclassification seems more significant, because of differences in clinical behaviour.

In *chapter 5* the role of postoperative radiotherapy in obtaining local control of intraoral adenoid cystic carcinoma when dealing with positive surgical margins is discussed. Fourteen of the 27 patients with an intraoral adenoid cystic carcinoma in the group of 101 intraoral salivary gland tumours had positive surgical margins of the resection specimen and received postoperative radiotherapy. In all patients short-term (2-year) local control was obtained. In eight of these patients with a minimal follow-up period of 5 years also long-term local control was obtained. It is concluded from this study that high-dose radiotherapy seems an adequate treatment to deal with the problem of microscopic positive surgical margins in cases of intraoral adenoid cystic carcinoma, making additional surgical treatment redundant.

In *chapter 6* twenty-two patients with an intraoral adenoid cystic carcinoma, initially treated by surgery with or without postoperative radiotherapy, were examined for the presence of perineural spread in relation to primary site, size, local extension, histological status of the surgical margins and metastatic spread of the tumour. Perineural invasion was present in 72% of the resection specimens. There seems to be no correlation between perineural spread and location or size of the tumour. Perineural invasion was found more often in tumours with local extension and in cases with positive surgical margins. The incidence of distant metastases did not correlate with perineural invasion.

The difficulty of the differential diagnosis between adenoid cystic carcinoma and basaloid squamous carcinoma is illustrated in *chapter 7*. One of the 27 intraoral adenoid cystic carcinomas of the group of 101 tumours is described. It concerns a solid-type of adenoid cystic carcinoma with squamous metaplasia, epithelial dysplasia and an intimate relationship with the overlying squamous epithelium, which histologically could fit the diagnosis basaloid squamous carcinoma. However, ultrastructural findings seems to sufficiently support the diagnosis of adenoid cystic carcinoma.

In *chapter 8* a case of sialadenoma papilliferum is reported, an entity which is recently added to the WHO-classification (1991) and listed in the group of adenomas, subgroup ductal papilloma. It is a rare, benign exophytic neoplasm, predominantly occurring on the palate of male patients.

Finally, in *chapter 9* twelve cases of necrotizing sialometaplasia (NS), a benign salivary gland lesion, that clinically and histologically may mimic malignancy, are described. NS seems to be a histopathological phenomenon occurring a few days or weeks after trauma, rather than an entity in itself. Infarction of the salivary gland caused by compromised blood supply due to vascular injury is suggested to be the main etiologic factor. NS is a self-limiting lesion and, therefore, does not require treatment other than careful follow-up. In case of doubt a biopsy should be taken to exclude malignancy.

SAMENVATTING EN DISCUSSIE

11. SAMENVATTING EN DISCUSSIE

In dit proefschrift wordt een klinisch en pathologisch onderzoek beschreven naar tumoren en op tumor gelijkende laesies van de intra-orale speekselklieren. In *hoofdstuk 1* wordt een algemene inleiding op het onderzoek en een uiteenzetting van de belangrijkste doelstellingen gegeven. Aangezien dit onderzoek plaatsvond in een overgangsfase tussen twee classificatiesystemen is in sommige gevallen gebruik gemaakt van de oude WHO-classificatie (1972) en in andere gevallen van de nieuwe WHO-classificatie (1991).

In *hoofdstuk 2* wordt aan de hand van de literatuur een overzicht gegeven van de klinische en histopathologische aspecten van intra-orale speekselkliertumoren. Tevens worden 101 patiënten met een tumor van de intra-orale speekselklieren besproken die gedurende de periode 1970-1988 op de afdeling Pathologie van de Mondholte van het VU-ziekenhuis te Amsterdam zijn geregistreerd. Aan de hand van de nieuwe WHO-classificatie voor speekselkliertumoren (1991) worden de verschillende histologische typen en de resultaten van het immuun-histochemisch onderzoek besproken.

Ongeveer 10%-15% van alle speekselkliertumoren is gelokaliseerd in de kleine speekselklieren van de mondholte en de bovenste luchtwegen. In ons onderzoek werd 35% van de speekselkliertumoren in de kleine speekselklieren aangetroffen, waarvan 25% intra-oraal. Dit is mogelijk het gevolg van het feit dat het VU-ziekenhuis een Centrum voor Hoofd-Hals Oncologie is.

De meerderheid van de intra-orale speekselkliertumoren ontstaat tussen het veertigste en zeventigste levensjaar. Er is geen uitgesproken voorkeur voor één van de geslachten. De oorzaak van het ontstaan van speekselkliertumoren is veelal onbekend. Er zijn patiënten bij wie een in het hoofd-halsgebied uitgevoerde bestraling vele jaren later leidde tot het ontstaan van een speekselkliertumor. De overgang van het harde naar het zachte gehemelte blijkt een uitgesproken voorkeurslokalisatie te zijn. De meest voorkomende goedaardige tumor is het pleomorf adenoom, de meest voorkomende kwaadaardige tumor het adenoïd cysteus carcinoom. De behandeling van een intra-orale speekselkliertumor bestaat primair uit chirurgische verwijdering, op indicatie gevolgd door radiotherapie. De prognose hangt af van de lokalisatie, klinische stagering, histologie van de tumor en behandelingsfactoren. Bij de kwaadaardige processen blijkt metastasering zelden via de lymfbanen te verlopen en bijna altijd van hematogene aard te zijn.

De rol van de immuunhistochemie in de diagnostiek van speekselkliertumoren lijkt beperkt (Tabel 1). Enkele opmerkingen kunnen echter worden gemaakt:

- amylase karakteriseert de helder-cellige variant van het acinic cell carcinoom;
- een positieve reactie voor S-100, actine of myosine en de co-expressie van keratine en vimentine duidt op een myo-epitheliale differentiatie;
- GFAP kan van belang zijn voor het onderscheid tussen een pleomorf adenoom (positieve reactie) en een adenoïd cysteus carcinoom (negatieve reactie);

- in geval van maligniteit wordt een vermindering van basaal-membraan substanties en een verlies van bloedgroepsubstanties aangetroffen. Aankleuring voor lysozym wordt alleen in goedaardige tumoren gevonden;
- het verschil in aankleuring voor EMA van adenoïd cysteus carcinomen en "polymorphous low-grade adenocarcinomas" kan van nut zijn in het onderscheid tussen deze twee tumoren;
- het gebruik van tumormarkers kan inzicht geven in de cytologische differentiatie en histogenese van speekselkliertumoren.

Table 1. Expressie van tumormarkers in epitheliale speekselkliertumoren

		PA	MA	MET	ACT	ACC	AC	CPA	OC
COMPONENTEN VAN HET CYTOSKELET									
	actine	+	(+)	-	-	+	-	+	-
	myosine	+	-	-	-	(+)	-	-	-
	keratine	+	+	+	+	+	+	+	+
	vimentine	(+)	-	-	-	(+)	-	(+)	-
	desmine	-	-	-	-	-	-	-	-
	GFAP	+	-	-	-	-	-	(+)	-
CEL MEMBRAAN ANTIGENEN									
	CEA	+	(+)	+	-	+	+	+	-
	EMA	+	+	+	(+)	(+)	+	+	+
	S-100	+	(+)	-	-	+	(+)	(+)	-
CEL PRODUCTEN									
	amylase	-	-	-	+	-	-	-	-
	lactoferrine	+	+	(+)	+	+	+	+	-
	lysozym	(+)	(+)	-	-	-	-	-	-
	SC/IgA	+	+	(+)	-	+	(-)	(-)	-
BM-GERELATEERDE SUBSTANTIES									
	laminine	+	+	+	-	+	-	-	-
	type IV collageen	+	+	+	-	+	-	-	-
	fibronectine	+	+	-	-	+	-	-	-
	elastine	+	+	+	-	+	+	-	-
BLOEDGROEP SUBSTANTIES		+	+	+	-	+	+	-	-

(+) focaal positief + positief - negatief

PA pleomorf adenoom MET mucoepidermoid tumor ACC adenoïd cysteus carcinoom
MA monomorf adenoom CPA carcinoom in pleomorf adenoom AC adenocarcinoom
ACT acinie cel tumor OC ongedifferentieerd carcinoom

De histologische coupes van 101 intra-orale speekselkliertumoren zijn opnieuw geëvalueerd door een Europese (EORTC) studiegroep voor speekselkliertumoren *(hoofdstuk 3)*. Er werd gebruik gemaakt van een modificatie van de WHO-classificatie uit 1972. In 53% van de gevallen werd overeenstemming in de diagnose bereikt. In 33% van de gevallen waren er kleine verschillen in de diagnose, betrekking hebbend op de subtypering binnen de goedaardige of kwaadaardige tumorgroep. In 14% van de gevallen waren er relevante verschillen waarbij een verandering van diagnose van de goedaardige naar de kwaadaardige tumorgroep optrad en vice versa. Deze laatste gevallen werden opnieuw bekeken door de studiegroep, waarbij in 8 gevallen een relevant verschil bleef bestaan. De resultaten van dit onderzoek illustreren de problemen in de histologische typering van intra-orale speekselkliertumoren.

In 1990 werd een voorstel gedaan voor een nieuwe WHO-classificatie voor speekselkliertumoren. Deze classificatie bevat meer histologische typen, hetgeen tot een betere classificatie van de tumoren zou moeten leiden. De 101 intra-orale speekselkliertumoren zijn gereclassificeerd aan de hand van deze nieuwe, op dat moment nog voorlopige, WHO-classificatie *(hoofdstuk 4)*. In 29% van de gevallen werd de oorspronkelijke diagnose gewijzigd. In de meerderheid van de gevallen betrof het een verandering binnen de goedaardige of kwaadaardige tumorgroep. De uitgebreide subtypering van de adenomen lijkt enigszins twijfelachtig, aangezien het klinische gedrag van de subtypen over het algemeen gelijk is. De subclassificatie van de carcinomen daarentegen lijkt relevant vanwege de verschillen in klinisch gedrag van de diverse subtypen. Door middel van de subtypering is dan een betere voorspelling van de prognose mogelijk.

In *hoofdstuk 5* wordt de rol van postoperatieve radiotherapie in relatie tot het voorkomen van lokaal recidief bij intra-orale adenoïd cysteus carcinomen besproken. Veertien van de 27 patiënten met een intra-oraal adenoïd cysteus carcinoom hadden positieve resectieranden en kregen daarom postoperatief radiotherapie. Geen van deze patiënten ontwikkelde binnen 2 jaar een lokaal recidief. Acht patiënten waren ook na 5 jaar nog vrij van tumor. Hogedosis radiotherapie lijkt dan ook een adequate methode om het probleem van microscopisch positieve resectieranden bij patiënten met een intra-oraal adenoïd cysteus carcinoom aan te pakken. Aanvullende chirurgische therapie is dan overbodig.

In *hoofdstuk 6* worden 22 patiënten met een intra-oraal adenoïd cysteus carcinoom, behandeld door middel van chirurgie al dan niet gevolgd door radiotherapie, besproken. Speciale aandacht wordt geschonken aan de aanwezigheid van perineurale uitbreiding in relatie tot lokalisatie, grootte, lokale uitbreiding, status van de resectieranden en metastasering. Perineurale uitbreiding was in 72% van de resectiepreparaten aanwezig. Er lijkt geen relatie te zijn tussen perineurale uitbreiding en lokalisatie of grootte van de tumor. Wel werd perineurale uitbreiding vaker gezien in tumoren met lokale uitbreiding in omringende structuren en in geval van positieve resectieranden. Het gegeven dat metastasen op afstand vaker optreden wanneer er sprake is van perineurale uitbreiding in het resectiepreparaat is statistisch niet significant.

In *hoofdstuk 7* wordt het probleem van het onderscheid tussen een adenoïd cysteus carcinoom en een basaloïd squameus carcinoom besproken aan de hand van één van de 27 patiënten met een intra-oraal adenoïd cysteus carcinoom. Het betreft een solide variant van een adenoïd cysteus carcinoom met squameuze metaplasie, epitheliale dysplasie en een nauwe relatie met het oppervlakte-epitheel, hetgeen histologisch goed zou kunnen passen bij de diagnose basaloïd squameus carcinoom. Op electronenmicroscopisch niveau lijkt het beeld echter beter te passen bij de diagnose adenoïd cysteus carcinoom.

In *hoofdstuk 8* wordt een patiënt met een sialadenoma papilliferum besproken. Het sialadenoma papilliferum is een nieuwe entiteit in de WHO-classificatie van 1991 en valt in de categorie adenomen, subgroep "ductal papilloma". Het is een zeldzame, goedaardige, exofytisch groeiende tumor, die met name op het palatum van patiënten van het mannelijk geslacht voorkomt.

Tenslotte worden in *hoofdstuk 9* twaalf gevallen van necrotiserende sialometaplasie (NS) beschreven. NS is een goedaardige laesie van de speekselklieren die klinisch en histologisch op een maligniteit kan lijken. NS lijkt eerder een histopathologisch fenomeen dat een paar dagen of weken na trauma optreedt dan een op zichzelf staand ziektebeeld. De hoofdoorzaak voor het ontstaan van NS lijkt een infarcering van de speekselklier te zijn, veroorzaakt door ischemie ten gevolge van een vasculair trauma. Aangezien NS binnen enkele weken spontaan geneest, behoeft de laesie geen andere behandeling dan zorgvuldge controle. Indien er twijfel bestaat over de diagnose dient er een proefexcisie genomen te worden teneinde een maligniteit uit te sluiten.

APPENDIX I

WHO International Histological Classification of Tumours

Histological Typing of Salivary Gland Tumours, 1972

Histological Typing of Salivary Gland Tumours
World Health Organization, 1972

I. Epithelial tumours

- A. Adenomas
  1. Pleomorphic adenoma (mixed tumour)
  2. Monomorphic adenomas
     - a. Adenolymphoma
     - b. Oxyphilic adenoma
     - c. Other types
- B. Mucoepidermoid tumour
- C. Acinic cell tumour
- D. Carcinomas
  1. Adenoid cystic carcinoma
  2. Adenocarcinoma
  3. Epidermoid carcinoma
  4. Undifferentiated carcinoma
  5. Carcinoma in pleomorphic adenoma (malignant mixed tumour)

II. Non-epithelial tumours

III. Unclassified tumours

IV. Allied lesions

- A. Benign lymphoepithelial lesion
- B. Sialosis
- C. Oncocytes

APPENDIX II

WHO International Histological Classification of Tumours

Histological Typing of Salivary Gland Tumours, 1991

Histological Typing of Salivary Gland Tumours, World Health Organization, 1991

1.	**Adenomas**	
1.1	Pleomorphic adenoma	8940/0a
1.2	Myoepithelioma (myoepithelial adenoma)	8982/0
1.3	Basal cell adenoma	8147/0
1.4	Warthin tumour (adenolymphoma)	8561/0
1.5	Oncocytoma (oncocytic adenoma)	8290/0
1.6	Canalicular adenoma	
1.7	Sebaceous adenoma	8410/0
1.8	Ductal papilloma	8503/0
1.8.1	Inverted ductal papilloma	8053/0
1.8.2	Intraductal papilloma	8503/0
1.8.3	Sialadenoma papilliferum	8260/0
1.9	Cystadenoma	8440/0
1.9.1	Papillary cystadenoma	8450/0
1.9.2	Mucinous cystadenoma	8470/0
2.	**Carcinomas**	
2.1	Acinic cell carcinoma	8550/3
2.2	Mucoepidermoid carcinoma	8430/3
2.3	Adenoid cystic carcinoma	8200/3
2.4	Polymorphous low-grade adenocarcinoma (terminal duct adenocarcinoma)	
2.5	Epithelial-myoepithelial carcinoma	8562/3
2.6	Basal cell adenocarcinoma	8147/3
2.7	Sebaceous carcinoma	8410/3
2.8	Papillary cystadenocarcinoma	8450/3
2.9	Mucinous adenocarcinoma	8480/3
2.10	Oncocytic carcinoma	8290/3
2.11	Salivary duct carcinoma	8500/3
2.12	Adenocarcinoma	8140/3
2.13	Malignant myoepithelioma (myoepithelial carcinoma)	8982/3
2.14	Carcinoma in pleomorphic adenoma (malignant mixed tumour)	8941/3
2.15	Squamous cell carcinoma	8070/3
2.16	Small cell carcinoma	8041/3
2.17	Undifferentiated carcinoma	8020/3
2.18	Other carcinomas	

a Morphology code of the International Classification of Diseases for Oncology (ICD-O) and the Systematized Nomenclature of Medicine (SNOMED)

Histological Typing of Salivary Gland Tumours, World Health Organization, 1991 (cont'd)

3.	**Non-epithelial Tumours**	
4.	**Malignant Lymphomas**	
5.	**Secondary Tumours**	
6.	**Unclassified Tumours**	
7.	**Tumour-like Lesions**	
7.1	Sialadenosis	71000
7.2	Oncocytosis	73050
7.3	Necrotizing sialometaplasia (salivary gland infarction)	73220
7.4	Benign lymphoepithelial lesion	72240
7.5	Salivary gland cysts	33400
7.6	Chronic sclerosing sialadenitis of submandibular gland (Küttner tumour)	45000
7.7	Cystic lymphoid hyperplasia in AIDS	

DANKWOORD

Zoals een ieder wellicht weet, is een promotie geen solistenwerk, maar een produkt van velen. De kans is groot om bij het maken van een lijst van alle schakels in het produktie-proces van dit proefschrift, iemand te vergeten en daardoor tekort te doen. Daarom op deze plaats een dankbetuiging aan al diegenen die direkt of indirekt, bewust of onbewust, aan de totstandkoming van dit proefschrift hebben bijgedragen.

Bedankt.

Jacqueline

CURRICULUM VITAE

Jacqueline E. van der Wal werd geboren op 17 juni 1963 te Amsterdam.
In 1982 behaalde zij het eindexamen Gymnasium-ß aan de Christelijke Scholengemeenschap Buitenveldert te Amsterdam/Buitenveldert. In datzelfde jaar werd begonnen met de studie Tandheelkunde aan de Vrije Universiteit te Amsterdam. Het tandartsexamen werd behaald op 18 december 1987.
Vanaf 1 januari 1988 is zij als A.I.O. (Assistent-In-Opleiding) werkzaam op de afdeling Mondziekten & Kaakchirurgie en Orale Pathologie. Sinds 1990 studeert zij tevens Geneeskunde aan de Vrije Universiteit te Amsterdam.