EPITHELIAL TUMOURS OF THE PAROTID GLAND
A CLINICOPATHOLOGICAL STUDY

H. LEVERSTEIJN

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The study described in this thesis was performed at the departments of Otolaryngology/Head and Neck Surgery and Pathology, University Hospital Vrije Universiteit, Amsterdam.

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CONTENTS

INTRODUCTION

This study concerns a retrospective, clinicopathological analysis of 422 patients with an epithelial parotid gland tumour who were treated at the department of Otolaryngology / Head and Neck Surgery, University Hospital Vrije Universiteit, Amsterdam, in the period 1974-1995.

The introduction starts with a summary of the embryogenesis and the surgical anatomy of the parotid gland. Subsequently epidemiology, histopathological classification, diagnosis, and treatment of benign and malignant epithelial parotid tumours are briefly reviewed. Finally the aim of this study is summarized.

1. THE PAROTID GLAND

1.1 Embryogenesis

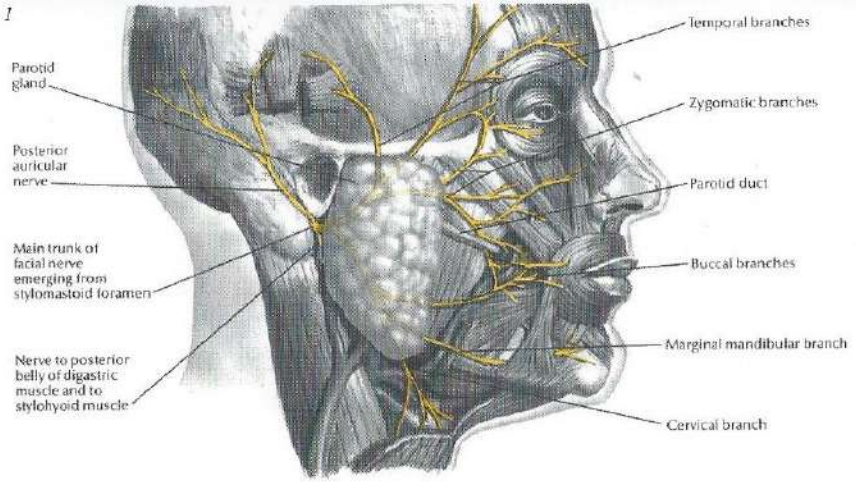
All of the salivary glands share a common embryogenesis in that they all develop from the ingrowth of local proliferations of surface epithelium and they have a similar overall structure. The parotid anlagen are the first of the salivary glands to develop, are of ectodermal origin, and appear between the fourth and sixth weeks of embryonal life. The submandibular and sublingual anlagen appear later, while the minor salivary glands do not start to develop until the twelfth week of embryonal life[1,2].

Although the parotid anlagen are the first to emerge, they become encapsulated only after the submandibular and sublingual glands have done so. This delayed encapsulation is critical to the parotid gland's adult anatomy because the emergence of the lymphatic system occurs after encapsulation of the submandibular and sublingual glands, but before that of the parotid glands. Thus, at completion of embryogenesis, the parotid glands contain lymph nodes and lymphatic channels within their capsule, while the submandibular and sublingual glands do not. Conversely, salivary epithelial cells can be included within the parotid and periparotid lymph nodes. The inclusion of salivary tissue within lymph nodes is unique to the parotid and periparotid lymph nodes[3,4].

1.2 Surgical anatomy

The parotid gland is the largest of the salivary glands and lies in the pre - and infraauricular region deep to the skin and subcutaneous tissue. The superior limit of the gland is the zygomatic arch. Posteriorly, the parotid gland is

Fig. 1



bounded by the external auditory canal, mastoid process and the oblique border of the sternocleidomastoid muscle. The anterior border is diagonal and extends from the anterior end of the superior border to the lower end of the posterior border of the parotid gland and overlies the masseter muscle. Medially, the gland is buttressed by the styloid process and its associated muscles[2,5,6] (Fig.1).

The body of the gland fills the space between the ascending ramus of the mandible and the surface bounded by the external auditory canal and the mastoid process. It is enclosed by a fascia from the superficial layer of the deep cervical fascia, which is of varying thickness, being thickest over the lateral and inferior portion and thinnest or incomplete over the medial surface of the gland[7,8].

The arterial supply in the region of the parotid gland is rich. The gland receives branches from the facial artery, occipital artery, posterior auricular artery, maxillary artery, and superficial temporal artery. Careful control of arterial and venous bleeding during an operation on the gland is essential to avoid complications during identification and dissection of the facial nerve and its branches. Adjacent to the medial portion of the gland and embedded in it for some distance, deep to the facial nerve, are the external carotid artery and the retromandibular vein; in this position the external carotid artery divides into the superficial temporal artery and the maxillary artery while the retromandibular vein receives the corresponding venous branches. Other important vascular structures are the internal jugular vein and the internal carotid artery which are medial to the styloid process and the deep portion of the gland.

The facial nerve emerges from the skull base at the stylomastoid foramen, which is immediately posterior to the base of the styloid process and anterior to the attachment of the digastric muscle to the mastoid tip. The usual approach to identify the main stem of the facial nerve is to free the posterior border of the parotid gland from the anterior border of the sternocleidomastoid muscle up to the mastoid tip. More superiorly the posterior border of the parotid gland is freed through blunt dissection from the cartilaginous portion of the external auditory canal. A triangular process or 'pointer' at the inferior edge of the cartilage is exposed. This process points medially to the facial nerve as it leaves the stylomastoid foramen. Subsequently the posterior belly of the digastric muscle is identified and dissection is continued along the muscle up to its insertion to the mastoid. At this point important bony surgical landmarks like the anterior surface of the mastoid process, the tympanomastoid suture line and the styloid process are identified through careful palpation. The location of the main trunk of the facial nerve is quite constant in relation to the various muscular and bony landmarks. It lies just superior to the attachment of the posterior belly of the digastric muscle to the digastric groove of the mastoid process and usually a little deeper. Further more the nerve lies approximately 6 to 8 mm anteroinferior to the tympanomastoid suture line, while the styloid process lies medial to the main trunk of the nerve. In the great majority of cases the main trunk of the facial nerve can thus be easily identified. In some patients however, due to the location and size of the tumour, it can be extremely troublesome, or even impossible, to identify the main stem of the facial nerve and yet preserve the integrity of the tumour. In these circumstances it is preferable to refrain from the traditional approach and instead identify the main stem of the nerve through retrograde dissection of one or several of its peripheral branches[9].

After leaving the stylomastoid foramen the nerve turns laterally to enter the parotid gland posteriorly. Before entering the substance of the parotid gland it gives off small motor branches to: the stylohyoid muscle, the posterior auricular muscle, and the posterior belly of the digastric muscle. Subsequently, the main trunk divides in the parotid gland into two major divisions: the temperofacial and cervicofacial branch. This point of branching is known as the pes anserinus (goose's foot). These two subdivisions then branch to form five major branches: temporal, zygomatic, buccal, marginal mandibular, and cervical. Communications between the branches are common. The primary division is constant, there is however a considerable variation in the distribution of the further branching pattern[2,13-15] (Fig.2a,2b).

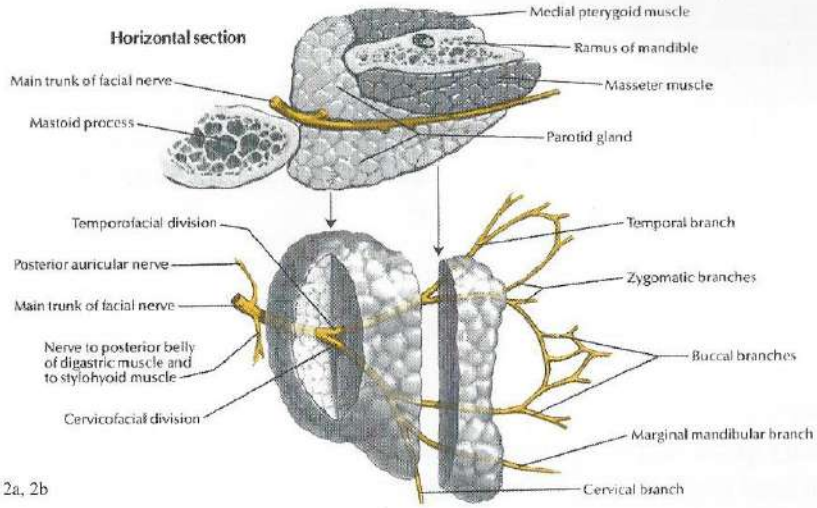


Fig 2a, 2b

Although the parotid gland is a single anatomic entity, it is common practice to designate the part of the gland that lies medial to the nerve 'deep lobe' and anything lateral to the nerve 'superficial lobe'. The superficial lobe contains approximately 80% of the parenchymal tissue of the gland. Hence, most neoplasms arise superficially to the nerve.

Stenson's duct passes from the anterior edge of the gland over the masseter muscle. At the anterior margin of the muscle, it turns medially to pierce the buccinator muscle and enter the oral cavity at the level of the second upper molar tooth. Accessory gland tissue is occasionally found along the course of the duct[12].

The great auricular nerve supplies sensation to the skin over the gland and the mastoid process, and to the skin of the auricle except for the tragus[16]. The greater auricular nerve is the largest branch of the cervical plexus. It passes around the posterior border of the sternocleidomastoid muscle (Erb's point), and ascends obliquely across the sternocleidomastoid muscle to enter the parotid gland before providing the posterior branch that innervates the major part of the auricle and the surrounding skin. In surgery for parotid gland tumours, traditionally attention was focused particularly on the preservation of the facial nerve. Only in the last decade concern has been expressed about the potential sequelae of the sacrifice of the greater auricular nerve, thus

resulting in an increased interest to preserve the posterior branch of this nerve[17,18].

Secretion of the gland is stimulated by the auriculotemporal nerve which carries postganglionic parasympathetic fibres from the otic ganglion to the parotid gland. When injured during parotidectomy, aberrant reinnervation of the severed postganglionic sympathetic fibres that supply the sweat glands of the skin of the auriculotemporal region by the postganglionic secremotor parasympathetic nerve fibres which innervate the parotid gland can result in gustatory sweating (Frey's syndrome)[19-21].

2. PAROTID TUMOURS

2.1 Epidemiology & Etiology

Salivary gland neoplasms are rare and account approximately for 3 per cent of all head and neck neoplasms[22]. The incidence is reported to range from 0.4 to 13.5 annual cases per 100.000 in different populations[23]. Racial and geographic prevalence of salivary gland tumours do exist. For instance, there is a high prevalence of salivary gland tumours in Eskimos and amongst survivors of atomic bomb blasts[24-28].

The majority of salivary gland tumours are of epithelial origin. Non-epithelial salivary gland tumours account for only 5 per cent of all salivary gland neoplasms and most frequently occur in the major salivary glands[29-33], particularly in the parotid gland[34]. Approximately 90 per cent of the epithelial salivary gland neoplasms are located in the major salivary glands: 75-85 per cent in the parotid gland, 5-10 per cent in the submandibular glands, and less than 1 per cent in the sublingual glands[33-36]. Approximately 20 per cent of parotid neoplasms are malignant. Of the submandibular neoplasms approximately 50 per cent is malignant while for the minor salivary gland neoplasms the rate of malignancy is reported to be over 60 per cent; neoplasms of the sublingual gland are almost always malignant[37].

The etiology of salivary gland tumours is still unknown[27,38]. In a few per cent of patients with a salivary gland tumour there is a history of previous low dose irradiation of the head and neck area. An epidemiologic study has shown that the incidence of salivary gland tumours in Hiroshima Atomic bomb survivors was 2.0 times higher than among the non-exposed[39]. Other studies demonstrated that tumours of the parotid gland were related to prior exposure of the parotid gland to occupational dusts (nickel), to diagnostic medical and dental radiography[40,41], and x-ray therapy for acne[42].

2.2 Histopathological classification

Epithelial salivary gland tumours make up a heterogeneous group of lesions with great morphological variation, which presents difficulties in histological classification. Until recently these tumours were classified according to the international histological classification of salivary gland tumours published by the World Health Organization in 1972[43] (Table 1).

The proposed nomenclature was widely accepted and has contributed to improved uniformity in correlating the findings at histopathological examination[44]. However, since 1972 a great deal of information has been collected about new tumour entities as well as about the behaviour and prognosis of the established tumour types, necessitating a reappraisal of the WHO classification. Subsequently, in the revised classification (Table 2), more than 30 different types of epithelial tumours have been included[45].

Table 1. 1972 WHO histological classification of epithelial salivary gland tumours.

A. Adenomas
   1. Pleomorphic adenoma (mixed tumour)
   2. Monomorphic adenomas
      (a) Adenolymphoma (Warthin tumour)
      (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)

Table 2. 1991 WHO histological classification of epithelial salivary gland tumours.

1.	**Adenomas**
1.1.	Pleomorphic adenoma
1.2.	Myoepithelioma (Myoepithelial adenoma)
1.3.	Basal cell adenoma
1.4.	Warthin tumour (Adenolymphoma)
1.5.	Oncocytoma (Oncocytic adenoma)
1.6.	Canalicular adenoma
1.7.	Sebaceous adenoma
1.8.	Ductal papilloma
	1.8.1. Inverted ductal papilloma
	1.8.2 Intraductal papilloma
	1.8.3 Sialadenoma papilliferum
1.9.	Cystadenoma
	1.9.1 Papillary cystadenoma
	1.9.2 Mucinous cystadenoma
2.	**Carcinomas**
2.1.	Acinic cell carcinoma
2.2.	Mucoepidermoid carcinoma
2.3.	Adenoid cystic carcinoma
2.4.	Polymorphous low-grade adenocarcinoma (Terminal duct adenocarcinoma)
2.5.	Epithelial-myoepithelial carcinoma
2.6.	Basal cell adenocarcinoma
2.7.	Sebaceous carcinoma
2.8.	Papillary cystadenocarcinoma
2.9.	Mucinous adenocarcinoma
2.10.	Oncocytic carcinoma
2.11.	Salivary duct carcinoma
2.12.	Adenocarcinoma
2.13.	Malignant myoepithelioma (Myoepithelial carcinoma)
2.14.	Carcinoma in pleomorphic adenoma (Malignant mixed tumour)
2.15.	Squamous cell carcinoma
2.16.	Small cell carcinoma
2.17.	Undifferentiated carcinoma
2.18.	Other carcinomas

The introduction of immunohistochemical markers like S-100 protein, myosin, desmin, vimentin, carcinoembryonic antigen, and cytokeratin provided new possibilities in differentiating between distinct tumour entities[46]. However, although quoted by some authors as a valuable tool in the differential diagnosis of salivary gland tumours its applicability for the subtyping of these tumours seems to be limited[47-52].

2.2.1 Adenomas

The 1972 histological classification subdivided adenomas into pleomorphic and monomorphic adenomas. However, many of the latter were neither monomorphic nor monocellular. Furthermore, the wide range of tumours in the group of monomorphic adenomas and their distinct morphologic features justify their separation for purposes of identification. Therefore, in the 1991 WHO histological classification for salivary gland tumours, clearly defined tumours, even if uncommon, were categorized separately. The most common adenomas are described briefly.

Pleomorphic Adenoma. The pleomorphic adenoma is the most common benign tumour occurring in the parotid gland. Microscopically, these tumours do not have a true capsule but compress the surrounding normal salivary gland tissue, occasionally having microscopic excrescences into normal tissue[3].

Histopathologically, these tumours are characterized by cellular pleomorphism in which epithelial and myoepithelial components are embedded in a stroma which may be mucoid, myxoid, chondroid or osteoid in origin. The stroma varies from tumour to tumour and may have a combination of any of these types within a single tumour. Malignant transformation of this tumour may occur.

Myoepithelioma. Although several tumours of the salivary glands, especially pleomorphic adenomas, contain myoepithelial cells, tumours consisting only of myoepithelial cells were considered as a separate entity. This distinction is important because myoepithelioma is more aggressive than pleomorphic adenoma and occasionally transforms into malignant myoepithelioma[45].

Warthin Tumour. In the first edition of the WHO histological classification the term adenolymphoma was preferred. As there was confusion with lymphomas, this designation was replaced by the term Warthin tumour. It is the second most common benign tumour of the parotid gland. Histologically Warthin's tumour is composed of a lymphoid stroma containing germinal

centres surrounding cystic spaces lined by a double cell layer of oncocytic epithelium[53]. The failure to observe both a lymphoreticular and an epithelial (oncocytic) component has led to the erroneous description of Warthin's tumours in unusual extraparotid sites[54,55]. This tumour is usually seen after the age of 40 and is more common in men than in women. Malignant transformation in a Warthin tumour is exceedingly rare[56].

2.2.2 Carcinomas

In comparison with the first edition of the WHO histological classification of salivary gland tumours various types of (adeno)carcinomas are distinguished for purposes of recognition, prognosis, and treatment. The most frequently encountered of these in the parotid gland are described in short detail.

Acinic Cell Carcinoma. For many years, controversy on the biologic potential of this tumour persisted. In the first edition the term acinic cell tumour was used. Currently, most investigators recognize this as a special type of adenocarcinoma with at least low grade malignant potential. No histological features, special growth patterns or grading schemes seem to have prognostic value. Prognosis depends of local invasion and completeness of surgical removal[57-60].

Mucoepidermoid Carcinoma. By contrast with the first edition, the term mucoepidermoid tumour was replaced by carcinoma. Like acinic cell carcinomas, mucoepidermoid carcinomas are capable of metastasizing, regardless of their histologic appearance. Mucoepidermoid carcinoma can be categorized into low and high grade, and lesions so classified provide relatively good and bad prognostic groups with respect to local recurrence and metastatic ability. However, in individual cases this grading is not absolute. Of greater importance is the adequacy of primary surgical excision with respect to local recurrence[61,62].

Adenoid Cystic Carcinoma. All adenoid cystic carcinomas, regardless of their histologic type, are biologically aggressive. Metastases, usually by haematogenous spread, may become manifest many years after excision of the primary tumour. Perineural or intravascular spread, mitotic activity, and pleomorphism appear to have no exact correlation with prognosis. Tumours of glandular or tubular type have a better prognosis with regard to the duration of survival; the solid type seems to have the worst prognosis and is characterized by numerous early recurrences, early metastases, and high mortality. Important prognostic factors are the size, clearness of surgical margins, and clinical stage[63-65].

Adenocarcinoma. In the revised WHO histological classification of salivary gland tumours the adenocarcinomas have been subdivided into a number of entities, such as polymorphous low grade adenocarcinoma, basal cell adenocarcinoma, papillary cystadenoma, mucinous adenocarcinoma, and the adenocarcinoma that does not fit into the previous categories, sometimes also designated as 'adenocarcinoma, not otherwise specified'. The polymorphous low grade adenocarcinoma rarely if ever occurs in the parotid gland. Of the other rare categories of adenocarcinoma the basal cell adenocarcinoma is the most common one.

Basal Cell Adenocarcinoma. The term basal cell adenocarcinoma distinguishes this tumour from the basal cell carcinoma of the skin and is more suitable than the older term malignant basel cell tumour. Although the tumour has cytologic characteristics of basal cell adenoma, morphological growth patterns are indicative for malignant disease. Invasive growth is another distinctive diagnostic feature that separates it from basal cell adenoma. A minority of these tumours display perineural - and intravascular invasion. Basal cell adenocarcinomas are low grade adenocarcinomas with a relatively good prognosis. In accordance with the histological patterns for basal cell adenomas, basal cell adenocarcinomas can be divided into four subtypes: solid, trabecular, tubular, and membranous. Recurrence is relatively frequent, but metastasis is less common, usually to the regional lymph nodes.

Malignant Myoepithelioma. This tumour is distinguished from benign myoepthelial neoplasms by its infiltrating destructive growth, increased mitotic activity, and cytologic pleomorphism. Most of these tumours occur in the parotid gland of adults older than 50 years of age. Although locally destructive, metastasis is infrequent.

Carcinoma in Pleomorphic Adenoma. Histological features indicative of malignant changes in pleomorphic adenomas consist of microscopic foci of necrosis, haemorrhage, calcification, and/or excessive hyalinisation. The presence, absence, and degree of infiltrating growth and the histological differentiation allow four subtypes[45,66,67]. The first is a noninvasive carcinoma in pleomorphic adenoma and consists of circumscribed malignant areas in a pleomorphic adenoma without infiltration of the surrounding tissue. The noninvasive carcinoma has an excellent prognosis when there is complete surgical removal. The second is invasive carcinoma, and the extent of invasion is a guide to prognosis and biological behaviour[45]. The third is carcinosarcoma, a rare tumour consisting of carcinomatous and sarcomatous

features. The latter component shows mostly a chondrosarcomatous pattern. This true malignant tumour is highly lethal. The fourth type is the extremely rare metastasizing pleomorphic adenoma, in which the primary salivary gland tumour and its metastases are composed of 'benign' mixed tumour structures.

Undifferentiated carcinoma. In the revised WHO histological classification for salivary gland tumours the undifferentiated carcinoma has been defined as a malignant tumour of epithelial structure that is too poorly differentiated, i.e. being devoid of any phenotypic expression by light microscopy, to be placed in any of the groups of carcinoma[45]. The single most important clinicopathological factor influencing the outcome of the disease is the size of the primary tumour[68,69].

2.3 Diagnostic work-up

2.3.1 History and physical examination

Almost always history, inspection and especially palpation form the corner stones of the diagnosis on which adequate treatment of a parotid tumour rests.

Dealing with swellings in the parotid area it is first of all important to determine whether the tumour lies within the parotid gland or if it arises from a neighbouring structure. An atheromatous cyst, hypertrophy of the masseter muscle, diseases of the ascending ramus of the mandible and unilateral enlargement of the transverse process of the atlas can be mistaken for a parotid tumour[70]. Lymph nodes occur both in the immediate surroundings of the parotid gland and within the gland itself, and they may be divided into a superficial and deep group. The superficial nodes lie in the drainage area of the scalp, the eyelids, the corresponding half of the face, the external part of the nose and the auricle, whereas the deep nodes drain the nasopharynx, oropharynx, and the nasal cavity. Inflammatory diseases and tumours in these areas can cause lymph node enlargement in the parotid area. It is therefore important to include these areas in the examination and to ask the patient if a tumour has previously been removed from the scalp, etc.

If it appears that the swelling arises from the gland itself it must be determinated whether the swelling is neoplastic in origin or otherwise. In practice this is seldom difficult. Non-specific infections of the parotid gland occur much less commonly than in the submandibular gland. The history of a recurrent swelling of the gland associated with eating, and diffuse enlargement of the parotid usually indicate the correct diagnosis. When doubts remains whether the swelling is inflammatory in nature, a sialogram is helpful, but this is rarely needed. Diffuse parotid enlargement may be the first clinical presentation of an HIV infection. Usually the parotid enlargement then is bilateral and symmetrical, with multiple cyst formation (characteristic on MRI or CT), but it may be unilateral[71-73].

It is important to determine whether a parotid tumour is benign or malignant. Unfortunately, this is not possible in many cases. It cannot be emphasized strongly enough that at least half of all malignant parotid tumours can not be differentiated clinically from benign tumours, for example pleomorphic adenoma[74]. Only in less than half of the malignant cases there are frank clinical features of malignancy like fixation to skin or neighbouring tissues, involvement of the facial nerve, lymph node metastases or trismus. Pain and rapid growth must always be taken seriously; however, 50 per cent of patients with a parotid carcinoma have a history of more than two years. On the other hand, most benign tumours i.e. the pleomorphic adenoma, have a firm consistency which could pass for a malignant tumour. Only the adenolymphoma can be recognized often with reasonable certainty as a benign tumour by virtue of its sex, age, and site predilection and its soft elastic consistency on palpation.

The deep lobe of the parotid gland is related to the pharynx. Since a tumour of any size arising from the deep lobe of the parotid gland quickly gets jammed between the mandible and the mastoid, it extends medially and/or laterally and then produces a bulge of the pharyngeal wall, or pushes the superficial lobe of the parotid gland externally. The latter can easily give the impression that the tumour arises from the superficial lobe. The pharynx should therefore be inspected in every patient with a parotid tumour, especially if it appears to involve the whole superficial lobe.

2.3.2 Imaging

With regard to the diagnosis of parotid gland tumours by imaging modalities, the last two decades, a formidable improvement has been achieved from one that primarily relied on plain films[75], sialograms[76,77], radionuclide scanning[78], and computed tomography with simultaneous sialography[79-82], to one that relies on computed tomography (CT)[83-85], and particularly ozxn magnetic resonance imaging MRI[86-89]. Especially the ability of CT and MRI to depict the extent of the disease in the axial plane, posterior and medial to the ascending ramus of the mandible has contributed considerably to their clinical usefulness.

While MRI and CT remain to be subjected to a continuous evolving process, at present MRI is considered to be superior to CT for parotid tumours due to its superior soft tissue resolution[90,91] and for obtaining information concerning the differential diagnosis of parapharyngeal tumours which may be of deep lobe, parotid gland origin[92,93].

Additional examination using MRI is required in those patients with a parotid tumour in whom it is difficult to delineate the extent of disease. The indications may include: 1. tumours with reduced mobility or fixation to the underlying tissues, 2. tumours with medial displacement of the lateral oropharyngeal wall, and 3. locally recurrent tumours after previous surgical treatment.

Many attempts have been made to correlate MR imaging findings with specific histological types of parotid gland tumours and although some authors reported that tumour homogeneity and signal intensity correlate well with the histological findings[94,95], in general a poor relationship has been reported[96-100].

2.3.3 Fine needle aspiration cytology.

Aspiration cytology as a method for tumour diagnosis was first reported by Kun[101] in 1847. In 1930 this modality was advocated by Martin and Ellis for the diagnosis of head and neck tumours[102]. Initially large bore (18-gauge) needles were used and this turned out to be associated with a considerable risk of tumour seeding and bleeding. Therefore and because of lack of uniform criteria for diagnosis the use of aspiration cytology declined[103,104]. Later, in the 1960s, through the establishment of uniform cytologic criteria for the diagnosis of salivary gland tumours and the introduction of fine bore needles Eneroth and colleagues laid the ground work for the general acceptance of this technique[105-110].

Since the advent of (ultrasound guided) fine needle aspiration cytology (FNAC) several studies reported it to be a safe, cost effective, and accurate method for evaluating salivary gland tumours[111,112]. Regarding FNAC of parotid gland tumours a review of the recent literature indicated a sensitivity of approximately 90 per cent and a specificity of 75 per cent. Additionally, it proved to be much better at predicting and differentiating benign lesions than malignant lesions[113].

At present, by many surgeons treating parotid gland tumours, it is considered as a valuable tool, in the preoperative assessment of patients with a tumour in the parotid region[114-116]. Especially regarding the question whether or not the tumour is of salivary gland origin, and if so, if the tumour is benign or malignant. Additionally an attempt can be made to type the tumour in either the benign or malignant group of tumours. However, others reported that FNAC of the major salivary glands tumours often lack clinical utility. Especially when FNAC does not provide information to be used in the surgical approach[117,118]. In our opinion however, specific findings on FNAC may change treatment policy in those patients who present with an asymptomatic, clinically benign parotid tumour. In the event of benign disease on FNAC the surgical procedure will include partial parotidectomy with careful palpation of the subdigastric region for enlarged lymph nodes. If, however, FNAC reveals malignant disease, in each surgical procedure subdigastric lymph nodes will be sent for frozen section analysis. If, subsequently, frozen section analysis reveals no malignant disease only the draining portion of the parotid gland inferior to the tumour will be resected, while in the case of metastatic disease an additional en bloc radical neck dissection will be performed.

2.4 Treatment

Before the 1940s the surgical management of parotid tumours was highly unrewarding due to the excessive rate of permanent facial nerve paresis and paralysis and tumour recurrences (20-45 per cent)[119-124]. The poor results in the treatment of these tumours stemmed from inadequate resection through the fear of injuring the facial nerve and the lack of the knowledge of technique in dissecting the nerve from parotid tissue[125,126].

After the introduction of parotidectomy with identification and dissection of the facial nerve first and subsequent removal of the superficial and/or deep lobe by Janes[127] and Bailey[128,129] recurrence rates for benign parotid tumours declined dramatically, approaching zero[130-136], while permanent facial nerve dysfunction became very rare. This became established as the appropriate treatment for benign and low grade malignant lesions[137-141]. However, in malignant tumours the incidence of local recurrence after surgery alone continued to be high, especially in patients with locally advanced disease[130-133,142].

With these favourable developments in reducing the incidence of recurrent benign tumours and that of permanent facial nerve paresis and paralysis, attention gradually focused on other sequelae of parotid surgery including loss of sensation of the auricle due to transection of the greater

auricular nerve, cosmetic aspects and Frey's syndrome. To reduce such morbidity subsequently several modifications of the traditional surgical procedure were implemented in our department. These included: 1. an attempt, in each procedure, to preserve the posterior branch of the greater auricular nerve, unless precluded by the position of the tumour,. 2. for each tumour lateral to the nerve, in principle, to perform a 'partial' superficial parotidectomy, and 3. to perform, in principle, for each deep lobe tumour a 'selective' deep lobe resection.

Initially, radiotherapy was seldom used in the treatment of malignant salivary gland tumours as these were believed to be radioresistant[134]. As a result, radiation therapy was usually only considered as a palliative measure in the treatment of patients with locally unresectable disease, and it was recommended only for certain histological types[143-146]. However, with the introduction of modified techniques such as megavolt radiation therapy, computerized tomography, and computer assisted treatment planning a more homogeneous dose distribution could be obtained in the target volume through which subsequent investigators have described observable sensitivity for the majority of histological types of salivary gland tumours[147,148]. Others have reported radiotherapy to be highly effective as an adjunct to surgery in improving local control and survival when administered postoperatively to patients with suspected residual microscopic disease, close surgical margins or other unfavourable findings such as the presence of perineural and perivascular spread[149-154].

The most hazardous problem which one may experience operating on a patient with a malignant tumour, who's preoperative facial nerve function was symmetrically intact, is the finding of an intimate relationship between the main stem of the facial nerve and/or one of its branches and the tumour[74]. In this situation the two objects of parotid surgery, i.e. removal of the tumour with a healthy margin of parotid tissue and preservation of the facial nerve may be in conflict. The decision whether or not to perform a conservative, nerve preserving approach will be dictated by the findings during surgery and the experiences with the use of postoperative radiotherapy to eradicate microscopic disease left behind.

3. AIM OF THE STUDY.

The principal aim of the work presented in this thesis is to evaluate the results of treatment in 422 patients with an epithelial parotid gland tumour at the department of Otolaryngology / Head and Neck Surgery, University Hospital Vrije Universiteit, Amsterdam. Except for the surgical experience with forty recurrent/residual pleomorphic adenomas after previous treatment elsewhere, described in chapter four, all tumours discussed concern previously untreated epithelial parotid gland tumours. For each chapter additional objectives were assessed.

In *chapter 2* the results of the reclassification of 478 previously untreated epithelial parotid gland tumours according to the 1991 WHO histological classification of salivary gland tumours are presented. For the aim of the study the patients operated by the department of General Surgery (n=56) at the University Hospital Vrije Universiteit, Amsterdam were included.

In *chapter 3* the experiences and results are described in 245 patients operated for a previously untreated pleomorphic adenoma. It reports on the introduction of several modifications of parotidectomy to reduce the specific surgical morbidity such as Frey's syndrome and the loss of sensation of the auricle. The study compares the results of the different surgical techniques with regard to recurrence rate and morbidity. Additionally the merit of postoperative radiotherapy in the event of tumour spill is being debated.

In *chapter 4* the experiences and results of treatment are described in 40 patients with recurrent and/or residual pleomorphic adenoma of the parotid gland after previous surgery elsewhere, with emphasis on recurrent tumour growth, risk of facial nerve damage, and malignant transformation. Additionally, the query when to refrain from further surgical treatment is being addressed.

In *chapter 5* the applicability of the implemented modifications of parotidectomy, as summoned in chapter three, in the treatment of 88 parotid gland Warthin's tumours is evaluated and related to the findings at histopathological examination.

In *chapter 6* the results of treatment are described in 65 patients with a previously untreated malignant epithelial parotid gland tumour. All patients underwent some type of parotidectomy, twenty of whom with an en bloc radical neck dissection. Fifty-one patients received postoperative radiotherapy. Patient presentation characteristics, histological classification, and

disease free and overall survival rates are reviewed. Additionally, the results of the applied treatment policy regarding the facial nerve and the neck are evaluated.

In *chapter 7* the value and results of MR imaging in the differential diagnosis of parapharyngeal space tumours, which may or may not be of deep lobe parotid gland origin, is described with special emphasis on the assessment of tumour vascularity and vessel displacement.

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Chapter 2.

PAROTID GLAND TUMORS: HISTOLOGICAL REEVALUATION AND RECLASSIFICATION OF 478 CASES

J.E. van der Wal[1], H. Leverstein[2], G.B. Snow[2],

H.A. Kraaijenhagen[1], I. van der Waal[1].

[1]: Department of Oral & Maxillofacial Surgery/Pathology

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

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ABSTRACT

Background. The histological classification of epithelial salivary gland tumours may present difficulties due to their great morphologic diversity.

Methods. In this study 478 parotid gland tumours were reevaluated and reclassified according to the 1991 WHO histological classification of salivary gland tumours.

Results. In 56 cases the original diagnosis was changed, either within the benign or the malignant tumour group. In six cases (1.3%) the original diagnosis was changed from benign to malignant or vice versa.

Conclusions. During the mean follow-up period of 10.3 years no events occurred supporting or rejecting the proposed change in diagnosis in these six patients.

With regard to the three cases in which an original malignant diagnosis was made the possibility of an overdiagnosis, and therefore an overtreatment remains.

INTRODUCTION

Salivary gland tumours constitute a heterogeneous group of tumours with an annual incidence of about 1 per 100.000 population, comprising less than 3% of all neoplasms of the head and neck. Most of these tumours are located in the major salivary glands, especially the parotid glands[1,2,3].

The histological classification of epithelial salivary gland tumours may present difficulties due to their great morphologic variation[4]. The complexity of this group of tumours is illustrated in the second revision of the WHO-classification of Salivary Gland Tumours, where more than 30 different types of epithelial tumours are included[5] (Table I).

In this study 478 parotid tumours have been reevaluated and reclassified according to the 1991-WHO-histological classification of Salivary Gland Tumours.

Table I. Histological Typing of Epithelial Salivary Gland Tumours, WHO, 1991[5]

1.	**Adenomas**
1.1.	Pleomorphic adenoma
1.2.	Myoepithelioma (Myoepithelial adenoma)
1.3.	Basal cell adenoma
1.4.	Warthin tumour (Adenolymphoma)
1.5.	Oncocytoma (Oncocytic adenoma)
1.6.	Canalicular adenoma
1.7.	Sebaceous adenoma
1.8.	Ductal papilloma
1.9.	Cystadenoma
2.	**Carcinomas**
2.1.	Acinic cell carcinoma
2.2.	Mucoepidermoid carcinoma
2.3.	Adenoid cystic carcinoma
2.4.	Polymorphous low-grade adenocarcinoma (Terminal duct adenocarcinoma)
2.5.	Epithelial-myoepithelial carcinoma
2.6.	Basal cell adenocarcinoma
2.7.	Sebaceous carcinoma
2.8.	Papillary cystadenocarcinoma
2.9.	Mucinous adenocarcinoma
2.10.	Oncocytic carcinoma
2.11.	Salivary duct carcinoma
2.12.	Adenocarcinoma
2.13.	Malignant myoepithelioma (Myoepithelial carcinoma)
2.14.	Carcinoma in pleomorphic adenoma (Malignant mixed tumour)
2.15.	Squamous cell carcinoma
2.16.	Small cell carcinoma
2.17.	Undifferentiated carcinoma
2.18.	Other carcinomas

MATERIAL & METHODS

In the period 1974-1994 525 patients with a tumour of the parotid gland have been registered at the departments of Otolaryngology/Head & Neck Surgery, Oral & Maxillofacial Surgery/Pathology, and General Surgery. Forty-seven of these patients were previously treated elsewhere and were excluded from this study. The remaining group of 478 patients consisted of 228 men and 250 women. According to the original diagnoses, mostly typed by the 1972-WHO classification for salivary gland tumours[6] (table II) 405 (85%) of the 478 tumours were benign and 73 (15%) malignant, as shown in table III.

Treatment in all cases consisted of superficial or total parotidectomy. In nine benign cases surgery was followed by radiotherapy because of tumour spill during operation. In 22 of the malignant cases local surgery was combined with a neck dissection. In 53 of the malignant cases postoperative radiotherapy was instituted.

Table II. Histological Typing of Epithelial Salivary Gland Tumours, WHO, 1972[6]

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)

Table III. Original and revised histological diagnosis of 478 parotid gland tumours.

	Original diagnosis	Revised diagnosis
Benign		
Pleomorphic adenoma	290	264
Monomorphic adenoma	6	-
Myoepithelioma	2	29
Basal cell adenoma	-	3
Warthin tumour	100	101
Oncocytoma	3	3
Canalicular adenoma	-	1
Cystadenoma	2	3
Papillary cystadenoma	1	1
Benign, NOS[1]	1	-
Total	405	405
Malignant		
Acinic cell carcinoma	14	17
Mucoepidermoid carcinoma	7	5
Adenoid cystic carcinoma	14	13
Epithelial-myoepithelial carcinoma	-	2
Mucinous adenocarcinoma	-	1
Oncocytic carcinoma	1	1
Salivary duct carcinoma	-	1
Adenocarcinoma, NOS[1]	17	13
Malignant myoepithelioma	2	7
Carcinoma in pleomorphic adenoma	7	6
Squamous cell carcinoma	1	2
Undifferentiated carcinoma	7	3
Malignant Warthin tumour	1	1
Malignant, NOS[1]	2	1
Total	73	73

[1] NOS = Not Otherwise Specified

All slides have been reviewed and reclassified according to the 1991 WHO-classification by two pathologists with special expertise in salivary gland pathology (JEvdW;IvdW). Straight forward cases have been reviewed once; cases with disagreement in diagnosis have been reviewed twice. The reviewers were not informed about the clinical course.

Follow-up data were available in all patients. The mean follow-up period was 10.3 years (range 317).

RESULTS

The outcome of the histological reevaluation and reclassification is shown in table III. In 56 cases (11.7%) the original diagnosis was changed within the benign or malignant tumour group and consisted of different subtyping, e.g. pleomorphic adenoma into myoepithelioma, monomorphic adenoma into basal cell adenoma or myoepithelioma, adenocarcinoma into one of the new added subtypes of (adeno)carcinoma.

In six cases (1.3%) the diagnosis was changed from benign into malignant or vice versa (Table IV). In the first case the diagnosis of pleomorphic adenoma was changed into a myoepithelial tumour due to the prominence of myoepithelial cells. Because of the serious degree of cellular and nuclear pleomorphism and high mitotic rate, the diagnosis was changed to malignant myoepithelioma, in spite of well encapsulation. In the second case the tumour contained characteristic features of epithelial-myoepithelial carcinoma (a double layer of two cell types: duct lining cells and myoepithelial cells), and local areas of microinvasive growth. The diagnosis was therefore changed from pleomorphic adenoma into epithelial-myoepithelial carcinoma, possibly arising from pre-existing pleomorphic adenoma. The third case is a cystic tumour without a clear margin consisting of epidermoid areas and mucous cells. The diagnosis was changed from cystadenoma into low grade mucoepidermoid carcinoma. Case four was a cystic tumour with papillary projections into the lumen. On revision there was some doubt about the invasiveness of this tumour. Therefore the diagnosis was changed from adenocarcinoma into (papillary) cystadenoma. Case five was a tumour consisting of myoepithelial cells and myxoid areas with a focal cribriform area suggestive of adenoid cystic carcinoma within the content of the capsule. No malignant features could be found. Therefore, the diagnosis adenoid cystic carcinoma was replaced by pleomorphic adenoma. In the last case the diagnosis (non-invasive) carcinoma in pleomorphic adenoma was possibly based on the mitotic activity. At reevaluation the diagnosis benign pleomorphic adenoma was considered more appropriate.

Table IV. Changes in diagnosis from benign into malignant or vice versa in seven patients.

	Original diagnosis	Revised diagnosis
1.	Pleomorphic adenoma	Malignant myoepithelioma
2.	Pleomorphic adenoma	Epithelial-myoepithelial carcinoma
3.	Cystadenoma	Mucoepidermoid carcinoma
4.	Adenocarcinoma	(Papillary) cystadenoma
5.	Adenoid cystic carcinoma	Pleomorphic adenoma
6.	Carcinoma in pleomorphic adenoma	Pleomorphic adenoma

In all six cases the patients were treated by surgery. All resection specimens had tumour free margins. Only in case six the patient was further treated by postoperative radiotherapy.

During the follow-up period of these patients no events occurred supporting or rejecting the correctness of the revised diagnosis.

DISCUSSION

Clinical data of the patients in this study are in agreement with the findings in other studies on parotid tumours[1,2,3]. The histological typing of salivary gland tumours can be very difficult. Salivary gland tumours not only show morphologic variation among individual tumours but also within the same tumour mass. This leads to the difficult task to give an overall diagnosis based on the most prominent differentiated part of the tumour[4,7].

A change in diagnosis was made in 62 cases (13%). The majority of these changes were within the benign or malignant tumour category and were due to the more extended subtyping of the 1991-WHO-classification. A more detailed subtyping in the malignant tumour group may lead to a better prediction of the prognosis. The subtyping in the adenocarcinoma-group leads to a diminishing of the group of adenocarcinomas, not otherwise specified

(NOS)[8]. The group of adenocarcinoma, NOS contained tumours which were reclassified into tumours with different grades of malignancy (epithelial-myoepithelial carcinoma, salivary duct carcinoma), and therefore different prognosis[5]. Polymorphous low-grade adenocarcinoma (PLGA) is an entity that is almost restricted to the minor salivary glands[5]. However, there were tumours (2 cases) in the parotid glands that could be designated as PGA and that are now included in the group of adenocarcinoma, NOS. Some monomorphic adenomas, pleomorphic adenomas and the benign tumour,NOS have now been classified as myoepitheliomas. The recognition of myoepitheliomas is important because the cellular varieties can be misdiagnosed as malignancies[9].

In six cases the original diagnosis was changed from benign to malignant or vice versa. The determination of the biologic behaviour can be difficult because of the relatively bland histopathologic features of many of the malignant lesions. Several features, such as necrosis of lesional tissue and spotty calcification in the stroma, have been suggested to indicate potentially aggressive behaviour. However, these features can be found in both benign and malignant tumours[10]. The follow-up data in the six cases did not show any events supporting or rejecting the proposed changes in diagnosis. With regard to the three cases in which an original malignant diagnosis was made the possibility of an overdiagnosis and, therefore, of an overtreatment remains.

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Chapter 3.

SURGICAL MANAGEMENT OF 246 PREVIOUSLY UNTREATED PLEOMORPHIC ADENOMAS OF THE PAROTID GLAND

H. Leverstein[1], J.E. van der Wal[2], R.M. Tiwari[1],

I. van der Waal[2], and G.B. Snow[1].

[1]: Department of Otolaryngology, Head and Neck Surgery

[2]: Department of Oral & Maxillofacial Surgery/Pathology

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ABSTRACT

Background. Recent modifications of surgical technique may have influenced outcome following parotidectomy. This retrospective study compares the results of the different surgical methods with regard to recurrence rate and the effects on morbidity between 1974 and 1994.

Methods. A total of 246 primary surgical parotid procedures were performed on 245 patients for pleomorphic adenoma. These included: 131 'partial' superficial parotidectomies, 61 'total' superficial parotidectomies, 30 partial superficial/deep lobe parotidectomies, 8 total parotidectomies, and 16 'selective' deep lobe parotidectomies. In the recent past, the posterior branch of the greater auricular nerve was preserved in the majority of patients. Eleven patients received postoperative radiotherapy. The median follow-up was 95 months. Fourteen patients died without recurrent tumour.

Results. Two patients (0.8 per cent) developed a local recurrence, both after total parotidectomy for a deep lobe tumour. None of the patients experienced permanent facial nerve paralysis. The incidence of gustatory sweating for partial superficial parotidectomy was 6.9 per cent (nine of 131) as compared to 13.1 (eight of 61) for total superficial parotidectomy.

Conclusion. Partial parotidectomy is an effective treatment for the great majority of pleomorphic adenomas: local recurrence is rare, and morbidity is low. Prolonged follow-up is unnecessary.

INTRODUCTION

Salivary gland neoplasms account for 3 per cent of all tumours in the head and neck region[1]. Approximately 75-85 per cent of these neoplasms occur in the parotid gland of which 70-80 per cent are benign. The most common of these is pleomorphic adenoma.

The parotid gland is a single anatomic entity through which pass the branches of the facial nerve. Approximately 80 per cent of the parenchyma of the gland occupies the subcutaneous space lateral to the facial nerve, designated as the superficial lobe. A thin layer of parotid tissue lies beneath the facial nerve adjacent to the masseter muscle and ascending ramus of the mandible (deep lobe). Most neoplasms arise superficial to the nerve.

Histopathologically these tumours are characterized by cellular pleomorphism in which epithelial and myoepithelial components are embedded in a stroma which is mucoid, myxoid, chondroid or osteoid in origin. The stroma varies from tumour to tumour and may have a combination of any of these types within a single tumour. Microscopically these tumours do not have a true capsule but compress surrounding normal salivary gland tissue, frequently having microscopic excrescences (Fig. 1) into normal tissue[2,3]. Recurrence is thought to be due to these small islands of tumour which may be left behind at operation, especially after enucleation. Additionally, recurrence may occur due to intraoperative tumour rupture and seeding of tumour cells, often leading to multiple nodules of pleomorphic adenoma[4]. Primary multicentric origin of pleomorphic adenoma is another reason for recurrence although its incidence is very low (0.5 per cent)[2,5].

Before the 1940s the surgical management of pleomorphic adenomas was unsatisfactory because of the excessive rate of permanent facial nerve palsy and recurrence (20-45 per cent)[6-10]. Janes[11] and Bailey[12,13] advocated identification of the main trunk of the facial nerve first, then dissection of the nerve with removal of the superficial and/or deep lobe of the parotid. This became established as the appropriate treatment for benign and low grade malignant lesions[14-18]. With this technique recurrence rates declined dramatically, approaching zero while permanent facial nerve paralysis became rare[19-23].

With these favourable developments in reducing the incidence of recurrent disease and permanent facial nerve paralysis attention gradually focused on other sequelae of parotid surgery including loss of sensation of the auricle (due to transection of the greater auricular nerve), cosmetic aspects and Frey syndrome. To reduce such morbidity several modifications have been

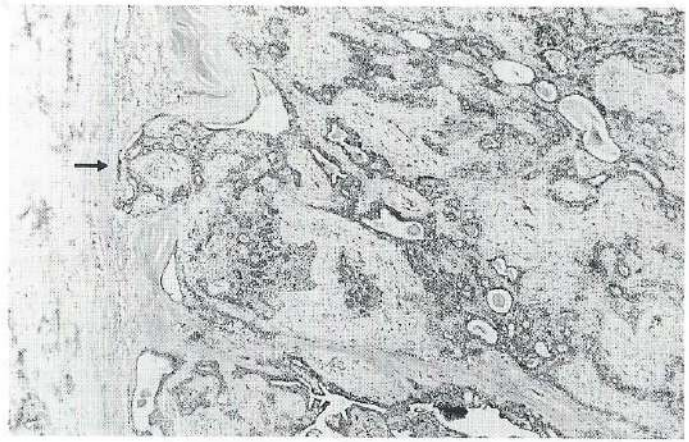


Fig. 1.
A microscopic excrescence projecting into the surrounding capsule (arrow). Haematoxylin and eosin stain (original magnification x 50).

implemented: 1. In each procedure, an attempt is undertaken to preserve the posterior branch of the greater auricular nerve, unless precluded by the position of the tumour. 2. For each tumour lateral to the nerve, in principle, a 'partial' superficial parotidectomy is performed. 3. In principle, for each deep lobe tumour a 'selective' deep lobe resection is performed.

This study compares the results of the different surgical techniques with regard to recurrence rate and morbidity.

MATERIAL & METHODS

Patients

During a 21-year period beginning 1974, 583 surgical parotid procedures were performed. Preoperative assessment and diagnosis was based on patient history and physical examination. Patients operated for 'parapharyngeal' deep lobe parotid pleomorphic adenoma were excluded. In the great majority fine needle aspiration cytology was used. For fixed tumours, such as those in the deep lobe, computed tomography and later magnetic resonance imaging were performed when these modalities became available. In 245 patients 246 parotid procedures were performed for a primary pleomorphic adenoma. After several years one patient developed a pleomorphic adenoma on the contralateral side for which another parotidectomy was performed. The tumours were classified according to the World Health Organization classification of 1972 for salivary gland tumours[24]. Long-term follow-up was either by outpatient clinic attendance for at least 10 years, or by written enquiry to the general practitioner for those patients who had been discharged by the summer of 1995.

There were 154 women and 91 men; their ages ranged from 13 to 82 years, mean 44.1. Two patients were lost to follow-up. Fourteen patients died at varying intervals without tumour recurrence. Some 243 patients were successfully followed with a median follow-up of 95 months.

In 61 patients a 'total' superficial parotidectomy was performed. One patient was found to have a synchronous Warthin tumour. In 131 patients a 'partial' superficial parotidectomy was performed. In 24 patients the tumour was located deep to the facial nerve. Eight of these patients had a total parotidectomy while in 16 patients a 'selective' deep lobe parotidectomy was performed. In 30 patients the tumour was both superficial and deep to the facial nerve, all of whom were treated by a partial superficial/deep lobe parotidectomy.

In ten patients tumour spillage occurred due to limited capsular rupture. In each instance the material was aspirated from the wound as carefully as possible while the defect in the capsule was sutured. In each procedure after resecting the tumour, in order to sterilize the wound, it was extensively irrigated. Initially this was done using a solution of Mercuric Chloride (1mg/ml), in the later period using Dakin's solution (0,5% Sodium Hypochlorite).

Eleven patients received postoperative external beam radiotherapy (dose range; 4800 - 6120 cGy), administered in 5 to 7 weeks for: spill (n=4), capsular tumour dissection (n=3), non-radical tumour resection (n=3), and multinodular origin of the tumour (n=1).

Surgical procedures

Superficial - and total parotidectomy was performed as described elsewhere[25]. Modifications employed were as follows:

Preservation of the greater auricular nerve. After the nerve is identified running obliquely near the angle of the mandible it is followed through the parotid gland to its posterior branch (Fig. 2). This branch which innervates the auricle and surrounding skin, is completely exposed after sacrificing the more anterior branches. Subsequently the nerve can be translocated posteriorly so as to avoid injury to it during identification of the main stem of the facial nerve.

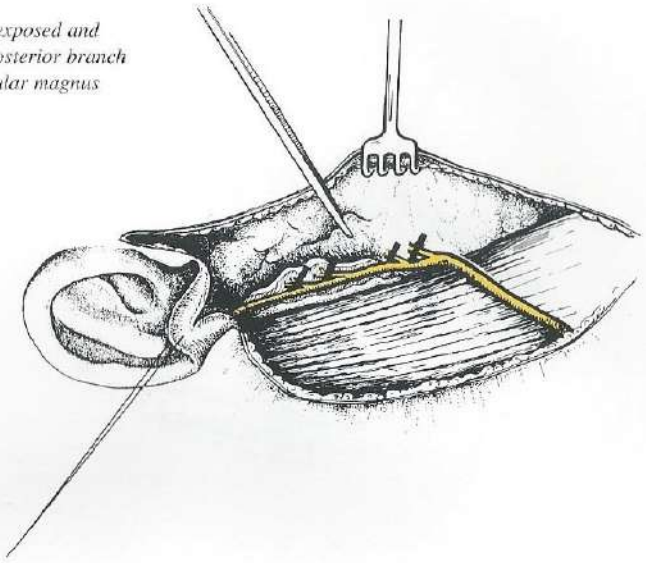
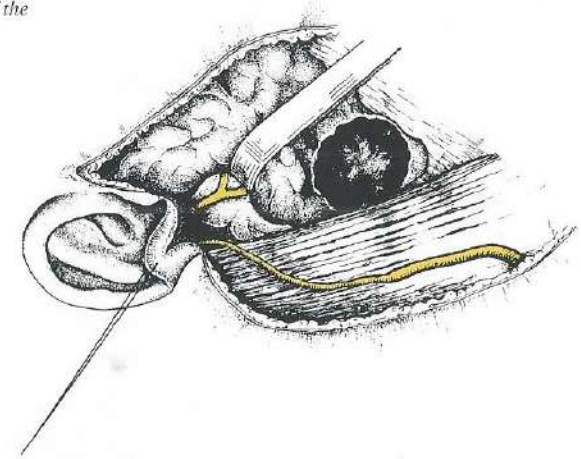


Fig. 2. The exposed and preserved posterior branch of the auricular magnus nerve.

Partial superficial parotidectomy. Initially the same procedure as for formal superficial parotidectomy is performed. However, after identification and exposure of the main stem of the facial nerve (Fig. 3a), only those branches that prove to have an intimate relation with the tumour are exposed. After displaying the involved branches adjacent to and beyond the tumour this is resected with an appropriate cuff of normal salivary gland tissue (Fig. 3b), often leaving a minimal soft tissue deficit (Fig. 3c). This procedure is especially suitable for those patients in whom the tumour is located in the posterior part of the superficial lobe.

Fig. 3a. Identification of the main stem of the facial nerve.



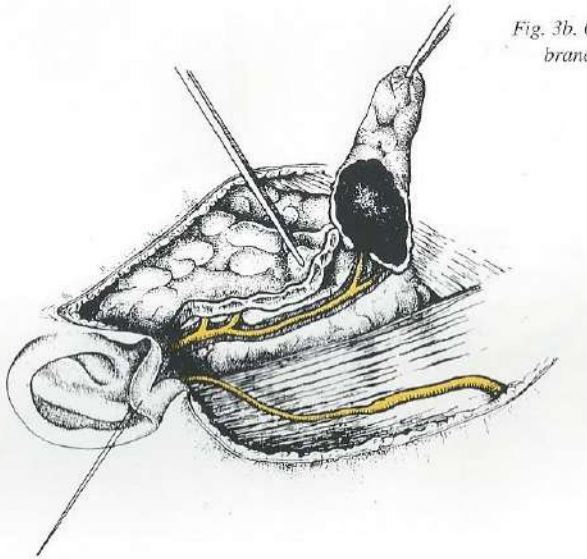


Fig. 3b. Only the involved branches are exposed.

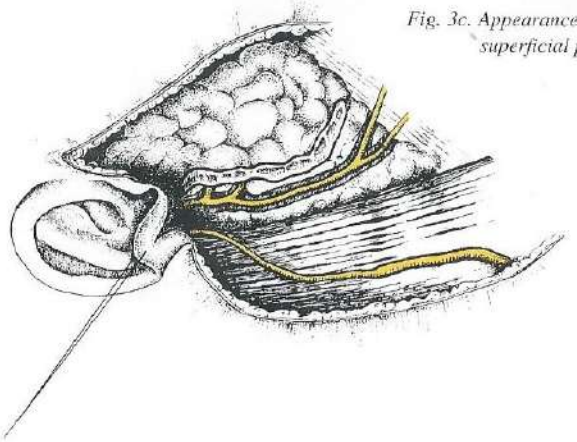
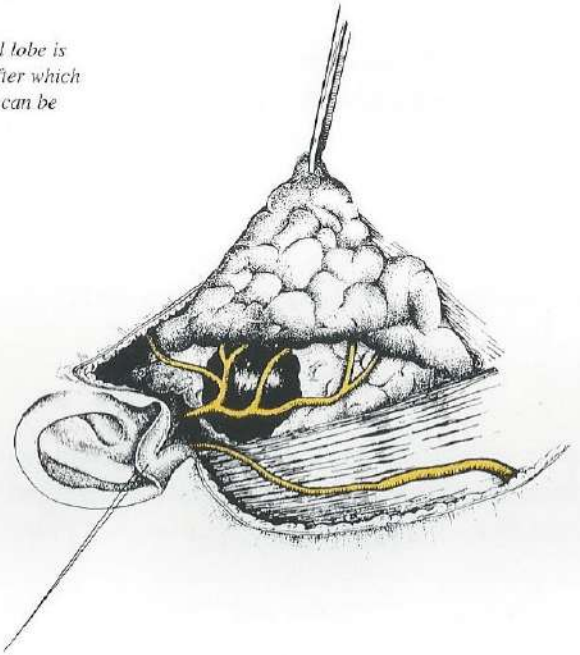


Fig. 3c. Appearance after 'partial' superficial parotidectomy.

Selective deep lobe parotidectomy. This commences with the same technique as for total superficial parotidectomy. However, after serial dissection of the nerve branches from the superficial lobe up to the posterior edge of the ascending ramus of the mandible this is reflected away from the surgical field, leaving it attached at its anterior margin (Fig. 4). Subsequently the nerve branches are dissected from the deep lobe. Using slings the branches of the facial nerve are elevated from the deep lobe after which the deep lobe tumour can be mobilized and removed (Fig. 4). The superficial lobe is replaced *in situ* thus covering the facial nerve.

Fig. 4. The superficial lobe is reflected anteriorly after which the deep lobe tumour can be removed.



RESULTS

Two patients developed recurrent disease following parotidectomy for a deep lobe tumour after 3.5 and 9 years respectively. Both recurrences were excised *en bloc* with the involved skin. Histopathological examination of both specimen revealed a multinodular recurrence. Postoperative radiotherapy was given. After follow-up of 5 and 6 years respectively neither have recurred.

Tumour spillage occurred at ten operations. Four of these patients received postoperative radiotherapy (the last in 1987); none developed recurrent tumour, nor did the other six patients who did not receive postoperative radiotherapy. None of the other seven patients who received postoperative radiotherapy for different reasons developed a recurrence. No patient developed permanent facial nerve paresis or paralysis. Approximately 20 per cent of the patients had a temporary paresis of some or all branches of the facial nerve, the mandibular branch being the one most commonly affected. All recovered within several days to 5 months.

The incidence of Frey's syndrome declined dramatically for partial superficial parotidectomy, to 6.9 per cent (nine of 131) as compared to 13.1 per cent (eight of 61) for formal superficial parotidectomy.

In the majority of patients in whom the posterior branch of the greater auricular nerve was preserved, complete anaesthesia was observed after operation. However, sensation returned more rapidly and more extensively than in those in whom the nerve was transected.

In the group of patients in whom the greater auricular nerve was transected, three developed an amputation neuroma which in each case was surgically excised. One patient developed a small salivary fistula which healed spontaneously within 3 weeks.

The long-term complications of radiotherapy in three patients included: sensorineural hearing loss (n=1), and xerostomia (n=2).

DISCUSSION

In this series the preponderance of women (female:male ratio 1.7:1) and age distribution were similar to those reported in the literature[19]. The introduction of the technical modifications described seemed justified for two main reasons. In practically every parotid pleomorphic adenoma during dissection an intimate relationship can be observed between the tumour and the facial nerve or its branches. At these sites the margin of healthy tissue is often a fraction of a millimetre. Resection of the superficial lobe or entire gland would therefore only be sensible if there was a significant incidence of multiple tumours which is very rare[2,5]. None of the patients in whom a modified procedure was performed developed a recurrence. The recurrence rate in this series of 0.8 per cent is comparable to the best results reported in the literature[18-23].

The most feared complication in parotid surgery is permanent paralysis of some or all of the facial muscles. Exploration of the facial nerve should therefore, if possible, be restricted to those branches which prove to have a close relation to the tumour. In this study only a minority of the patients showed a temporary paresis of one or some branches of the facial nerve, the mandibular branch being mostly affected. None of the patients developed permanent facial nerve paresis or paralysis.

The most common complication after parotid surgery is Frey's syndrome. This is characterized by dermal flushing and sweating of the skin preliminary to or during salivary production, sometimes accompanied by paraesthesia at the surgical field. It presents 6-12 months after parotid surgery. This complication can be very distressing because there is no satisfactory treatment. Pathophysiologically this phenomenon is explained by the aberrant reinnervation of the severed postganglionic sympathetic fibres that supply the sweat glands of the skin of the auriculotemporal region by the postganglionic secremotor parasympathetic nerve fibres which innervate the parotid gland. An inverse relationship can be expected between the extent of the resection and the incidence of Frey's syndrome. Recently, one study reported an incidence of Frey's syndrome of 65.9 per cent after total parotidectomy for pleomorphic adenoma[26]. In this series the incidence of gustatory sweating after partial superficial parotidectomy proved to be considerably lower, 6.9 per cent (nine of 131), as compared to 13.1 per cent (eight of 61) for formal superficial parotidectomy.

In patients in whom the posterior branch of the greater auricular nerve was preserved sensation returned more rapidly and more completely than in those in whom the nerve was sacrificed. This may be an important consideration for those using a hearing aid and for ladies wearing earrings. In only a minority of patients could the nerve not be preserved because of the infra-auricular position of the tumour.

The cosmetic appearance after partial superficial parotidectomy and or selective deep lobe parotidectomy was markedly improved compared with

that after total superficial and/or total parotidectomy with hardly any deformity of the facial contour.

In former years, postoperative radiation therapy was considered to be beneficial for patients with incomplete removal or recognizable tumour spill at operation[27]. In non-radically excised tumours postoperative radiotherapy is of value[28]. However, the risk of recurrent tumour after tumour spillage seems limited, especially if adequate measures as described above are taken when it occurs[29]. Additionally, the long term morbidity of postoperative radiotherapy should not be underestimated[30-34]. In this series none of the six patients who did not receive radiotherapy for tumour spill developed recurrent tumour. Postoperative radiotherapy should therefore only be considered after uncontrollable tumour spill and non-radical excision.

Initially, prolonged out-patient follow-up was pursued for at least 10 years. However, since it became clear that the implemented modifications had no adverse effects on the incidence of recurrent tumour we now only recommend one follow-up visit. At present only a minority of patients in whom something unusual occurred are receiving extended follow-up, the indications being tumour spillage or specific microscopic findings such as the presence of 'satellite tumours'.

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Chapter 4.

THE SURGICAL MANAGEMENT OF RECURRENT OR RESIDUAL PLEOMORPHIC ADENOMA OF THE PAROTID GLAND; ANALYSIS AND RESULTS IN 40 PATIENTS

H. Leverstein[1], J.E. van der Wal[2], R.M. Tiwari[1],

I. van der Waal[2], and G.B. Snow[1].

[1]: Department of Otolaryngology, Head and Neck Surgery

[2]: Department of Oral & Maxillofacial Surgery/Pathology

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ABSTRACT

From 1974 until 1995, 40 patients were treated surgically at the University Hospital Vrije Universiteit, Amsterdam for recurrent or residual pleomorphic adenoma of the parotid gland after previous surgery. The median interval between the initial procedure and the salvage surgery for the recurrence was 122 months. Eleven patients had one or more attempts to resect their recurrence prior to referral. During reoperation at this institution it was decided to refrain from tumour resection in three patients. Tumour control in two of these patients tumour control was achieved using radiotherapy. In the third patient a wait-and-see policy was adopted. The other 37 patients underwent surgical excision of their tumour en bloc with the involved skin and/or former incision. None of the 36 patients operated for histopathologically benign disease, of whom 17 received postoperative radiotherapy developed a further recurrence, the median follow-up being 106 months. Only one of these patients experienced a permanent segmental facial nerve paralysis. Malignant transformation of tumour occurred in two patients. One of these patients died of locoregional disease after surgery and radiotherapy. Radical tumour resection was deferred in the other patient, with tumour control achieved using radiotherapy. However, since recurrent disease tends to be multifocal in origin, prolonged routine follow-up is required.

INTRODUCTION

At present, treatment of pleomorphic adenomas of the parotid gland can be considered a well-standardized and safe treatment when carried out by an experienced surgeon. Avoidance of enucleation and acceptance of the concept of tumour resection after identification of the main trunk of the facial nerve with dissection of the nerve branches and removal of part of the superficial and/or deep lobe of the parotid have greatly decreased the incidence of recurrent tumour in experienced hands[1-7].

Microscopically, these tumours do not have a true capsule but compress surrounding normal salivary gland tissue, frequently having microscopic excrescences in normal tissue[8,9]. The mechanism of recurrence after simple enucleation is thought to be the result of disruption of these microscopic projections of the tumour outside the presumed capsule, leaving tumour cells behind at surgery. Additionally, recurrences may occur if intraoperative tumour rupture occurs, resulting in seeding of tumour cells. Such will often lead to multiple nodules at any site in the surgical wound[9]. Although a primary multicentric origin of pleomorphic adenoma is possible and produces tumour recurrences, its actual incidence is very low, amounting to 0,5 per cent in Batsakis's review[8].

Before treating recurrent disease it is important to assess the extent of disease: specifically multifocality, site, and possible extension to the base of skull and/or parapharyngeal space. To estimate radiologically the extent of any recurrent disease, magnetic resonance imaging (MRI) provides the most useful information due to its superior soft tissue contrast resolution. This allows visualization of normal anatomic detail and improved differentiation between normal and abnormal structures. Additionally, the capability of MRI in axial and coronal planes is a significant advantage over computed tomography (CT). MRI should include T1-weighted spin echo (SE), and T2-weighted SE images. In the majority of cases a low signal intensity will be produced on the T1-weighted SE images and a high signal intensity on the T2-weighted SE images[10].

When considering surgical resection of recurrent pleomorphic adenoma an increased risk exists for facial nerve damage, as the nerve is often ensheathed in scar tissue with significant distortion of local anatomy due to prior surgery. The chance for injury is compounded when the nerve is found to be adherent to or surrounded by recurrent tumour[11-13]. In these circumstances some authors[9,11,14] advocate resection of all tumour and surrounding tissue along with the involved nerve while others advise a complete parotidectomy but with an attempt to preserve nerve function[15-19]. Additionally, malignant change in a long-standing pleomorphic adenoma may occur and the risk of malignant degeneration is thought to increase in recurrent disease[11,13,20].

This study presents the experiences and results in 40 patients with recurrent or residual pleomorphic adenomas of the parotid gland after previous surgery, with emphasis on recurrent tumour growth, risk of facial nerve damage, and malignant transformation.

MATERIAL & METHODS

From 1974 until 1995, 583 surgical parotid procedures were performed at the University Hospital Vrije Universiteit, Amsterdam. In 40 patients this was undertaken for recurrent or residual pleomorphic adenomas after previous surgery. Of these four had recently undergone previous explorations, seven

non radical surgery, while 29 had recurrent disease. In 22 patients the initial procedure consisted of enucleation. Thirty-eight patients had their initial surgical treatment elsewhere. The other two patients were described by us in a separate report on the developments and results in the surgical management of 246 previously untreated parotid gland pleomorphic adenomas[7]. All tumours were classified according to the 1972 World Health Organization histological classification for salivary gland tumours[21]. Long-term follow-up was arranged either by clinical attendance when possible (generally at least 10 years after surgery) or by written enquiry to the general practitioner providing on-going case near the patients home.

Table 1.	No. of patients	Surgical procedures Tumour resection/exploration		Malignant transformation
Group I. recurrent disease	29	26	3	2
Group II: irradicle excision	7	7	-	-
Group III: recent exploration	4	4	-	-

In all, there were 28 women and 12 men. Ages ranged from 15 to 72 years (mean 44,8). The median follow-up after treatment was 106 months.

Patients were separated in three groups (Table 1). **Group I** comprised 29 patients of whom 27 patients had their initial procedures performed elsewhere. In 22 of these patients an enucleation was performed as the first operation. The other initial procedures were total parotidectomy (n=2) and standard superficial parotidectomy (n=2). In three patients the original procedure could not be ascertained.

Eleven patients had one or more attempts to resect their recurrence prior to referral to the University Hospital Vrije Universiteit, Amsterdam. Clinically, multiple nodules were noted in 10 patients (35 per cent), while the others had solitary recurrences. The median interval between the initial procedure and surgery for recurrence in our institution proved to be 122 months. The surgical procedures undertaken for the recurrences in group I included 19 standard superficial parotidectomies, 3 local excisions, 2 partial superficial/deep lobe parotidectomies, 1 combined transparotid/transoral resection, and 1 total parotidectomy with en bloc partial mandibulectomy and sacrifice of the facial nerve. In three patients it was decided intraoperatively to refrain from tumour resection because of extend of disease or fibrosis present. In the remaining 26 patients recurrent tumour was resected en bloc with the former scar and / or involved skin (Fig. 1a,b). In two cases the subsequent skin defect was reconstructed with local flaps while in another two cases a split skin graft was used.

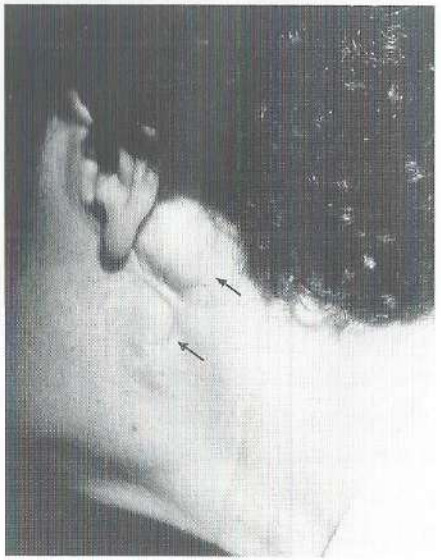

Fig. 1A. A multinodular recurrence (arrows) of a pleomorphic adenoma in a 58-year-old women.

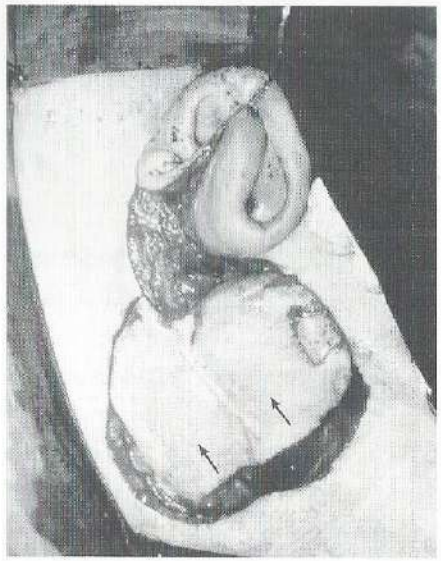

Fig. 1B. Resection of the recurrence 'en bloc' with the involved skin (arrows).

All 25 benign recurrences in group I showed multinodular recurrences on histopathological examination (Fig. 2). Fourteen of these patients received postoperative radiotherapy (dose range: 5000 - 6500 cGy). In another case the recurrence had become clinically malignant after previous surgery and radiotherapy. As histopathological examination revealed carcinoma in the pleomorphic adenoma further postoperative radiotherapy was administered (total dose 9600 cGy). After 2 years the patient died from locoregional disease.

In three patients it was intraoperatively decided to refrain from tumour resection. It is of particular interest to report on these three patients in more detail.

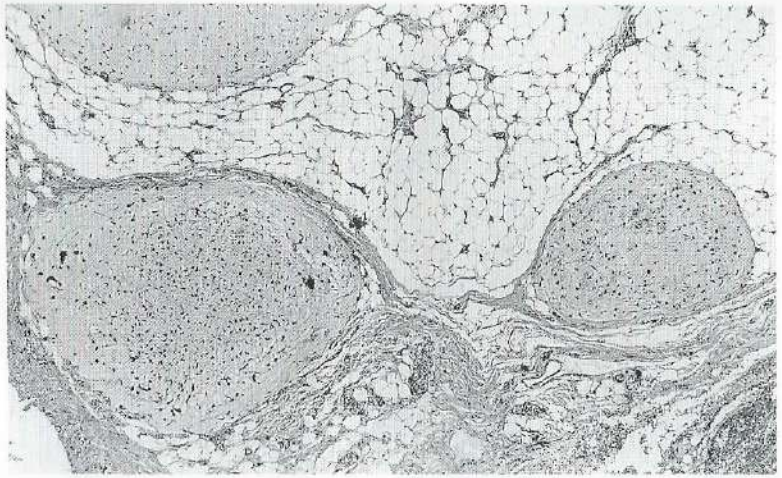

Fig. 2. Histopathology showing multiple nodules of recurrent pleomorphic adenoma. Haematoxylin and eosin stain. Original magnification x 50.

The *first* of these patients had his initial resection in 1972, then 32 years of age. In 1978 he was operated for multiple nodules in the former incision. In 1989 he was operated for a further recurrence. In all three operations the procedure proved to be an enucleation and the patient had not received any radiotherapy. In 1990, in our clinic, an attempt was undertaken to resect the tumour. However, after identification of the main stem of the facial nerve tumour resection was abandoned due to extensive fibrosis with tumour adherent to the main branches of the facial nerve. Histopathological examination of tissue taken from the main bifurcation revealed malignant tumour. Although the fibrosis did not allow accurate assessment of the total volume of the tumour, this was estimated to be low. The patient then received a full course of radiotherapy (7000 cGy), by external beam radiation using megavoltage methods in 8 weeks. At present, with a follow-up of 6 years, the patient is doing well without evidence of locoregional disease.

The *second* patient had her initial treatment in 1971 at the age of 59. In 1979 she was treated for a recurrence. Both procedures proved to be an enucleation. In 1981 at our institution an attempt to resect a small multinodular recurrence (three palpable nodules of several millimetre in diameter) was abandoned as safe identification and preservation of the facial nerve proved to be impossible due to extensive fibrosis. The patient then received a full course of radiotherapy (6000 cGy), by external beam radiation using megavoltage methods in 6 weeks. The patient died at the age of 74 without evidence of disease.

The *third* patient had a deep lobe parotid gland parapharyngeal pleomorphic adenoma transorally excised at the age of 37. After 8 years (1987) an unsuccessful attempt to resect a recurrence via a transparotid/transoral approach was performed elsewhere. Another year later, in our clinic an attempt was undertaken to resect the tumour and although all facial nerve branches could be exposed the tumour proved to be irresectable due to extension along the base of skull up to the nasopharynx (Fig. 3). As the patient had refused permission for mandibulotomy tumour resection could not be carried out. Due to the benign origin of the tumour and its slowly progressive growth, a wait and see policy was conducted. At present, with a follow-up of 7 years, the patient is doing well with a palpable tumour 5 cm in diameter behind the angle of the mandible with normal facial nerve function.

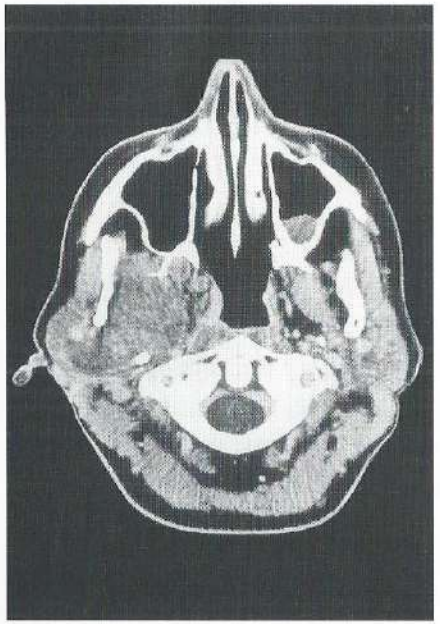

Fig. 3. Recurrent pleomorphic adenoma occupying the parapharyngeal space in a 47-year-old woman.

Group II comprised seven patients who were immediately referred to our department after non-radical surgery elsewhere. In each patient enucleation was the initial procedure. The salvage surgical procedures in this group included one partial superficial parotidectomy and six standard superficial parotidectomies. In each procedure the residual tumour was resected en

bloc with the former incision. Two of these patients received postoperative radiotherapy (6000 cGy).

In four patients, *group III* an attempt to resect tumour was abandoned during initial surgery elsewhere. In three patients this occurred while attempting to enucleate the tumour and in one patient while attempting to resect the tumour via a standard superficial parotidectomy. The salvage surgical procedures included one selective deep lobe parotidectomy, one partial superficial parotidectomy, one partial superficial/deep lobe parotidectomy, and one standard superficial parotidectomy. One patient received postoperative radiotherapy (6000 cGy) because of tumour spillage.

Altogether 20 patients received postoperative radiotherapy (dose range: 4900 - 7000 cGy) by external beam radiation using megavoltage methods administered in five to seven weeks. The indications for this were: non-radical excision (n=8), multinodular recurrent disease approaching the surgical margins (n=6), malignant transformation of recurrent disease (n=2), abandoning an attempt to resect a benign recurrence due to the facial nerve being embedded in fibrosis (n=1), and tumour spill (n=1). Another two patients received postoperative radiotherapy following salvage surgery after previous non-radical enucleation in the early years of this series.

RESULTS

Of the 36 patients operated in our series for histopathologically benign disease, 16 received postoperative radiotherapy. None developed a further recurrence of tumour, the median follow-up being 106 months. Only one patient (group I), treated for an extensive deep lobe recurrence, developed a segmental paralysis of the facial nerve. Facial nerve function remained completely intact in the other 35 patients.

In three patients an attempt to resect recurrent tumour was abandoned. In two cases this was due to extensive fibrosis intermingled with recurrent tumour. In these two patients control of disease was achieved using radiotherapy. In the third patient in whom the tumour proved to be irresectable due to extension along the base of skull up to the nasopharynx a wait-and-see policy was adopted. At present, with a follow-up of 7 years there has been no further progression of tumour.

Two patients with multiple recurrences were treated elsewhere and developed malignant disease. One patient, a 54 year old male, in whom a carcinoma in pleomorphic adenoma was resected, required sacrificing the facial nerve with en bloc removal of a part of the ascending ramus of the mandible, died of locoregional disease. In the other patient, (one of those three cases in which an attempt to resect the recurrent disease was abandoned), control of disease was achieved using radiotherapy. At present, with a follow-up of 6 years the patient has remained healthy, without evidence of recurrent disease.

DISCUSSION

After the introduction by Janes[22] and Bailey[23,24] of superficial and total parotidectomies with identification of the facial nerve, recurrence rates after treatment for benign mixed tumours declined dramatically. This approach and the avoidance of enucleation soon became established as the appropriate treatment for benign and low-grade malignant lesions. Nevertheless, as also reported by others[19,25] most of our patients with a true clinical recurrence (22/29 cases) initially underwent enucleations of their tumour, illustrating that the generally accepted technique of superficial or total parotidectomy after identification of the facial nerve is still violated.

In our series, 36 patients underwent wide resections of residual or benign recurrent disease en bloc with the former scar and/or involved skin. In 33 cases this was accomplished after identification of the facial nerve first, while in three cases local excisions alone were performed. None of the 36 patients developed further recurrent disease. These results are similar to those described by others[25].

Although recurrent pleomorphic adenomas usually present no immediate threat to life since most are benign and slow-growing, the risk of malignant transformation requires further surgical treatment in most cases[26,27]. In our series two patients (6.9 per cent) with multiple recurrences developed malignant disease. Findings similar to those reported by Philips and Olsen[28]. However, both higher and lower rates of malignant degeneration related to recurrent pleomorphic adenoma have been reported, being in one series up to 40 per cent[2,29].

When treating recurrent disease the risk of permanent facial nerve damage is the most feared complication. In a second operation following previous identification and exploration of the facial nerve, the risk of facial nerve injury is much higher due to fibrosis, adherence of the nerve to the

recurrent tumour, and distortion of the normal anatomy. Intraoperative facial nerve monitoring has been demonstrated to be a useful adjunct in such difficult cases[30]. However, if an enucleation was the first procedure we have generally encountered no major difficulties identifying the facial nerve. In our series only one patient (2.5 per cent) suffered permanent facial nerve paralysis involving one nerve branch. This occurred after resection of a large deep lobe recurrence which grossly thinned and stretched the main stem of the facial nerve. In two other patients tumour resection was abandoned, because removal of the recurrent tumour would almost certainly have entailed permanent facial nerve paralysis due to extensive fibrosis intermingled with recurrent tumour being adherent to the main stem of the nerve in one patient and to the nerve branches in the other. As the total volume of recurrent disease in both patients appeared to be small, it was decided to irradiate both patients. One patient died 5 years after finishing her course of radiotherapy without evidence of disease. The other patient is at present alive and well, 6 years after completion of the radiotherapy.

Since recurrent pleomorphic adenomas can have a multifocal origin histological examination of the surgical margins is of relative value. Microscopic foci of tumour cells may well be left behind while the margins may seem free of tumour. As postoperative radiotherapy has proved its value in non-radically excised tumours[31], we initially considered radiotherapy in cases with tumour extending into the margins of the specimen as well as in all cases when microscopic examination revealed satellite tumours approaching the margins of the specimen. However, during the course of our study the use of postoperative radiotherapy has declined because of concern for the subsequent morbidity[32-36]. From 1974 to 1986 10 out of 12 patients who underwent excision for a benign recurrence received postoperative radiotherapy. In four patients this was due to a microscopically non radical excision while in the other six patients tumour deposits approached the surgical margins. From 1987 to 1994 only those patients (4/13) in whom microscopic examination revealed a non radically excised benign recurrence received radiotherapy (6000 cGy). The fact that no recurrences were observed in both patient groups seems to justify this more conservative approach. However, it should be noted that the median follow-up for the latter group is more limited (59 months as compared to 158 months for the former).

As recurrent pleomorphic adenomas in general are benign and slowly growing tumours it may be justified to refrain from ablative surgery if the anticipated morbidity becomes unacceptable. We agree with others that regardless of the initial operation, recurrent pleomorphic adenoma must be managed individually[25]. Factors paramount in making a decision include: nature of the previous surgery, the extent and location of the recurrent tumour on MRI, facial nerve status, age, and general health of the patient. Due to the multifocal nature of recurrent disease extended follow-up is required.

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Chapter 5.

RESULTS IN THE SURGICAL MANAGEMENT AND HISTOPATHOLOGICAL EVALUATION OF 88 PAROTID GLAND WARTHIN TUMOURS

H. Leverstein[1], J.E. van der Wal[2], R.M. Tiwari[1],

I. van der Waal[2], and G.B. Snow[1].

[1]: Department of Otolaryngology, Head and Neck Surgery

[2]: Department of Oral & Maxillofacial Surgery/Pathology

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ABSTRACT

With the introduction of parotidectomy after identification of the facial nerve the recurrence rates for benign tumours has declined rapidly. Subsequently, attention focused on other sequelae of parotid surgery. To reduce the specific surgical morbidity several modifications of parotidectomy have been implemented. This study compares the results of the different surgical techniques with regard to the histopathological findings and recurrence rate for Warthin's tumour of the parotid gland.

Eighty-eight primary surgical parotid procedures were performed on 85 patients for a Warthin's tumour. The surgical procedures included: 52 'partial' superficial parotidectomies, 22 'standard' superficial parotidectomies, 12 'partial' superficial/deep lobe parotidectomies, and two 'selective' deep lobe parotidectomies.

None of the patients developed a recurrence and/or experienced permanent facial nerve paresis/paralysis, the median follow-up being 93 months. Histopathological examination revealed a multifocal origin in 23 per cent (20/88) of the surgical specimens.

Partial parotidectomy is an effective treatment for Warthin's tumour. There is no need for extended follow-up.

INTRODUCTION

Warthin's tumour is the second most common benign neoplasm of the parotid gland and accounts for 6-10 per cent of all parotid tumours[1]. It is a neoplasm that exhibits distinct histological features unlike any other tumour[2,3]. Early descriptions of this entity were reported by Hildebrand[4], Albrecht[5] and, Nicholson[6], before the American pathologist Aldred Scott Warthin[7] described two unusual tumours of the parotid gland which he called papilliferous, or papillary, cystadenomas. Most cases occur in older men between the fourth and seventh decades of life, although the incidence is increasing among women[8-9].

Warthin's tumours most commonly present as an asymptomatic, slowly growing, soft mass in the tail of the parotid gland. A minor group of the patients however may present with a recent, painfully enlarged tumour after an insidious behaviour for years[1].

Unlike the submandibular and sublingual glands, the parotid gland is encapsulated at a late stage of embryological development. As a result, lymph nodes are found within the parotid gland and salivary gland tissue may be found within these nodes. Salivary tissue may also be found within lymph nodes adjacent to, but separate from, the parotid gland. The proliferation of these salivary epithelial rests results in the development of Warthin's tumours and explains the frequent observation of multiple Warthin's tumours as well as the finding of tumours separate from the parotid in the upper neck[10-11]. Approximately 12 per cent of Warthin's tumours occur bilaterally. Malignant Warthin's tumours, although rarely reported, may occur due to dysplastic changes of the entrapped salivary gland elements[12].

The diagnosis of Warthin's tumour requires the histological demonstration of both a lymphoreticular and an epithelial (oncocytic) component.

Oncocytes present in Warthin tumours account for the ability of these tumours to be visualised on a technetium 99m (^{99m}Tc) pertechnetate radionuclide scan. In general regarding preoperative diagnosis by imaging modalities, no investigation is demanded. However, in rare cases an MRI may be required to assess the extent of disease. Specifically: site, multifocality, and intra - or extraparotid origin[14].

After the acceptance of superficial and/or total parotidectomy for benign parotid tumours following initial identification of the facial nerve recurrence rates have diminished substantially while permanent facial nerve paralysis has become very rare[15-21]. More recently attention has focused on other less serious, but significant sequelae of parotid surgery including Frey's syndrome, hypaesthesia of the auricle, and cosmetic aspects. To reduce such surgical morbidity in our institution several modifications have been introduced in the treatment of benign parotid gland tumours[22]. These include: 1. for each tumour lateral to the nerve, when appropriate, a 'partial' superficial parotidectomy is performed; 2. in each procedure, an attempt is undertaken to preserve the posterior branch of the greater auricular nerve, unless the position of the tumour precludes such an attempt; 3. in principle, for each deep lobe tumour a 'selective' deep lobe resection is performed.

As Warthin's tumours tend to have a well developed capsule and are usually located in the inferior and superficial portion of the parotid gland they are readily amenable to removal with a margin of normal salivary gland tissue. If however a too conservative approach is attempted, recurrences may occur as a proportion of these tumours are multifocal in origin[23].

The purpose of this study was to report the results of the different surgical techniques in relationship to the findings at histopathological examination of the specimen.

MATERIAL & METHODS

Patients

From 1974 until 1995, 422 surgical parotid procedures were performed for a previously untreated salivary gland tumour. In 88 cases the tumour was a Warthin's tumour. Preoperative assessment and diagnosis was based on patient history and physical examination. In the great majority of patients (81 per cent) fine needle aspiration cytology (FNAC) was performed (Table 1). Only when serious doubts remained about the origin of the tumour was a computed tomographic (CT) scan or magnetic resonance imaging (MRI) scan acquired when these modalities became available. The tumours were classified according to the World Health Organization histological classification of 1972 for salivary gland tumours[22]. Long-term follow-up was either by outpatient clinic attendance for at least 3 months, or by written enquiry, summer 1996, to the general practitioner for those patients who had been discharged from follow-up.

Table 1.

Fine needle aspiration cytology (FNAC).

Warthin's tumour	47
Cyst	6
Other	3
Inconclusive	15
total	71

In 17 patients FNAC was not performed.

There were 22 women and 63 men; their ages ranged from 32 to 81 years, mean 59.9 (man 60.2 / women 59.3). One patient was lost to follow-up. Twenty patients died at varying intervals without tumour recurrence while the remaining 64 patients are alive, the median follow-up being 93 months (range: 17 to 266 months).

Three patients presented initially with bilateral parotid gland disease. During follow-up an additional five patients developed a contralateral Warthin's tumour. Three of these eight patients underwent some type of parotidectomy on the contralateral side. The peak incidence occurred in the fifth decade. In each procedure, after resecting the tumour, careful examination of the remainder of the gland was performed to exclude other, simultaneous lesions. The surgical procedures included: 22 formal superficial parotidectomies, 52 partial superficial parotidectomies, 12 partial superficial/deep lobe parotidectomies, and two selective deep lobe parotidectomies.

In each procedure after resecting the tumour, in order to sterilize the wound, it was extensively irrigated. Initially this was done using a solution of Mercuric Chloride (1 mg/ml), in the later period using Dakin's solution (0.5 per cent Sodium Hypochlorite).

Surgical procedures

For a brief description of the modifications and surgical approaches which included 'partial' superficial parotidectomy and 'selective' deep lobe resection, both with preservation of the posterior branch of the greater auricular nerve, the reader is referred to an earlier published report on the developments and results in the surgical treatment of 246 parotid gland pleomorphic adenomas[22].

In the earlier period of this study the majority of the formal superficial parotidectomies were performed. After the introduction of the modified surgical techniques the type of the surgical procedure was dictated by the position of the tumour, not by the findings on FNAC.

RESULTS

None of the patients developed recurrent tumour, the median follow-up being 93 months. None of the patients developed a permanent facial palsy.

Histopathological examination revealed a multifocal Warthin's tumour in 23 per cent (20/88) of the specimens. This related to 13 cases after 'partial' parotidectomy (13/66). In particular in 11 cases after 'partial' superficial parotidectomy (52) and in two cases after 'partial' superficial/deep lobe parotidectomy (12). In four of these cases, after resection of the tumour a simultaneous tumour was identified by careful palpation of the remainder of the gland and subsequently removed. Additionally a multifocal origin of the

tumour was found in seven out of 22 specimens after formal superficial parotidectomy. In five of these a simultaneous tumour was identified and removed after initial resection of the first tumour. In one patient histopathological examination revealed a synchronous pleomorphic adenoma.

In one patient in whom the greater auricular nerve was transected an amputation neuroma was surgically excised. Salivary fistulas after partial superficial parotidectomy were not encountered.

DISCUSSION

Reports over the past 10 years have shown the occurrence of Warthin's tumour in the parotid gland to be increasing such that this tumour constitutes 14-30 per cent of parotid neoplasms[25]. In our series of 422 surgical procedures for a previously untreated epithelial parotid gland tumour 88 (21 per cent) proved to be due to a Warthin's tumour. Our findings of a male to female ratio of 2.6 to 1 is consistent with others reporting a similar male preponderance[25]. Others have reported higher ratio's: Foote and Frazell [26] 10:1, Bernier and Bhaskar[27] 9:1, and Thompson and Bryant[28] 7:1. Some authors however, have reported no sex differences[29].

The modifications of surgical technique were implemented to reduce the specific surgical morbidity to a minimum. As reported for a much larger series of parotidectomies for previously untreated pleomorphic adenomas these modifications proved to decrease the incidence of Frey's syndrome, to improve the cosmetic appearance while no adverse effect was noticed on the incidence of recurrent disease[22]. Additionally, in those patients in whom the posterior branch of the auricular magnus nerve was preserved, sensation of the auricle returned more rapidly and more extensively as compared to those patients in whom the nerve was transected. However, with the introduction of these modifications the question was raised whether the reported multiplicity of Warthin's tumours would preclude a 'partial' superficial parotidectomy for a tumour in the lateral portion of the gland.

In 22 patients a formal superficial parotidectomy was performed. In 7 histopathological examination revealed a multifocal origin of the tumour whereas this was observed in 13 out of 66 patients whom underwent a 'partial' parotidectomy. In nine out of the 20 cases in whom histology revealed a multifocal origin a synchronous Warthin tumour was removed following excision of the first tumour, stressing the need for careful inspection and palpation of the remainder of the gland for other lesions. In the remaining 11 cases the synchronous tumours were identified only after microscopical examination of the tumour. None of the patients developed recurrent disease in either group.

Based on these findings one may speculate whether or not, founded on the typical findings on palpation of the tumour or on the presence of a Warthin's tumour on FNAC, a preoperative ultrasound examination of the parotid gland should be performed. In our opinion the answer to this is no. The findings on ultrasound examination will only be of limited value as: 1. The retromandibular portion of the deep lobe can not be visualized through ultrasound and 2. Due to frequent incidence of microscopic synchronic tumours. If, however, additional examination is required using imaging modalities, an MRI should be obtained due to its superior soft tissue contrast resolution as compared to CT scan[14]. The indications for such an examination may include specific findings on palpation and inspection such as: a multinodular tumour or reduced mobility of the tumour to the underlayer.

The recurrence rates reported in the literature, with superficial parotidectomy being the primary surgical procedure, vary from 1-12 per cent[25,26,30,31]. As recurrent tumour in our series was not encountered, we disagree with those authors emphasizing the need to perform a formal superficial parotidectomy for a Warthin's tumour in the lateral portion of the gland. In the majority of cases it is unnecessary and increases the risk of damage to the branches of the facial nerve and the incidence of Frey syndrome[21].

For each parotid gland tumour we recommend preoperative examination using FNAC. In our opinion the findings of a Warthin's tumour does not demand additional examination using ultrasound, as a proper assessment of the retromandibular portion of the parotid gland is not possible and because a proportion of the synchronous tumours will be microscopic in origin. It can be concluded that 'partial' parotidectomy is an effective treatment for Warthin's tumour: the risk of a second Warthin's tumour in the remainder of the parotid gland becoming clinically manifest is to be considered extremely low.

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Chapter 6.

MALIGNANT EPITHELIAL PAROTID GLAND TUMOURS; ANALYSIS AND RESULTS IN 65 PREVIOUSLY UNTREATED PATIENTS.

H. Leverstein[1], J.E. van der Wal[2], R.M. Tiwari[1],

H. Tobi[3], D.M. Mehta[4], I. van der Waal[2], and G.B. Snow[1].

[1]: Department of Otolaryngology, Head and Neck Surgery

[2]: Department of Oral & Maxillofacial Surgery/Pathology

[3]: Department of Epidemiology & Biostatistics

[4]: Department of Radiotherapy

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ABSTRACT

Background. Optimal management of malignant epithelial parotid tumours requires knowledge of the available therapeutic modalities and the different biological characteristics. The aim of the study was to review patient presentation characteristics, histological classification, disease free and overall survival rates and the results of the applied treatment policy regarding the facial nerve and neck.

Methods. Between 1974 and 1995 a total of 65 patients were treated with curative intent for a previously untreated malignant epithelial parotid gland tumour. All patients underwent some type of parotidectomy, twenty of whom underwenth an en bloc radical neck dissection. In selected cases the facial nerve or its branches were peeled off the tumour thus violating the objective of tumour free margins and relying heavily on the efficacy of postoperative radiotherapy. In total fifty-one patients received postoperative radiotherapy. None of the patients were lost to follow-up.

Results. There were 12 (18.5 per cent) locoregional failures. In only one of these 12 patients was salvage therapy successful, the remaining 11 patients dying of their tumour. All but one of the eight (12.3 per cent) patients with distant metastasis only, died of their tumour. The estimated five and ten year disease free rates were 68 - and 59 per cent. The corresponding survival rates were 75 per cent and 67 per cent, respectively. A significant relation could be observed between tumour stage and survival. The presence of lymph node metastases proved to be the strongest single prognostic factor.

Conclusion. In selected cases a conservative approach towards the facial nerve is justified.

INTRODUCTION

Salivary gland neoplasms account for 3 per cent of all tumours in the head and neck region[1]. Approximately 75-85 per cent of these neoplasms occur in the parotid gland of which 20-25 per cent are malignant[2,3]. Their behaviour varies according to the histopathological subtype[4,5].

Approximately 50 per cent of malignant parotid gland neoplasms present as an asymptomatic, slowly growing, firm elastic swelling, freely mobile under the skin at or near the angle of the mandible or in front of the ear, and usually there are no obvious features to differentiate these from nign parotid neoplasms[6]. The remaining group of patients shows signs nsistent with malignant disease such as facial nerve dysfunction, suspicious nph nodes in the neck, trismus, or fixation of the tumour to the skin and/or underlying tissues. Pain is suspicious for malignancy[7].

Diagnostic imaging studies are rarely required in those patients who esent with a typical asymptomatic mass. If, however, assessment of the tent of disease is required this should be performed preferably using ignetic resonance imaging (MRI)[8]. Preoperative fine needle aspiration tology (FNAC) is advocated by some authors[9-11].

Surgery is the primary treatment for malignant tumours of the parotid nd while postoperative radiotherapy has been proven to be effective as an junct to surgery in improving local control and survival[12-15]. Additionally, liotherapy is applicable as a treatment modality for inoperable tumours, in patients who are unfit for surgery[16].

Optimal management of these rare tumours requires knowledge t only of the available therapeutic modalities, but also of the different ological characteristics of this heterogeneous group of tumours.

This study reviews patient presentation characteristics, histological ssification, disease free and overall survival rates between 1974 and 1994. lditionally, it evaluates the results of a treatment policy regarding the facial rve and the neck.

PATIENTS & METHODS

tients

om 1974 until 1995, 81 patients were treated for a malignant epithelial rotid gland tumour, of which 16 were recurrences after previous treatment ewhere. These were excluded from the study. There were 28 women and men; their ages ranged from 11 to 92 years, mean 58,8 years. The peak idence occurred in the eighth decade.

For the patients treated from 1974-1990 the 1972 WHO classification salivary gland tumours was used[3]. For the patients treated after 1990 the HO classification of 1991 was applied[4]. For practical reasons the patients presented as one group. Clinical classification as well as stage grouping re retrospectively performed using the 1992 UICC TNM classification[17]. e T-classification and the stage grouping according the UICC are sented in tables 1 and 2 respectively. In table 3 the division of the total group 65 patients according to histological type and stage grouping is presented.

Table 1.

1992 UICC TNM Clinical Classification

T - Primary Tumour

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour 2 cm or less in greatest dimension
T2	Tumour more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumour more than 4 cm but not more than 6 cm in greatest dimension
T4	Tumour more than 6 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.

Table 2.

Stage grouping according to 1992 UICC TNM Clinical Classification

Stage I	T1a	N0	M0
	T2a	N0	M0
Stage II	T1b	N0	M0
	T2b	N0	M0
	T3a	N0	M0
Stage III	T3b	N0	M0
	T4a	N0	M0
	Any T (except 4b)	N1	M0
Stage IV	T4b	Any N	M0
	Any T	N2,N3	M0
	Any T	Any N	M1

ble 3.

stologic diagnosis:	No.	Tumour stage I	II	III	IV
:inic cell carcinoma	12	8	3	1	-
ucoepidermoid carcinoma	6	2	2	2	-
lenoid cystic carcinoma	13	7	4	1	1
yoepithelial cell carcinoma	1	1	-	-	-
ıcocytic carcinoma	1	1	-	-	-
lenocarcinoma	17	3	7	3	4
ırcinoma in pleomorphic adenoma	6	2	3	1	-
uamous cell carcinoma	1	-	-	-	1
ıdifferentiated carcinoma	6	-	1	3	2
ırcinoma NOS	2	-	1	-	1
total	65	24	21	11	9

tient distribution (1974 - 1994) according to histologic diagnosis and nour stage.

Thirty-two patients (49.2 per cent) presented with an asymptomatic ıss of whom 14 (43.8 per cent) had a history of more than 1 year duration ıedian 3.0 years). Facial nerve paresis/paralysis and pain were the exclusive mplaint in 5 and 17 patients respectively while in 11 further cases pain was companied by facial nerve dysfunction. Facial nerve paresis/paralysis ıs thus present in 16 of the 65 patients (24.6 per cent) ten of whom had a mplete facial nerve paralysis while in six patients a paresis of one of the ıjor branches was observed. In 50 per cent of the patients this related to an enocarcinoma, confirming the findings that facial nerve dysfunction is ore common in adenocarcinoma than in other cancers. Seven of these tients were initially under surveillance of the referring physician as the ial nerve dysfunction was attributed to a Bell's palsy.

In each patient fine needle aspiration cytology (FNAC) was performed. the early period of this study a computed tomographic (CT) scan was rformed in patients with clinically suspicious malignant disease. In the later riod these patients were radiologically evaluated using MRI.

Long-term follow-up was pursued either by clinical attendance, generally at least 10 years, or by an enquiry to the general practitioner for those patients who were dismissed from out-patient review. None of the patients were lost to follow-up.

Treatment

All patients were surgically treated with curative intent. Those patients with an asymptomatic lump (n=35) underwent some form of (partial) parotidectomy with preservation of the facial nerve while in the remaining group of patients (n=30) who presented with clinical evidence of malignant disease a total parotidectomy was performed. An en bloc radical neck dissection was performed in 20 patients.

In 10 patients a radical neck dissection was planned preoperatively as clinically positive lymph nodes were present. Furthermore, during surgery, frozen section analysis of one or more subdigastric lymph nodes was performed in all those patients who presented with clinical evidence of a malignant tumour as well as in all those patients with an asymptomatic mass in the parotid in whom FNAC revealed malignant disease. In six of these patients frozen section revealed malignant tumour and thus neck dissection was carried out. In another four patients elective en bloc neck dissection was performed as the risk of occult lymph node metastases was considered to be high on the basis of cytological findings (eg. high grade tumour) or because of extent of the primary tumour into the neck.

Radical removal at a clinical and gross examination level has been obtained in all cases. Radicality at histopathological examination was defined as tumour free margins of at least 5 mm. In case of tumour presence less than 5 mm from the margin, which is often unavoidable when preserving the facial nerve, the radicality of the excision was regarded as questionable.

In general in each patient with facial nerve impairment the involved part of the nerve was sacrificed. In 16 patients preoperative facial nerve dysfunction was observed. In 11 of these cases the facial nerve was completely sacrificed while in two patients a segmental facial nerve transection was performed as in these 13 cases the tumour either engrossed the entire nerve or one of its related branches. In another three patients the nerve was preserved. It seems of interest to report on these three patients in more detail.

The *first* of these three patients was a 60 year old female, operated in 1979 for a T2N0 parotid gland tumour. Preoperative examination revealed a paresis of the facial nerve on the involved side, particularly the marginal mandibular branch. During surgery the tumour proved to have an intimate relation with the facial nerve. As the involved branches could be peeled from the tumour it was decided to preserve the nerve. Histopathological examination revealed an adenocarcinoma with perineural and perivascular spread. The patient received a full course of postoperative radiotherapy (7000 cGy in seven weeks). At present with a follow-up of 214 months this patient is doing well with a symmetrical, unimpaired facial nerve function.

The *second* patient was a 83 year old male, operated in 1988 for a T2N0 parotid gland tumour. Preoperative examination revealed a pronounced dysfunction of the marginal mandibular branch of the facial nerve. FNAC revealed malignant cells. Frozen section analysis from a suspicious subdigastric lymph node revealed malignant disease after which it was decided to perform an en bloc radical neck dissection. During surgery, the tumour was found to have an intimate relationship with the main trunk and the marginal mandibular branch of the facial nerve. As the main stem and its mandibular division tumour could be peeled from the tumour it was decided to preserve the nerve. Histopathological examination revealed a non-radically excised adenocarcinoma with multiple lymph node metastases. The patient received a full course of postoperative radiotherapy (7000 cGy in five weeks). During follow-up the facial nerve remained paretic. After 28 months the patient died of distant metastasis without locoregional recurrent disease.

The *third* patient was a 76 year old male, operated in 1992 for a T2N0 parotid gland tumour. Examination revealed a moderate paresis of the facial nerve affecting all divisions. FNAC was inconclusive. As the position of the tumour precluded identification of the nerve according to the standard surgical procedure, the main stem was identified through retrograde dissection of its peripheral branches. During this procedure the tumour displayed an intimate relationship with the temperofacial division of the nerve. As the nerve could be dissected from the neighbouring tumour it was decided to preserve it. Frozen section analysis of a subdigastric lymph node disclosed initially no tumour. Histopathological examination revealed a salivary gland carcinoma not otherwise specifiable. The subdigastric lymph node proved to contain tumour. The patient then received a full course of postoperative radiotherapy (6500 cGy in six weeks) to the primary tumour and the neck. The facial nerve function

recovered completely within 6 months. Unfortunately, the patient died after 13 months of distant metastatic disease without locoregional recurrent disease.

In an additional six patients: acinic cel carcinoma (1), mucoepidermoid carcinoma (2), adenocarcinoma (1), undifferentiated carcinoma (2), in whom normal preoperative facial nerve function was present, it was decided to perform a complete (n=1) or segmental (n=5) facial nerve transection as the nerve or one of its main branches was completely engrossed by tumour.

Altogether in three out 12 patients who underwent a transection of the main stem of the nerve an attempt to reconstruct the nerve was performed. In the other nine patients reconstruction was precluded due to perineural tumour spread or because of disease advancing up to the stylomastoid foramen. In one patient a nerve graft of the cervical plexus was used. In another patient reconstruction was performed using a nerve graft from the greater auricular nerve while in the third patient the facial nerve itself was reanastomosized on its proximal end.

Fifty-one patients received postoperative external beam radiotherapy beginning five to seven weeks after the surgical treatment, (dose range, 4000 - 7000 cGy; mean 63.5 Gy), using megavoltage methods (electron, photon or combination) administered in 4 to 7 weeks by 1 fraction/day, 5 days/week. One of the patients received after 6480 cGy an additional 2035 cGy using radiumimplant. The irradiated fields were individually designed to incorporate primary tumour and neck and the areas of potential perineural and perivascular spread. The indications for postoperative radiotherapy included: histologic type, questionable radicality at histological examination, perineural and/or perivascular tumour spread, and lymph node metastases.

Statistical analysis

Disease free and survival curves were estimated using Kaplan-Meier estimators, also known as product-limit estimators. These estimators make use of the information of all patients, including the patients whose observations are censored. The curves were compared using the Mantel Cox test. For all curves, time of event is time following the initial surgical treatment.

For the disease free curves, the event 'recurrence' was defined as having developed recurrent locoregional and/or distant metastatic disease. Observations were regarded censored when the patient was free of recurrent disease at the last out-patient clinic attendance, or when the patient died free of recurrent disease.

For the survival curves, the event 'death' was defined as death due to a recurrent locoregional and/or distant metastatic disease. The data of a patient were regarded censored when the patients was alive at the last out-patient clinic attendance or when the patient died due to natural courses or other diseases, including other tumours.

Lymph node metastasis, facial nerve dysfunction and age at diagnosis were examined as predictors for survival using Cox proportional hazards model stratified on tumour stage.

RESULTS

In the total series of 65 patients 20 experienced locoregional recurrence or distant metastases (Table 4).

Locoregional recurrence. Twelve patients (18.5 per cent) developed a locoregional recurrence, none of whom had stage I disease (Table 5a).

The type of surgical procedures in these patients included a 'partial' (n=3) or total parotidectomy (n=9).

An en bloc radical neck dissection was performed in seven patients because of clinical evidence of lymph node metastases (n=4) or tumour on frozen section analysis of subdigastric lymph nodes (n=3). In four of these 12 patients preoperatively a complete facial nerve paralysis was observed. In all these four patients the facial nerve was sacrificed. In one of them an attempt was undertaken to reconstruct the facial nerve using a graft from the greater auricular nerve. Unfortunately, no functional recovery was observed. In the other three patients nerve reconstruction was precluded by perineural spread or disease progressing up to the stylomastoid foramen. In an additional two patients, with an intact facial nerve function it was decided to perform a segmental facial nerve resection as the tumour engrossed individual branches.

All these 12 patients, except two who refused, received postoperative radiotherapy while in another patient, due to general complications, serious delay occurred (more than 3 months) prior to the start of the radiotherapy.

Four patients with recurrent locoregional tumour received further surgical treatment, which was successful in one patient. This patient died of unrelated disease without evidence of recurrent tumour after 51 months. All other patients died with disease.

Distant metastasis. Distant failure alone occurred in another eight patients, the majority of whom had stage III/IV disease (Table 5b).

The type of surgical procedures in these patients included a 'partial' (n=1) or total parotidectomy (n=7).

In five patients an en bloc radical neck dissection was carried out due to: clinical evidence of lymph node metastases (n=2), malignant disease on frozen section analysis of subdigastric lymph nodes (n=1), disease extending into the neck (n=1), and the findings of a squamous cell carcinoma on frozen section analysis of the primary tumour (n=1).

In three of these eight patients, preoperatively a facial nerve paralysis was observed. In each of them it was decided to sacrifice the facial nerve. Facial nerve reconstruction was performed in two of these patients. In the third patient reconstruction was precluded by perineural tumour spread. One patient regained an almost complete facial function while in the other no functional recovery was observed.

All eight patients received postoperative radiotherapy. All of them, except one who has been followed for only 29 months, died of distant metastases.

Tumour control. In 46 patients tumour control was achieved. The surgical procedures for these patients included a 'partial' (n=29) or total parotidectomy (n=17).

In nine patients an en bloc radical neck dissection was performed because of clinical evidence of lymph node metastases (n=5), malignant disease on frozen section analysis of subdigastric lymph nodes (n=2) while in another two this was carried out because the primary tumour extended into the neck and high grade tumour.

In five patients, four of whom had facial nerve dysfunction, it was decided to sacrifice the facial nerve. In none of these patients was facial nerve reconstruction performed. In another five patients, three of whom had a normal preoperative facial nerve function, a segmental resection was performed. In another 10 patients, all of whom had a normal preoperative facial nerve function, during surgery an intimate relation was observed between the main stem of the nerve (1) or one of its major branches (9) and the tumour. In all these cases: adenocarcinoma (1), adenoid cystic carcinoma (6), mucoepidermoid carcinoma(3), the nerve could be peeled from the tumour. All these patients received a full course of postoperative radio-therapy. None of them developed recurrent locoregional disease while in each of these patients the facial nerve function remained completely intact, the median follow-up for these 10 patients being 68 months.

None of the 46 patients, of whom thirty-four received postoperative radiotherapy, developed recurrent tumour. Ten patients died during follow-up at varying intervals of unrelated disease. Of the entire group of 65 patients 36 patients are alive with a median follow-up of 90 months.

Facial nerve involvement. Eight out of the 16 patients with preoperative facial nerve dysfunction died of locoregional or distant metastatic disease the median survival time being 38 months. Forty-nine patients had symmetrical facial nerve function. In six of these patients either a complete (n=1) or segmental (n=5) facial nerve transection was performed as the nerve or one of its main branches was completely engrossed by tumour. In the remaining 43 patients the facial nerve was preserved. In forty-one of these patients, 6 months postoperatively, symmetrical facial nerve function was observed. In the remaining two patients no functional recovery of the facial nerve was noted. One of these patients developed a locoregional recurrence within one year in which histopathological examination revealed a radically excised adenocarcainoma with 8 lymph nodes in the neck dissection specimen.

Histology. None of the patients treated for an acinic cell carcinoma (n=12) developed recurrent or metastatic disease, the median follow up being 95 months. Of the six patients treated for a mucoepidermoid carcinoma only one patient died of distant metastatic disease, the median follow up being 85 months. Three out of 12 patients treated for an adenoid cystic carcinoma died of disease, the median follow up for the remaining 9 patients being 95 months. Six out of 17 patients treated for an adenocarcinoma died of locoregional and/or metastatic disease. Another four of these patients died of unrelated disease. At present seven patients are alive, one of whom with distant metastatic disease only, the median follow up being 96 months. Six patients were treated for a carcinoma in a pleomorphic adenoma. Four of these patients died of disease three of whom within three years. Three out of six patients treated for an undifferentiated carcinoma died of their tumour.

In 15 patients radicality at histological examination, being defined as tumour free margins of at least 5 mm, was obtained. In the remaining 50 patients tumour cells were present at a distance less than 5 mm from the surgical margins, occasionally even extending into the margin.

Twenty patients underwent an en bloc neck dissection. In 17 of these specimens lymph node metastases were demonstrated. This related to the following histology: adenocarcinoma (8/17), undifferentiated carcinoma (3/6), squamous cell carcinoma (1/1), carcinoma not otherwise specifiable (1/2), carcinoma in pleomorphic adenoma (1/6), mucoepidermoid carcinoma (1/6), acinic cell carcinoma (1/12), and adenoid cystic carcinoma (1/13).

Table 4.

Stage	Recurrent disease		
	no	yes	total
I	23	1 (4%)	24
II	12	6 (33%)	18
III	8	6 (43%)	14
IV	2	7 (78%)	9
total	41	20 (31%)	65

Incidence of locoregional recurrent disease and/or distant metastases related to tumour stage.

Table 5a.

Tumour stage		No. of Patients	Failure	Histology
I	T1a N0	-		
	T2a N0	-	0/24	
II	T1b N0	-		
	T2b N0	3		carc.in pl.ad.(2x)/ad. carc
	T3a N0	1	4/18	undiff.carc.
III	T3b N0	2		undiff.carc./ad. carc.
	T4a N0	1		ad.cyst.carc.
	AnyT N1	-	3/14	
IV	T4b AnyN	2		ad.carc./ad.cyst.carc
	AnyT N2,N3	3	5/9	sq.c.carc./carc. NOS/ad.carc.

Locoregional failure related to tumour stage and histopathological findings.

Table 5b.

Tumour stage		No.of Patients	Failure	Histology
I	T1a N0	-		
	T2a N0	1	1/24	carc. in pl. ad.
II	T1b N0	-		
	T2b N0	2		ad.carc.(2x)
	T3a N0	-	2/14	
III	T3b N0	2		carc. in pl.ad./ad.cyst.carc
	T4a N0	-		
	AnyT N1	1	3/11	m.epid.carc.
IV	T4b AnyN	1		undiff.carc.
	AnyT N2,N3	1	2/4	ad. carc.

Distant metastatic disease without locoregional failure, related to tumour stage and histopathological findings.

Survival

The disease free and corresponding survival curves for the entire group of patients is presented in fig. 1. The estimated 5 and 10 disease free rates were 68 - and 59 per cent. The corresponding survival rates were 75 - and 67 per cent, respectively.

Using the Kaplan Meier estimators a significant relation could be observed between tumour stage and decreasing disease free and overall survival rates (Mantel Cox $p < 0.001$). The disease free and survival curves related to tumour stage are shown in fig. 2 and 3.

The only significant prognostic variable in the Cox proportional hazards model, stratified on tumour stage, was the presence of lymph node metastases.

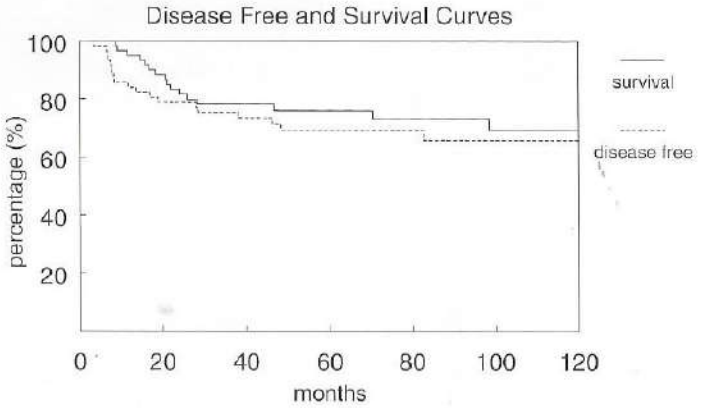

Fig. 1. Disease free and survival curves for the entire group of patients.

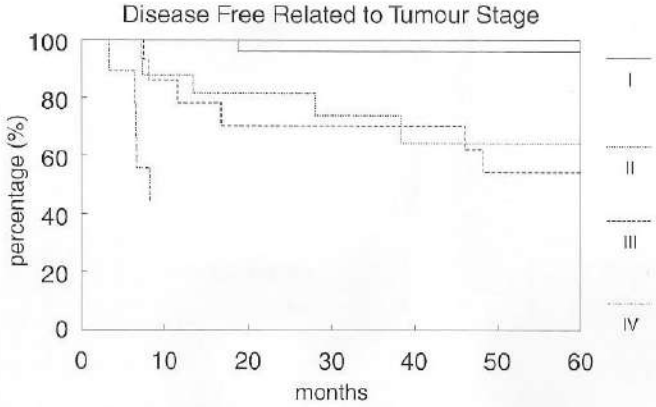

Fig. 2. The disease free survival curves related to tumour stage.

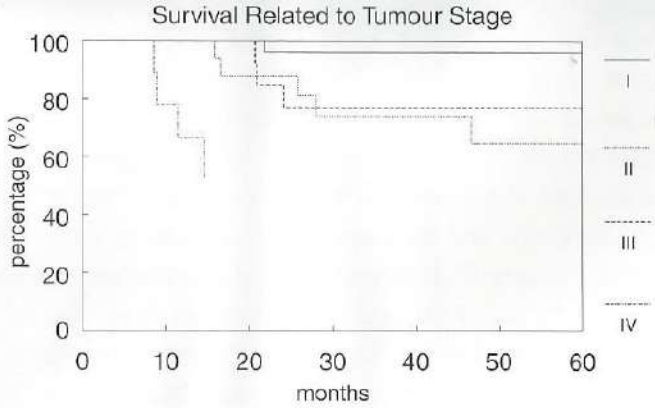

Fig. 3. The survival curves related to tumour stage.

DISCUSSION

Studies of epithelial parotid gland tumours are difficult to compare as different authors used different classification systems and different ways of reporting their results.

The 5 - and 10 year survival rates in our series of 75 - and 67 per cent are comparable with the best recently published results[18-20].

As reported in other studies the clinical stage, particularly lymph node metastasis and preoperative facial nerve involvement, as well as the histopathological type, were paramount factors, strongly influencing the incidence of recurrence and survival rates[4,18-22]. None of the patients with a T1 tumour experienced recurrent disease while 13/20 or 65 per cent of the patients who developed recurrent disease were treated for a T3 tumour and/or N+ neck.

Tumour histologic features had a serious influence on survival. In our study, as reported by others, survival rates were highest for patients with acinic cell carcinomas, mucoepidermoid carcinomas, and adenoid cystic carcinomas[23]. The poorest survival was observed in those patients with an adenocarcinoma, carcinoma in pleomorphic adenoma and undifferentiated carcinoma.

The incidence of manifest cervical lymph node metastasis (n=10 or 15 per cent) was similar to those reported by others[24,25]. Moreover lymph node metastases were demonstrated during surgery in another six patients with an asymptomatic tumour on frozen section examination of subdigastric lymph node(s). This emphasises the importance of peroperative lymph node sampling and immediate frozen section analysis.

Histologic cell type appears to be related to the risk of lymph node metastases. In our series especially adenocarcinoma and undifferentiated carcinoma were associated with a high incidence of lymph node metastases, while in contrast lymph node metastases were rare in adenoid cystic carcinoma and in acinic cell carcinoma. In the literature it is reported that also squamous cell carcinoma and mucoepidermoid carcinoma carry a high risk for lymph node metastases[3,26]. Histopathological examination revealed lymph node metastases in 17 out of 20 neck dissection specimen. Ten of these 17 patients (58.8 per cent) died of locoregional and/or metastatic disease, the medial survival time of these ten patients being 24 months. As compared to these cases forty-five patients underwent a resection of the tumour alone. Of this group six patients (13.3 per cent) died of locoregional or distant metastatic disease, the median survival time for these six patients being 64 months. These findings confirm the poor prognosis in the event of lymph node metastases and stress again the significance of instantaneous frozen section analysis of subdigastric lymph nodes in the event of a parotid gland carcinoma.

The incidence of facial nerve palsy due to tumour infiltration was similar to those reported by others[27]. Facial nerve involvement before treatment is more common in high grade tumours and is associated with a worse prognosis. Indeed, eight out of 16 cases related to an adenocarcinoma while 50 per cent of the patients died of locoregional and / or metastatic disease, the median survival time being 38 months, thus supporting the bad prognostic statement.

One of the most difficult problems which can occur during surgery is that in which the tumour lies very close to the facial nerve, whose function was intact before operation. The 2 objects of parotid surgery, i.e. removal of the tumour and preservation of the facial nerve are then in conflict. In our series we encountered this treatment dilemma in 16 patients. Our surgical philosophy in such cases is conservative. However, if the facial nerve is surrounded by tumour, and this happened to be the case in six of these patients, and preservation of the nerve would indicate that macroscopic remnants of tumour would be left behind, the nerve ought to be resected with a healthy margin. Usually this requires resection of the main trunk and its primary branches. In such cases an immediate microsurgical reconstruction of the continuity of the nerve is carried out using a graft, provided that the size of the defect and the age of the patient provide a reasonable chance of success of such a procedure. However, if the tumour extends close the nerve, and this happened to be the case in 10 patients, the facial nerve is peeled carefully off the tumour although this transgresses the classical oncological principle that malignant tumours ought to be removed with a wide healthy margin. After a full course of postoperative radiotherapy none of these 10 patients, with a median follow-up of 68 months, developed a locoregional recurrence while in each patient facial nerve function remained completely intact. Furthermore, we have even preserved the facial nerve in three patients with preoperative facial nerve dysfunction out of a total group of 16 patients. None of these three patients developed a locoregional recurrence, whereas facial nerve function recovered completely in 2 out of the three patients. These results support in our opinion the validity of a conservative approach with regard to the facial nerve in selected cases, and confirm the efficacy of postoperative radiotherapy in eradicating microscopic remnants of tumour after surgery.

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Chapter 7.

THE VALUE OF MR IMAGING IN THE DIFFERENTIAL DIAGNOSIS OF PARAPHARYNGEAL TUMOURS

H. Leverstein[1], J. Castelijns[2], and G.B. Snow[1].

[1]: Department of Otolaryngology, Head and Neck Surgery

[2]: Department of Radiology

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ABSTRACT

Between 1987 and 1993 fourteen patients with a parapharyngeal space tumour were imaged by magnetic resonance imaging (MRI). The vagal body tumours, presenting in the poststyloid compartment, all showed flow voids with anterior and medial displacement of the internal carotid artery. None of the salivary gland tumours, all presenting in the prestyloid compartment with posterior displacement of the internal carotid artery, showed flow voids. MRI is superior as compared to other modalities in evaluating the differential diagnosis, especially regarding vascular versus non-vascular tumours. It should encompass T1 SE images to assess the presence or absence of flow voids. If present an angiography must be acquired to assess feeding vessels, multiplicity, and sides involved. T1 GE images should be acquired as they allow superior identification of the internal carotid artery and its relation with the tumour accordingly. In additional to T1 SE images, T2 SE images should be acquired as they may help in the evaluation of the differential diagnosis. However, in all non-vascular tumours aspiration cytology is required to differentiate between benign and malignant disease.

INTRODUCTION

The parapharyngeal space is an potential space which encircles the upper pharynx. It is often described as an inverted pyramid with its base at the inferior surface of the petrous bone and the apex at the greater cornu of the hyoid. The lateral boundary is formed respectively from anteriorly to posteriorly by the medial pterygoid muscle, the ascending ramus of the mandible, the deep lobe of the parotid gland, and part of the posterior belly of the digastric muscle. Posteriorly it is limited by the fascia of the vertebrae and paravertebral muscles. The medial boundary is formed by the bucco-pharyngeal fascia covering the superior constrictor pharyngeal muscle and tonsillar fossa.

The parapharyngeal region is compartimentilized by thick fascial layers into three compartments. The prestyloid compartment is the only one most consistently visualized on MRI as a fat filled space. It contains mainly fat and a variable portion of the deep lobe of the parotid gland. The retrostyloid compartment containing the internal carotid artery, internal jugular vein, cranial nerves IX, X, XI, XII, cervical sympathetic chain, lymph nodes, glomus tissue, and the retropharyngeal space which is separated from the retrostyloid compartment by a thin fascial layer.

There are three major groups of tumours that affect the parapharyngeal space[1]. They represent 0,5 per cent of all head and neck tumours[2]. The most common are the salivary gland tumours (40-50 per cent), originating from the deep lobe of the parotid or from the minor salivary glands. Between 80 and 85 per cent of these tumours are pleomorphic adenomas. The second most common are the tumours of neurogenic origin (17-25 per cent). These are either schwannomas or neurofibromas (arising from the nerve sheath), or ganglioneuromas or neuroblastomas (arising from ganglion cells). The third most common group of tumours within the parapharyngeal space are paragangliomas (10-15 per cent), particularly the glomus vagale tumour which arise from nests of paraganglionic cells within the perineurium of the vagus nerve at or near the inferior (nodose) ganglion[3,4]. The remaining group of parapharyngeal tumours (10-33 per cent) represents a very diverse group of lesions which include: pathologic lymph nodes, lipomas, sarcomas, branchial cleft cyst and other rare tumours.

Since the base as well as the posterior - and the lateral walls of the parapharyngeal space are bony of origin, parapharyngeal space masses enlarge inferiorly and medially. They are clinically detectable as a mass just near the angle of the mandible and/or by medial displacement of the lateral pharyngeal wall. As the majority of parapharyngeal space tumours are asymptomatic they are often discovered during routine physical examination. Evaluation of the mass depends to a great extend on radiological studies with ultimately surgical intervention for excision.

MRI is an excellent modality for imaging of the parapharyngeal space due to its superior depiction of tumour extension into soft tissues[5-7]. For the surgical treatment of parapharyngeal space tumours the assessment of tumour vascularity and vessel displacement is of paramount importance.

This article describes the retrospective analysis of 14 patients who had an MRI on clinical suspicion of a parapharyngeal space tumour.

MATERIALS AND METHODS

Fourteen patients (Table 1), were imaged with MRI during the years 1987 - 1993 in their pre-treatment work-up for a parapharyngeal space tumour. The absence or presence of flow voids, the position and displacement

of the internal carotid artery, and tumour associated MRI characteristics such as presence or absence of infiltrative growth were assessed. Twelve patients were treated surgically. One patient received radiotherapy and one patient was treated conservatively.

Images were made within four weeks before surgery on a 0.6 Tesla MR system (teslacon II, Technicare), using a surface (half saddle-shaped) coil. Axial slices were obtained from the base of skull down to the hyoid bone. Axial T1-weighted Spin Echo (SE) images and T2-weighted SE images with a slice thickness of 5 mm were made in all patients. Additional to these, in some patients T1-weighted Gradient Echo (GE) images with a slice thickness of 3-5 mm were acquired.

Table 1.

				Signal Int.		Compartment	Displacement		Tumour		
pt.	sex	age	F.V	T1SE	/T2SE	Pre/Post St	Int.Car.Art	I.G.	Left	Right	Therapy
1.	M	38	+			Post St.	DA+M.	-		V.B.T	4
2.	F	36	+			Post St.	DA+M	-	V.B.T.	V.B.T.	7/1
3.	F	46	+			Post St.	DA+M	-	V.B.T.		7
4.	M	44	-	2	3	Pre St.	ND	-	Pl.Ad.		5
5.	M	23	-	2	3	Pre St.	ND	-	Pl.Ad.		6
6.	F	38	-	2	3	Pre St.	DP+L	-		Pl.Ad.	5
7.	M	68	-	2	3	Pre St.	ND	-		Pl.Ad.	6
8.	F	46	-	2	3	Pre St	ND	-		Pl.Ad.	5
9.	F	21	-	2	3	Pre St	DP+L	-	Pl.Ad.		6
10.	M	42	-	2	3	Pre St.	DP+L	-		Pl.Ad.	5
11.	M	38	-			Pre St	ND	-		Liposarc.	7
12.	M	60	-	2	NA	Pre St	ND	+		Ad.Carc	2
13.	F	56	-	2	NA	Post St	DA+L	+		Carc?	1
14.	F	76	-	4	NA	Pre St	ND	-	Ad.carc.		3

Displacement Internal Carotid Artery:

DA : displaced anteriorly
DA+M : displaced anteriorly and medially
DA+L : displaced anteriorly and laterally
DP+L : displaced posteriorly and laterally
ND : no displacement

Compartment: Pre St.: Prestyloid
Post St. : Poststyloid

List of tumours : V.B.T. : Vagal Body Tumour
Pl..ad. : Pleomorphic adenoma
Liposarc. : Liposarcoma
Ad carc. : Adenocarcinoma
Carc.? : Carcinoma of unknown origin

F.V.: Flow Voids: + present, - absent

I.G.: Infiltrative Growth in muscle and/or bone: + present, - absent

Signal Intensity T1 SE / T2 SE: 1: low
2: interermediate
3: intermediate to high
4: high
NA: not acquired

Therapy:
1. conservatively
2. radiotherapy
3. total parotidectomy
4. transpharyngeal with midline osteotomy
5. combined transoral/transcervical excision with facial nerve identification
6. combined transoral/transcervical excision without facial nerve identification
7. transcervical excision without mandibular split

Case reports

Patient No. 1. A 38-year-old male was presented with a 4 month old history of a silent tumour on the right side in his throat which he noticed whilst brushing his teeth. On intraoral inspection a tumour displacing the right lateral oropharyngeal wall to the midline was observed. On palpation of the neck there was a soft elastic, diffuse swelling in the subdigastric area. The MR T1-weighted SE images showed a tumour of the parapharyngeal space with an homogeneous and intermediate signal intensity. The internal carotid artery showed anterior and medial displacement (Fig. 1a). Flow voids were present. Signs of infiltrative growth were absent. Angiography showed a vascular

lesion displacing the internal carotid artery anteriorly, compatible with a vagal body tumour (Fig. 1b).

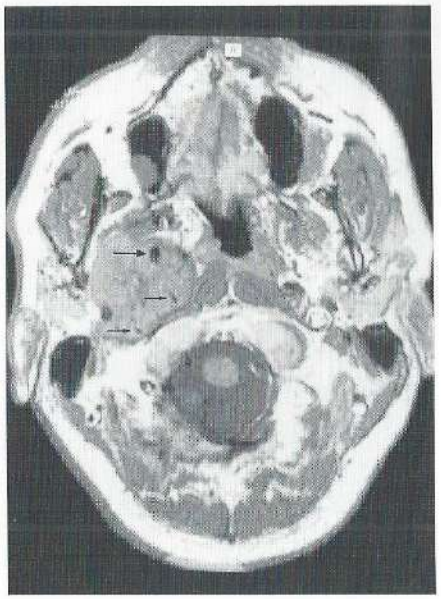

Figure 1a: This MR T1-weighted SE image shows a well circumscribed tumour of the parapharyngeal space with a homogeneous and intermediate signal intensity displacing the internal carotid artery anteriorly and medially (arrow). Flow voids (small arrows), well demarcated small areas with a low signal intensity, are clearly visible.

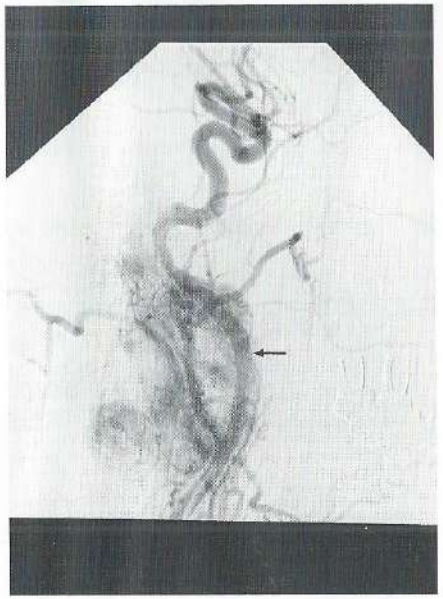

Figure 1b: Angiography confirms the vascular nature of the tumour with anterior displacement of the internal carotid artery (arrow).

Because the tumour at the time did not cause any discomfort the patient was reluctant to have surgical treatment. Taking into account that this treatment would almost certainly result in serious cranial nerve deficit, a policy of observation was decided upon. During follow-up, after 1 year a paralysis of the hypoglossal nerve as well as a Horner syndrome was observed. It was felt that surgical treatment should not be delayed any longer. Via a transpharyngeal approach with midline mandibulotomy a glomus tumour with a maximum diameter of 9 cm was removed with the help of the vascular surgeons. The cranial nerves X and XII, as well as the sympathic trunk and the internal carotid artery had to be sacrificed as the latter was completely encapsulated within the tumour. Histopathological examination of the surgical specimen showed a paraganglioma with an unusual high cellular (lymphoid) infiltrate. Postoperatively, a left-sided hemiparesis was present which completely resolved within 1 week. At present, 9 months after surgical intervention patient can cope with a normal diet.

Patient No. 9. A 21-year-old woman presented herself with a 3 month old history of dysphagia. On examination a tumour displacing the left lateral oropharyngeal wall to the midline was seen. Palpation of the neck revealed no abnormalities. The MR T1-weighted SE images showed a well circumscribed tumour of the parapharyngeal space with an homogeneous and intermediate signal intensity. The internal carotid artery showed posterior and lateral displacement (Fig. 2a). Flow voids were absent. The MR T1-weighted GE images revealed superior identification of the internal carotid artery (Fig. 2b). The MR T2-weighted SE images showed a tumour with an inhomogeneous, intermediate to high signal intensity (Fig. 2c). Signs of infiltrative growth were absent. Aspiration cytology revealed a pleomorphic adenoma. The tumour was removed via a combined transoral/transcervical approach. Histopathological examination of the surgical specimen showed a pleomorphic adenoma. At present, 4.5 years after surgical removal of the tumour, the patient is free of disease and doing well.

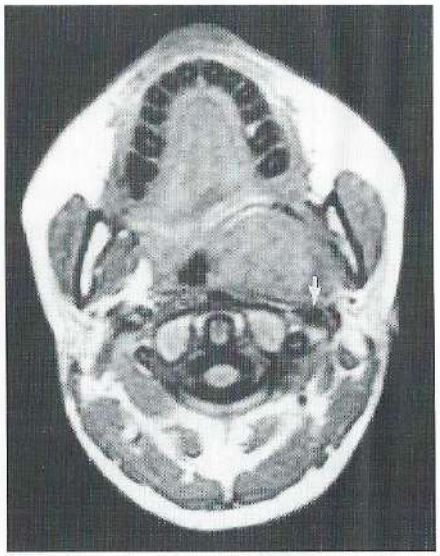

Figure 2a:This MR T1-weighted SE image shows a well circumscribed tumour of the parapharyngeal space with a homogeneous and intermediate signal intensity displacing the internal carotid artery posteriorly and laterally (arrow).

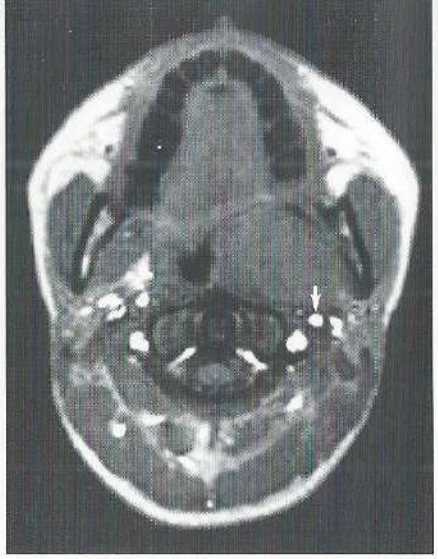

Figure 2b:MR T1-weighted GE imaging enabled superior identification of the posteriorly and laterally displaced internal carotid artery that is visualized with a high signal intensity (arrow).

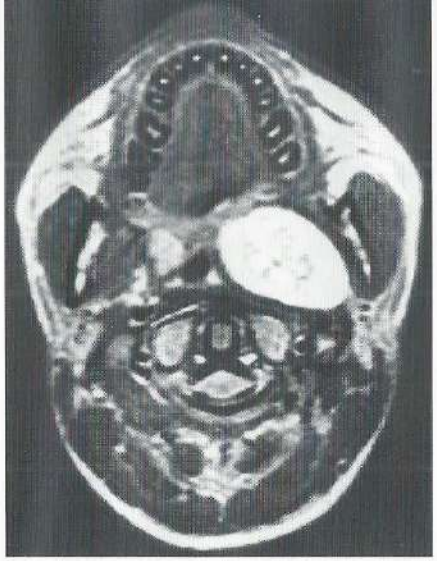

Figure 2c:This MR T2-weighted SE image shows a well circumscribed tumour of the parapharyngeal space with an inhomogeneous and intermediate to high signal intensity.

Patient No. 14. A 76-year-old woman presented herself with a history of diminishing hearing in her left ear and a recent painful progressive swelling on the left side of her neck. On intraoral inspection a moderately medially displaced left lateral oropharyngeal wall was observed. Palpation of the neck revealed a diffusely swollen parotid region and a painful poorly circumscribed tumour behind the angle of the mandible on the left side. On otoscopy a serous otitis media on the left side was found. The MR T1-weighted SE images showed a tumour in the parapharyngeal space with a high signal intensity originating from the deep lobe of the parotid gland displacing the left lateral oropharyngeal wall medially. The internal carotid artery showed no displacement (Fig. 3a). Flow voids were absent. The MR T1-weighted GE images showed a tumour with a signal intensity, superiorly identifying the internal carotid artery (Fig. 3b). Signs characteristic for infiltrative growth were absent. Via a transparotid approach, preserving the facial nerve, a cystic tumour originating from the deep lobe of the parotid gland with a maximum diameter of 7 cm was removed. Histopathological examination of the surgical specimen revealed an haemorrhaged multicystic adenocarcinoma. Patient received postoperative (6500 cGy) radiotherapy. At present, 5 years after completion of her therapy, patient is free of disease and doing well.

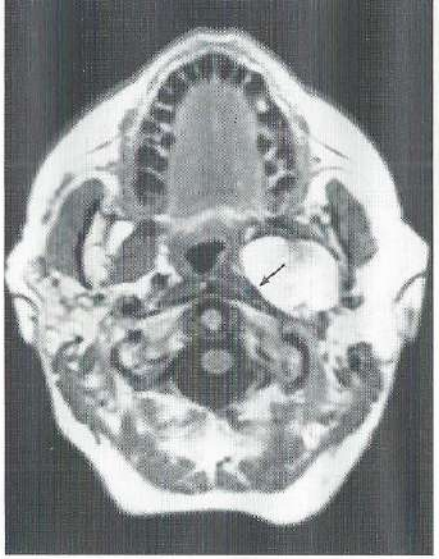

Figure 3a:This MR T1-weighted SE image shows a well circumscribed tumour of the parapharyngeal space with a high signal intensity. It is located anterior to the internal carotid artery leaving it in a normal position (arrow).

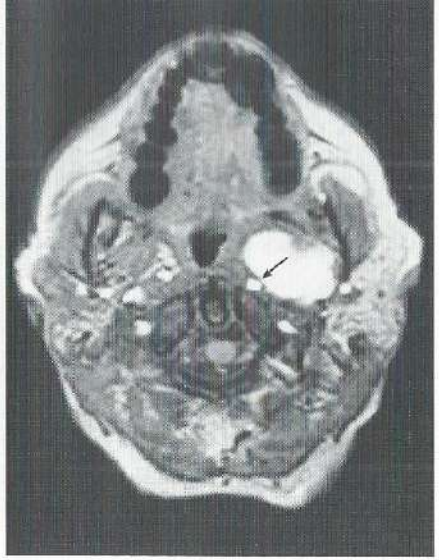

Figure 3b:MR T1-weighted GE imaging enabled superior identification of the internal carotid artery that is visualized with a high signal intensity (arrow).

RESULTS

In patient 1-3 the tumour originated in the poststyloid compartment with anterior and medial displacement of the internal carotid artery. For each tumour the MR T1-weighted SE images showed an intermediate signal intensity with the presence of flow voids. The feeding vessels were clearly identified using angiography. In patient 4-10, the tumour was located in the prestyloid compartment. Each tumour showed well circumscribed margins with intermediate signal intensity on the MR T1-weighted SE images and intermediate to high signal intensity on the MR T2-weighted SE images. MR T1-weighted GE images enabled clear identification of the vascular structures. Flow voids and signs of infiltrative growth were absent. In each patient aspiration cytology was compatible with a pleomorphic adenoma.

In patient no. 11 MR T1- and T2-weighted SE images showed a well circumscribed tumour in the prestyloid compartment with a high signal intensity similar to that of fat. Flow voids and signs of infiltrative growth were absent. The tumour proved to be a liposarcoma.

In patient no. 12 the MR T1-weighted SE images showed a tumour in the prestyloid compartment with an intermediate signal intensity and irregular

margins. Flow voids were absent. Signs characteristic for infiltration into bone and/or muscle were present. Aspiration cytology revealed an adenocarcinoma.

In patient no. 13 the MR T1-weighted SE images showed a tumour in the poststyloid compartment with an intermediate signal intensity and irregular margins. Flow voids were absent. Signs characteristic for infiltration into bone and/or muscle were present. Aspiration cytology showed signs of malignancy.

In patient no. 14 the MR T1-weighted SE images showed a tumour in the prestyloid compartment with a high signal intensity and regular margins. Both flow voids and signs complying with invasion of muscle and/or bone were absent. Histopathological examination revealed a haemorrhaged multicystic adenocarcinoma. The cystic origin explaining for the high signal intensity on the MR T1-weighted SE images.

DISCUSSION

Parapharyngeal space tumours mainly consist out of three types. Salivary gland tumours are located in the prestyloid compartment, anterior to the carotid artery, leaving it in a normal position or displacing it posteriorly[8,9]. Tumours of neurogenic origin arise in the poststyloid compartment. They are located posterior to the internal carotid artery and displace the carotid artery anteriorly. The third most common group of tumours to arise in the parapharyngeal space are paragangliomas. Particularly the vagal body tumour may present itself with a medial displacement of the oropharyngeal wall. It originates, in the poststyloid compartment along the vagus nerve and which in the majority of cases will displace the internal carotid artery anteriorly and medially[10].

In order to assess a patient who presents with a parapharyngeal tumour MRI is the first choice of radiological examination. It should answer two paramount questions. Firstly, whether or not the tumour is of vascular origin. An MRI should encompass axial T1-weighted SE images assessing the presence or absence of flow voids which are characteristic for a glomus tumour[5,11,12] (patient 1-3). If present, angiography of both the carotid arteries should be done to assess feeding vessels, multiplicity and sides involved. As paragangliomas less than 2 cm in diameter may present with a more homogeneous appearance, lacking flow voids[13], additional information may be obtained using angiography.

Secondly, the relation between the tumour and the internal carotid artery should be identified accurately. To answer this question axial MR T1-weighted GE images should be acquired. They allow identification of the internal carotid artery (Fig.2b - Fig.3b), and displacement accordingly.

To improve differentiation between benign and malignant tumours additional to MR T1-weighted SE images, MR T2-weighted SE images should be acquired. The combination of both images may demonstrate absence of infiltrative growth suggesting benign disease (patients 1-11) or destruction and infiltrative growth in the surrounding structures by the tumour characteristic for malignancy (patient 12 and 13). However clear margins and the absence of infiltrative growth don't exclude malignant disease (patient 14). Freling et. al.[14] reported in their study of malignant parotid tumours that only 51 per cent of the patients with unclear margins proved to have a malignant tumour whereas infiltration into bone and/or muscle was characteristic of a malignant tumour.

As discussions remain whether or not a significant correlation exists between signal intensity, tumour grade, and the histologic nature[7,14,15] we agree with Freling that signal characteristics do not enable differentiation between malignant and benign tumours. Therefor in non-vascular tumours an aspiration cytology is required to differentiate between benign and malignant disease.

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Chapter 8.

SUMMARY AND CONCLUSIONS

This study concerns a retrospective clinicopathological analysis of 422 patients with an epithelial parotid gland tumour, who were treated at the department of Otolaryngology / Head and Neck Surgery, University Hospital Vrije Universiteit, Amsterdam, in the period 1974 - 1995.

In ***chapter 1*** a general introduction is presented. Firstly the embryogenesis and the surgical anatomy of the parotid gland are reviewed. Subsequently epidemiology, histopathological classification, diagnosis and treatment of epithelial parotid gland tumours are discussed.

Until recently these tumours were classified according to the 1972 international histological classification of the World Health Organization (1972). However, in 1991 the WHO has published a revised, much more refined, histological classification. The introduction of computed tomography (CT) in the seventies and magnetic resonance (MR) imaging in the eighties have been a great advance for the assessment of the extension of parotid tumours, particularly of tumours of the deep lobe with involvement of the parapharyngeal space. During the period under observation modifications of surgical treatment for benign tumours have been introduced with the aim to reduce the morbidity associated with such treatment. Furthermore, the important role of adjunctive postoperative radiotherapy in the treatment of malignant tumours has been firmly established and this in turn influenced the surgical philosophy in selected cases.

The aim of this retrospective clinicopathological analysis is to report on the results in a large series of patients in relation to the forementioned modifications in histological classification, diagnostic work-up and particularly treatment.

In ***chapter 2*** the results of the reclassification of 478 previously untreated parotid gland tumours according to the 1991 WHO histological classification of salivary gland tumours is presented. According to the original diagnosis, mostly typed by the 1972 WHO histological classification, 405 (85 per cent) tumours were benign while 73 tumours (15 per cent) were malignant. In 56 cases (11.7 per cent) the original diagnosis was changed within the benign or malignant group of tumours and this was due to the more extended subtyping of the 1991 WHO histological classification. Each of the six patients (1.3 per cent) in whom the original diagnosis was changed from benign to malignant (3) or vice versa (3) had tumour free margins. During follow-up no events occurred supporting or rejecting the correctness of the revised diagnosis.

At present, it is to early to conclude on the clinical relevance of the revised WHO histological classification for salivary gland tumours.

In ***chapter 3*** the developments in the surgical treatment of benign parotid tumours are briefly described in historical perspective.

With the favourable developments in reducing the incidence of recurrent disease and permanent facial nerve paralysis attention gradually focused on other sequelae of parotid surgery including loss of sensation of the auricle, cosmetic aspects, and Frey syndrome. To reduce such morbidity several modifications of parotidectomy were introduced: 1. In each procedure, an attempt is undertaken to preserve the posterior branch of the greater auricular nerve, unless precluded by the position of the tumour. 2. For each tumour lateral to the nerve, in principle, a 'partial' superficial parotidectomy is performed. 3. In principle, for each deep lobe tumour a 'selective' deep lobe resection is performed.

A total of 246 primary surgical parotid procedures were performed on 245 patients for pleomorphic adenoma. These included: 131 'partial' superficial parotidectomies, 61 total superficial parotidectomies, 30 partial superficial/deep parotidectomies, 8 total parotidectomies, and 16 'selective' deep lobe parotidectomies. Two patients (0.8 per cent) developed a local recurrence, both after total parotidectomy for a deep lobe tumour. None of the patients experienced permanent facial nerve dysfunction. The incidence of gustatory sweating after partial superficial parotidectomy proved to be considerably less, 6.9 per cent, as compared to 13.1 per cent for formal superficial parotidectomy. In those patients in whom the posterior branch of the greater auricular nerve was preserved sensation returned more rapidly and more completely as compared to those in whom the nerve was sacrificed. The cosmetic appearance after partial superficial parotidectomy and or selective deep lobe parotidectomy was markedly improved as compared to respectively total superficial and total parotidectomy. Additionally, none of the patients in whom a 'modified' procedure was performed developed a recurrence. Four out of ten patients in whom tumour spillage occurred, received postoperative radiotherapy. None of these 10 patients developed recurrent disease.

It is concluded that partial parotidectomy is an effective treatment for the great majority of pleomorphic adenomas: local recurrence is rare, and

morbidity is low. In general prolonged follow-up is unnecessary. In the event of 'controlled' tumour spill there is no indication for postoperative radiotherapy.

In ***chapter 4*** the experiences with 40 patients, initially treated elsewhere, for a residual or recurrent pleomorphic adenoma is described with special emphasis on recurrent tumour growth, risk of facial nerve damage, and malignant transformation.

Thirty-seven patients underwent surgical excision of their tumour en bloc with the involved skin and or former incision. None of the 36 patients operated for histopatho-logically benign disease, of whom 17 received postoperative radiotherapy, developed a further recurrence. Only one of these 36 patients, treated for an extensive deep lobe recurrence, developed a segmental paralysis of the facial nerve. Facial nerve function remained completely intact in the other 35 patients. It is important to note that during the course of the study the use of postoperative radiotherapy has declined. One patient operated for a recurrence which had become clinically malignant after previous surgery and radiotherapy, died of locoregional disease. In the remaining three patients, during reoperation at this institution, it was decided to refrain from tumour resection. In two of these patients tumour control was obtained using radiotherapy. In the third patient in whom the tumour proved to be irresectable a wait-and-see policy was adopted.

It is concluded that wide surgical excision including involved or overlying skin gives excellent results in the majority of recurrent pleomorphic adenomas of the parotid gland. There is a limited role for postoperative radiotherapy. In selected cases it may be justified to refrain from ablative surgery if the anticipated morbidity becomes unacceptable. Due to the multifocal nature of recurrent disease extended follow-up is required.

In ***chapter 5*** the concept of partial parotidectomy and it's applicability in the treatment of parotid gland Warthin's tumour is being discussed. This is important, as it is generally recognized that this type of tumour may be multifocal in origin. This study reports on the different surgical techniques used in relationship to the findings at histopathological examination of the specimen.

Eighty-eight procedures were performed for a Warthin's tumour. These included: 22 formal superficial parotidectomies and 66 'partial' parotidectomies. Histopathological examination revealed in 7 out of 22 formal superficial parotidectomies and 13 out of 66 partial parotidectomies a multifocal origin of the tumour. In nine out of these 20 cases in whom histology revealed a multifocal origin a synchronous Warthin tumour was identified and subsequently removed following excision of the index tumour, stressing the need for careful inspection and palpation of the remainder of the gland for other synchronous lesions. In the remaining 11 cases the synchronous tumours were identified only after microscopical examination of the specimen. None of the patients developed recurrent disease in either group.

We conclude that a formal superficial parotidectomy for a Warthin's tumour in the lateral portion of the gland in the majority of cases is unnecessary. It increases the risk of damage to the branches of the facial nerve and the incidence of Frey syndrome. Partial parotidectomy is an effective treatment for Warthin's tumour: the risk of a second Warthin's tumour in the remainder of the parotid gland becoming clinically manifest is to be considered extremely low.

In ***chapter 6*** is reported on the analysis and results of 65 patients treated with curative surgical intention for a previously untreated malignant epithelial parotid gland tumour with special emphasis on patient presentation characteristics, histological classification, management, disease free, and overall survival rates. Additionally, it evaluates the results of the applied treatment policy regarding the facial nerve and the neck.

All patients underwent some type of parotidectomy, twenty of whom with an en bloc radical neck dissection. In selected cases the facial nerve or its related branches were peeled off the tumour, thus violating the objective to obtain tumour free margins. Fifty-one patients received postoperative radiotherapy. Twelve patients (18.5 per cent) developed a locoregional recurrence, none of whom with stage I disease. Distant failure alone occurred in another eight patients, the majority of whom with stage III/IV disease. The estimated 5 and 10 years disease free survival rates were 68 per cent and 59 per cent, respectively. The corresponding 5 and 10 year overall survival rates were 75 per cent and 67 per cent, respectively. A significant relation could be observed between tumour stage and decreasing disease free and overall survival rates. The presence of lymph node metastases proved to be the strongest single prognostic factor. This emphasises the importance of perioperative subdigastric lymph node sampling and immediate frozen section

analysis. Preoperative facial nerve dysfunction was present in 24.6 (16/65) per cent of the patients. In 50 per cent of these 16 patients this related to an adenocarcinoma, confirming that facial nerve dysfunction is more common in adenocarcinoma than in other cancers. Facial nerve involvement before treatment is associated with a worse prognosis. Indeed, half of these patients died of locoregional and/or metastatic disease. None of those ten patients in whom the facial nerve was peeled carefully off the tumour, all of whom received a full course of radiotherapy, developed locoregional disease while in each patient the facial nerve function remained completely intact. These findings support the validity of a conservative approach with regard to the facial nerve in selected cases, and confirm the efficacy of postoperative radiotherapy in eradicating microscopic remnants of tumour after surgery. It is furthermore concluded that early diagnosis of a malignant epithelial parotid gland tumours is of paramount importance in the clinical outcome of this type of disease.

In ***chapter 7*** the value of Magnetic Resonance Imaging (MRI) in the differential diagnosis of parapharyngeal space tumours is studied in 14 patients with special reference to tumour specific signal characteristics, tumour location in the different parapharyngeal space compartments and presence or absence of vessel displacement accordingly. All vagal body tumours (n=3), presenting in the poststyloid compartment of the parapharyngeal space, showed flow voids on the axial MR T1 Spin Echo (SE) images with anterior and medial displacement of the internal carotid artery. None of the salivary gland tumours (n=9), all presenting in the prestyloid compartment of the parapharyngeal space, some of which with posterior displacement of the internal carotid artery, showed flow voids. MRI is superior as compared with other modalities in evaluating the differential diagnosis, especially regarding vascular vs non-vascular tumours. It should encompass T1 SE images to assess the presence or absence of flow voids. In vascular tumours angiography must be used to assess feeding vessels, multiplicity, and sides involved. T1 Gradient Echo (GE) images are useful as they allow superior identification of the internal carotid artery and its relation with the tumour accordingly. Additional to T1 SE images, T2 SE images may help in the evaluation of the differential diagnosis. In all non-vascular tumours aspiration cytology may be helpful to differentiate between benign and malignant disease.

Chapter 9.

SAMENVATTING EN CONCLUSIES.

In dit proefschrift wordt een retrospectief, klinisch-pathologisch onderzoek beschreven van 422 patiënten met een epitheliale speekselkliertumor van de glandula parotis die hiervoor in de periode van 1974 tot 1995 op de afdeling Keel-, Neus- en Oorheelkunde / Heelkunde van het Hoofd-Halsgebied van het Academisch Ziekenhuis van de Vrije Universiteit werden behandeld.

In ***hoofdstuk 1*** wordt een algemene inleiding gegeven. Allereerst wordt ingegaan op de embryogeneses en de chirurgische anatomie van de glandula parotis. Daarnaast worden de epidemiologie, de histopathologische classificatie, de diagnostiek alsmede de behandeling van epitheliale speekselkliertumoren beschreven.

Tot voor kort werden deze tumoren geclassificeerd volgens de World Health Orginization (WHO) histologische classificatie voor speekselkliertumoren van 1972. In 1991 werd door de WHO een herziene, meer gespecificeerde editie gepubliceerd. De introductie van computer tomography (CT) in de jaren zeventig en Magnetic Resonance Imaging (MRI) in de jaren tachtig zijn van grote waarde geweest voor de beeldvorming en diagnostiek van parotis tumoren, met name voor tumoren uitgaande van de diepe kwab met uitbreiding in de parapharyngeale ruimte. Gedurende deze studie werden in de loop der jaren voor de benigne parotis tumoren enkele modificaties van parotidectomie ingevoerd ten einde de chirurgische morbiditeit tot een minimum te kunnen beperken. Tevens werd in deze periode het belang van postoperatieve radiotherapie in de behandeling van maligne parotis tumoren algemeen onderkend. Dit resulteerde in een verandering van de behandelingsstrategie ten opzichte van de nervus facialis in geselecteerde patiënten.

Het doel van deze retrospectieve, klinisch-pathologische studie is om de resultaten van behandeling in een grote groep van patiënten nader te evalueren, in relatie tot de modificaties in de histopathologische classificatie, de diagnostiek en de behandeling, met name de toegepaste operatietechnieken.

In ***hoofdstuk 2*** worden de bevindingen van de reclassificatie van 478 primaire epitheliale parotis tumoren volgens de WHO histologische classificatie voor speekselkliertumoren van 1991 beschreven. Op basis van de originele diagnose, in de meerderheid van de gevallen gebaseerd op de WHO histologische classificatie van 1972, betrof het 408 (85%) benigne en 73 maligne (15%) tumoren. In 56 gevallen (11.7%) werd de originele diagnose herzien binnen de benigne en of maligne groep van tumoren dankzij de uitbreiding van de subtypering van deze tumoren in de WHO histologische classificatie voor speekselkliertumoren van 1991. Bij zes patiënten (1.3%) bij wie de diagnose werd veranderd van maligne naar benigne (3) of vice versa (3) was er sprake van een radicale excisie. Gedurende de follow-up deden zich bij de zes patiënten geen omstandigheden voor die de herziene diagnoses verwierpen of ondersteunden.

Het is op dit moment te vroeg om commentaar te leveren op de klinische relevantie van de herziene WHO histologische classificatie voor speekselkliertumoren van 1991.

In ***hoofdstuk 3*** wordt allereerst een kort historisch overzicht gegeven over de ontwikkelingen in de chirurgische behandeling van epitheliale speekselkliertumoren uitgaande van de glandula parotis.

Als gevolg van de gunstige ontwikkelingen met betrekking tot het voorkomen van lokaal recidief en dat van letsel van de nervus facialis ontstond geleidelijk meer belangstelling voor de eventuele overige gevolgen en complicaties van parotidectomieën zoals respectievelijk: de sensibiliteitsstoornis van de oorschelp, het kosmetische aspect en het syndroom van Frey. Hiermee samenhangend werden in onze kliniek, ter beperking van de morbiditeit, in de loop der jaren de volgende modificaties van parotidectomie ingevoerd: 1. Bij iedere parotidectomie wordt getracht het posterieure takje van de nervus auricularis magnus te sparen, tenzij de lokalisatie van de tumor dit bij voorbaat ongewenst maakt. 2. Voor een tumor in de oppervlakkige kwab wordt in principe een 'partiële' oppervlakkige parotidectomie verricht. 3. Voor een tumor in de diepe kwab wordt in principe een 'selectieve' diepe kwab resectie verricht.

In totaal werden 246 parotidectomieën verricht bij 245 patiënten. Het betrof 131 'partieel' oppervlakkige parotidectomieën, 61 volledige oppervlakkige parotidectomieën, 30 partieel oppervlakkig/diepe kwab parotidectomieën, 16 'selectieve' diepe kwab resecties en 8 totale parotidectomieën. Twee patiënten (0,8%) ontwikkelden een lokaal recidief, beide na totale parotidectomie voor een diepe kwab tumor. Geen van de patiënten ontwikkelde een permanente nervus facialis parese of paralyse. De incidentie van het syndroom van Frey bedroeg voor de 'partieel' oppervlakkige parotidectomieën 6,9% (9/131) in vergelijk met 13,1% (8/61) voor de volledige oppervlakkige parotidectomieën. Bij die patiënten bij wie het posterieure takje van de nervus auricularis magnus gespaard kon worden

keerde de sensibiliteit sneller en vollediger terug dan na doorsnijding van deze zenuw. Het kosmetisch aspect van de partiële oppervlakkige parotidectomie en selectieve diepe kwab resectie toonde een duidelijke verbetering in vergelijking tot de volledig oppervlakkige - en totale parotidectomie. Geen van de patiënten bij wie een gemodificeerde ingreep werd verricht ontwikkelde recidief tumor. Bij de tien patiënten bij wie sprake was van tumor spill, van wie er vier werden nabestraald, werd geen recidief waargenomen.

Er wordt geconcludeerd dat een partiële parotidectomie zeer effectief is voor de behandeling van een pleomorf adenoom: een lokaal recidief doet zich zelden voor terwijl de morbiditeit over het algemeen gering is. Langdurige controle is slechts bij hoge uitzondering geïndiceerd. In het geval van gecontroleerde tumor spill bestaat er geen indicatie voor postoperatieve radiotherapie.

Hoofdstuk 4 beschrijft de analyse en resultaten van behandeling bij 40 patiënten met recidief/residu pleomorf adenoom van de glandula parotis na eerdere behandeling elders met speciale aandacht voor recidief tumorgroei, het risico op nervus facialis beschadiging en dat op maligne transformatie.

Zevenendertig patiënten ondergingen een chirurgische excisie van hun residu/recidief tumor en bloc met de betrokken huid en/of litteken van de eerdere excisie. Geen van de 36 patiënten bij wie histopathologisch sprake was van een benigne tumor ontwikkelde een hernieuwd recidief; 17 van hen werden nabehandeld middels radiotherapie. Slechts één patiënt, behandeld voor een groot recidief in de diepe kwab van de glandula parotis, ontwikkelde een permanente partiële nervus facialis paralyse. Bij de overige 35 patiënten bleef de functie van de nervus facialis volledig intact. De patiënt bij wie het recidief reeds klinisch maligne was ontaard na eerdere chirurgie en radiotherapie, overleed met locoregionaal recidief tumor. Bij drie patiënten werd durante operationem besloten af te zien van ablatieve chirurgie. Bij twee van deze patiënten werd tumor controle verkregen middels radiotherapie. Bij de derde patiënt bij wie sprake was van recidief tumor met uitbreiding langs de schedelbasis tot aan de nasopharynx werd besloten af te zien van een resectie en te kiezen voor een afwachtend, conservatief beleid.

Er wordt geconcludeerd dat bij het recidief pleomorf adenoom met ruime chirurgische excisie en bloc met de betrokken en/of overliggende huid in de meerderheid van de gevallen uitstekende resultaten worden behaald. In uitzonderlijke gevallen is het verantwoord om, indien de te verwachten

morbiditeit van chirurgische excisie onacceptabel hoog is, af te zien van ablatieve chirurgie. Gezien het veelal multifocale karakter van recidief pleomorf adenoom dient langdurige poliklinische controle te worden verricht.

In ***hoofdstuk 5*** wordt de toepasbaarheid van het concept van partiële parotidectomie voor de chirurgische behandeling van de Warthin tumor nader geëvalueerd met speciale aandacht voor de multifocale origine die bij deze tumor is beschreven.

Achtentachtig parotidectomieën werden verricht. Het betrof 22 volledige oppervlakkige parotidectomieën, bij de overige 66 patiënten werd een partiële parotidectomie verricht. Histopathologisch onderzoek toonde bij respectievelijk 7/22 en 13/66 een multifocale origine van de tumor. Bij negen van de in totaal 20 patiënten met een multifocale tumor werd de synchrone tumor ontdekt na zorgvuldige inspectie en palpatie van de restklier na resectie van de index tumor. Bij de overige 11 patiënten werden de synchrone tumoren pas ontdekt bij het microscopisch onderzoek van het resectiepreparaat. Geen van de patiënten ontwikkelde een recidief.

Geconcludeerd wordt dat een volledige oppervlakkige parotidectomie voor een Warthin tumor in de oppervlakkige kwab van de glandula parotis veelal overbodig is. Het verhoogt het risico op beschadiging van de takjes van de nervus facialis alsmede de kans op het postoperatief voorkomen van het syndroom van Frey. Een 'partiële' parotidectomie is een effectieve behandeling voor de Warthin tumor: het risico op de ontwikkeling van een klinisch manifeste tweede Warthin tumor in het achtergebleven parotis weefsel is als uitzonderlijk laag te beschouwen.

In ***hoofdstuk 6*** wordt gerapporteerd over 65 in opzet curatief chirurgisch behandelde patiënten voor een maligne epitheliale parotis tumor met speciale aandacht voor het klachtenpatroon, de histopathologische classificatie, de ziektevrije en algehele overlevingspercentages. Daarnaast werd de behandelingsstrategie, in het bijzonder ten aanzien van de nervus facialis en de hals nader geëvalueerd.

Iedere patiënt onderging een resectie van zijn tumor van wie 20 met een en bloc radicale halsklierdissectie. In geseleceerde gevallen werd het betrokken deel van de nervus facialis van de tumor gepeld waarmee het chirurgisch oncologisch principe om ruime tumorvrije resectieranden te nemen werd overtreden. Eenenvijftig patiënten werden nabehandeld met

radiotherapie. Twaalf patiënten (18.4%), van wie geen enkele met tumor stadium I, ontwikkelden een locoregionaal recidief. Acht patiënten ontwikkelden, bij locoregionale controle, metastasen op afstand; de meerderheid van hen had een stadium III/IV tumor. De geschatte 5 - en 10 jaar ziektevrije overleving bedroegen 68% en 59%. De corresponderende 5 - en 10 jaar algehele overleving waren respectievelijk 75% en 67%. Een significante relatie werd waargenomen tussen het klinisch stadium en de ziektevrije en algehele overleving. De aanwezigheid van lymfkliermetastasen in de hals bleek de belangrijkste factor te zijn. Dit onderstreept het belang van peroperatieve 'sampling' met microscopisch onderzoek van subdigastrisch gelegen lymfkliertjes. Bij 24.6% (16/65) van de patiënten was préoperatief sprake van dysfunctie van de nervus facialis of één van haar takken. Bij 8 van deze patiënten betrof het een adenocarcinoom. De helft van deze groep van 16 patiënten overleed aan hun ziekte, hetgeen de slechte prognose van betrokkenheid van de nervus facialis bevestigt. Geen van de tien patiënten bij wie de nervus facialis van de tumor werd gepeld, die allen werden nabestraald, ontwikkelde een recidief terwijl bij een ieder de functie van de nervus facialis volledig intact bleef. Deze bevindingen ondersteunen en rechtvaardigen in geselecteerde gevallen een conservatieve houding ten opzichte van de nervus facialis en onderstrepen de waarde van postoperatieve radiotherapie bij patiënten met microscopisch tumorresidu. Tenslotte kan niet genoeg benadrukt worden dat het van belang is de diagnose 'maligne speekselkliertumor' in een zo vroeg mogelijk stadium te stellen.

In ***hoofdstuk 7*** wordt de waarde van 'Magnetic Resonance Imaging' (MRI) voor de differentiële diagnostiek van parapharyngeale tumoren besproken. Tussen 1987 en 1993 werden 14 patiënten met een parapharyngeale tumor middels MRI geëvalueerd. Glomus vagale tumoren (n=3), presenteerden zich in het poststyloide compartiment van de parapharyngeale ruimte met 'flow voids' op de T1-Spin Echo (SE) opnamen waarbij de arteria carotis interna naar ventraal en mediaal was verplaatst. De speekselkliertumoren (n=9), presenteerden zich in het prestyloide compartiment van de parapharyngeale ruimte, zonder flow voids, terwijl de arteria carotis interna naar dorsaal was verplaatst of zich in een normale positie bevond. MRI is de eerste keuze van onderzoek methode bij de differentiële diagnostiek van parapharyngeale tumoren, met name betreffende het onderscheid tussen vasculaire en solide tumoren. Middels MRI vastgestelde 'flow voids' zijn

karakteristiek voor vasculaire tumoren. Zij worden aangetoond op T1- SE opnamen. Bij vasculaire tumoren dient vervolgens een angiografie te worden verricht. Met behulp van de T1-Gradient Echo (GE) opnamen wordt optimale informatie verkregen over de positie van de arteria carotis interna ten opzichte van de tumor. Voorts kunnen aanvullende T2-SE opnamen waardevolle informatie verschaffen over de aard van de tumor. Bij solide tumoren kan dunne naald aspiratie cytologie van nut zijn voor de differentiatie tussen benigne en maligne tumoren.

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Curriculum Vitae

De auteur van dit proefschrift werd geboren op 9 juli 1961 te Doorn. Hij studeerde van 1981 tot 1989 geneeskunde aan de Vrije Universiteit te Amsterdam. Van 1 september 1989 tot 1 juni 1990 was hij werkzaam als assistent chirurgie (AGNIO) in het Onze Lieve Vrouwe Gasthuis te Amsterdam. Van 1 juni 1990 tot 31 december 1996 was hij werkzaam bij de afdeling Keel-, Neus-, en Oorheelkunde van het Academisch Ziekenhuis van de Vrije Universiteit te Amsterdam. Oorspronkelijk als AGNIO, later, vanaf 1 januari 1992 als AGIO (assistent geneeskunde in opleiding). In september 1994, tijdens de perifere stage van de opleiding, werd deze klinisch-pathologische studie gestart. Sinds januari 1997 is de promovendus werkzaam als staflid op de afdeling Keel-, Neus-, en Oorheelkunde van het Academisch Ziekenhuis Utrecht. Vanaf 1 januari 1998 als 'Chef de Clinique'.

List of publications

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