Introduction: Epidemiology, Risk Factors, Pathology, and Natural History of Head and Neck Neoplasms

Vincent Vander Poorten

Contents

Abstract

This introductory chapter sets the scene for the book by defining the complex domain in which the head and neck radiologist is expected to make his diagnosis. The epidemiology of epithelial and non-epithelial head and neck tumors is discussed representing up-to-date frequency measures. The known risk factors are subsequently reported. After that the clinical and pathological specifics of the most frequent tumors are presented, along with the expected natural history, so that the head and neck radiologist is aware of the different stages of the disease and the radiological "snapshots" that can result from imaging at different points in the evolution of the disease. Both macroscopic and microscopic aspects are illustrated by to-the-point clinical and light-microscopical pictures.

Head and neck cancer can be divided into two major groups. The largest group, the epithelial malignancies of the mucosal membranes of the upper aerodigestive tract, is called head and neck squamous cell carcinoma (HNSCC) and accounts for 90% of all head and neck neoplasms (Greenlee et al. 2001). The second important but smaller group are the "glandular neoplasms", arising in the thyroid and in the salivary glands.

Skin cancer is considered a separate entity and so is non-melanoma skin cancer of the head and neck. Non-melanoma head and neck skin cancer includes mainly squamous cell carcinoma and basal cell carcinoma, the latter being 3–4 times more frequent than the former (IARC 2008a). Infrequent head and neck

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neoplasia include localized lymphoma, soft tissue and bone sarcoma, and neuroectodermal tissue tumors (paraganglioma, olfactory neuroblastoma, neuroendocrine carcinoma, malignant melanoma). For information about these types we refer the reader to the specific head and neck oncology literature.

In this introductory chapter the first paragraph deals with epidemiology and risk factors of head and neck neoplasms. An overview of the pathology and natural history of the most frequent benign and malignant head and neck neoplasms is outlined in the second paragraph.

1 Epidemiology: Frequency Measures and Risk Factors

1.1 Frequency Measure: Incidence

Head and Neck Cancer, excluding skin cancer and Hodgkin and Non Hodgkin lymphoma localized in the head and neck, is the sixth most frequent cancer worldwide. The currently estimated world incidence of epithelial malignancies of the mucous membranes is over 600,000 new cases per year, and these are 160,000 laryngeal, 389,000 oral, and 65,000 pharyngeal cancer cases, resulting in 300,000 deaths yearly (IARC 2008b). Thus, in 2008 6.8% percent of the incidence of cancer could be attributed to these neoplasms (Ferlay et al. 2010). Likewise, in the European Union 5% of the cancer burden was caused by oral, pharyngeal, and laryngeal cancer, and 1% by thyroid cancer (IARC CancerBase N°4 1999). Comparing the two largest groups, HNSCC and thyroid cancer, a definite gender difference in incidence is apparent. As an example, the most recent world incidence of laryngeal SCC shows a male–female ratio of 6/1, whereas for incidence of thyroid cancer, the odds are opposite with a ratio of 1/3 (Ferlay et al. 2010). The incidence of thyroid cancer has been steadily increasing in the last 40 years with a factor of 2.3, mainly due to a rise in papillary thyroid cancer, while the incidence of other types remained unchanged. This rise is mainly due to better detection methods and awareness, but also to a true rise in incidence as reflected by an increased incidence of large tumors and tumors displaying extrathyroidal extension (Morris and Myssiorek 2010; Sipos and Mazzaferri 2010). The incidence of salivary gland cancer is at the subpercentual level when looking at cancer in general, but is responsible for between 1 and 7% of head and neck cancer incidence (Kane et al. 1991; Spiro and Spiro 2001).

There is an important geographical variation in head and neck cancer incidence. A specifically high incidence is observed in much of Southern Asia, Australia, Brazil, Southern Africa, and parts of Central and Southern Europe. Nasopharyngeal cancer typically arises in southern China (Mehanna et al. 2010). The incidence of hypopharyngeal cancer is typically very high in Northern France (10/100,000 males/year) as compared to e.g. the United States of America (2/100,000 males/year). The incidence of laryngeal cancer in Northern Spain (20/100,000/year) is about 200 times as high as compared to certain regions in China (0.1/100,000/year) (IARC 1997; Hoffman et al. 1998). Besides probable differences in genetic susceptibility, a different prevalence of strong risk factors (e.g. Calvados drinking, smoking habits) undoubtedly explains these differences. In the same way, observed differences in incidence among races (higher incidence in African versus Caucasian Americans) (Day et al. 1993), and among men and women, can be largely attributed to differences in risk factor exposure (De Rienzo et al. 1991).

1.2 Risk Factors for the Development of Head and Neck Malignancies

1.2.1 Risk Factors for Development of HNSCC

The most important risk factor is chronic use of tobacco (smoking and smokeless such as betel quid chewing) and alcohol (Fig. 1). The reason that these factors are so important is twofold: a strong association with the disease on the one hand, and a very high prevalence among the population on the other. They are two independent risk factors that have been shown clearly to act in a multiplicative way when combined. Figure 2 shows that a 5.8 times increased risk for development of oral and pharyngeal cancer is observed in non-smokers who use 30 or more drinks/week, a 7.4 times increased risk in smokers not using alcohol with a history of 40 or more pack-years (smoking 20 cigarettes/day during 40 years), whereas the person combining the two has a 38 times increased risk (Blot et al. 1988; Hashibe et al. 2007).

Fig. 1 Smoking is the most prevalent and most powerful risk factor for the development of HNSCC. A doubled incidence of Warthin's tumor of the parotid gland has also been observed

Conversely, after cessation of the use of tobacco, the risk of oral mucosal dysplasia and cancer falls to the level in the population that never smoked after 15–20 years (Marron et al. 2010; Morse et al. 1996).

A recent pooled analysis based on over 11,000 cases and 16,000 controls shows that approximately 72% of HNSCC cancers are attributable to these two exposures, ranging from 64% for oral cavity cancer, over 72% for pharyngeal cancer, to 89% for laryngeal cancer. The strong interaction Blot et al. already described in 1988 between the two exposures was again confirmed (Hashibe et al. 2007).

The carcinogens in tobacco are nitrosamines, polycyclic aromatic hydrocarbons, and aldehydes. Nitrosamines are alkylating agents that induce mutational events. Alcohol acts as a solvent and thus enhances permeability of the mucosa for the toxic substances in tobacco.

A direct effect of alcohol is ascribed to mucosal enzymatic formation (alcohol dehydrogenase) of the carcinogenic acetaldehyde. This was recently supported by the finding that individuals homozygous for the *2 allele of aldehyde dehydrogenase 2 (ALDH2), who do not support alcohol intake because of their inability to metabolize acetaldehyde, have a significantly reduced incidence of head and neck cancer. People who have an efficient *1*1 homozygous variant allele of ALDH2 do produce acetaldehyde and do develop HNSCC, whereas *1*2 heterozygous ALDH2 patients who have a sixfold increased level of acetaldehyde in their blood following alcohol consumption due to a sixfold reduced metabolism of acetaldehyde have the highest incidence of HNSCC (Boccia et al. 2009).The sites that are most at risk for alcohol induced carcinogenesis are the oro- and hypo-pharyngeal mucosal surfaces (Brugere et al. 1986), much more than the glottic larynx, where only very high alcohol intakes can be shown to independently increase HNSCC risk.

Indirectly, alcohol consumption brings along intake of non-alcoholic carcinogenic compounds in alcoholic drinks e.g. nitrosodimethylamine in beer and tannin in wine. Furthermore, high intake of alcoholic beverages entails nutritional deficiencies, which in turn also increases the risk of HNSCC development. With poor nutrition, the proven protective effect of high intake of fruits and vegetables is lost. Indeed, a diet rich in fresh fruit and vegetables is associated with a 50–70% reduction in the incidence of HNSCC (De Stefani et al. 1999). Especially dark yellow vegetables, citrus fruits (rich in vitamin C) and the carotene-rich vegetables (fresh tomatoes, carrots, pumpkins) are protective, mainly due to antioxidant micronutrients in these vegetables such as vitamin C, vitamin E, beta carotene, and flavonoids (La Vecchia et al. 1997). Less proven but also suggested protective is the use of olive oil (Franceschi et al. 1999) and high fibre intake (De Stefani et al. 1999). A recent study pooling available data indicates a significant protective effect of coffee drinking on the risk of developing oral and pharyngeal cancer (Galeone et al. 2010).

Given the factors enumerated above, it is understandable that socio-economic status is strongly associated with the development of HNSCC. A total of 75% of patients live in the lower social classes, in terms of level of education and income. One in three patients has no partner and one in six patients is unemployed at the time of diagnosis. This social situation is a risk factor for having the direct risk factors of tobacco, alcohol, and poor dietary habits. There is also a lower level of oral hygiene. Once cancer is established, people in lower socio-economic groups will seek medical help later because of less education

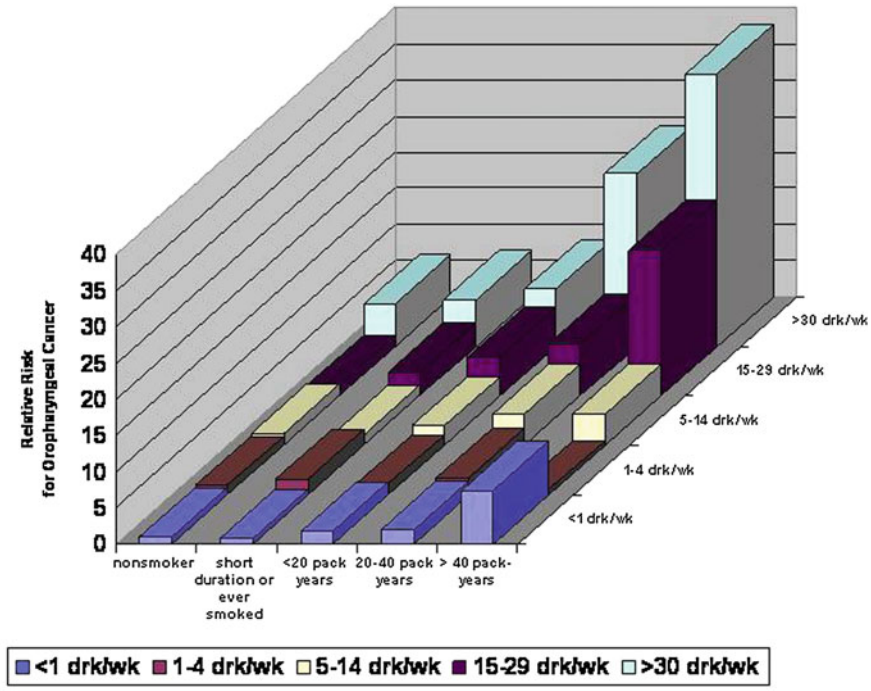

Fig. 2 Relative risk for oropharyngeal cancer for males according to amount of tobacco and alcohol use. (based on data from Blot WJ, et al. Cancer Research 1988; 48:3282–7, with permission)

and more difficult access to the health system, and thus will present with more advanced stages of disease. Another reason for advanced disease at presentation lies in the fact that often a significant part of caloric intake is provided for by alcohol and thus symptoms such as dysphagia for solid food will become problematic later. Stage at presentation is the strongest negative prognostic factor for outcome of treatment in HNSCC. Treatment of the advanced stages of HNSCC often has a serious impact on physical and psychological functioning. Great effort is needed to adapt to the resulting altered body image, to get integrated back into society, and also to achieve the change in lifestyle needed to prevent occurrence of second primary HNSCC. Unfortunately, following treatment, patients in lower social classes are often isolated to face this difficult challenge. Return to occupation thus becomes an illusion for the majority of these patients (Lefebvre et al. 2001). It is clear that a lower socio-economic environment is a strong negative prognostic factor for the oncologic results following treatment, and also for survival in general because of the impact of many of the comorbidities that result from the previous way of living (pulmonary insufficiency, atherosclerosis, liver disease, etc.) (Robertson et al. 2010).

Recently the role of genetic predisposition, previously suggested by small studies, has been confirmed. A family history of HNSCC in a first degree relative is associated with a 1.7 fold increased risk of developing the disease (Conway et al. 2009). This is attributed to polymorphisms in genes encoding enzymes for the metabolism of tobacco and alcohol, reduced metabolism implying an increased risk of the disease. A meta-analysis of 31 studies showed that a polymorphism in *GSTM1*, which encodes glutathione S transferase, involved in the metabolism of xenobiotics, was associated with a 1.23 increased risk of developing head and neck cancer (Hashibe et al. 2003). In the same way ALDH2 zygozity has been linked to differences in HNSCC development, as previously outlined (Boccia et al. 2009).

Viral infections also have been implicated in the carcinogenesis of HNSCC (Franceschi et al. 1996). Human Papilloma Virus (HPV) DNA is in the spotlight nowadays and held responsible for the recently observed increased incidence of oropharyngeal squamous cell carcinoma. This incidence showed no change between 1975 and 1999 but increased by 22% between 1999 and 2006 in the United States. The United Kingdom has seen a 51% increase in oral and oropharyngeal squamous cell carcinoma in men. This increased incidence seems accounted for by a rise in HPV-related oropharyngeal carcinoma, itself related to

altered sexual behavior (Heck et al. 2010). In a recent trial 64% of oropharyngeal cancers included were found to be HPV positive and these had a significantly better treatment outcome (Ang et al. 2010). Epstein–Barr Virus (EBV) is strongly associated with nasopharyngeal cancer. EBV antibody titres are much higher in cases than in controls, and biopsy specimens of undifferentiated nasopharyngeal carcinoma patients are 100% EBV positive and monoclonal as to this virus (Jeannel et al. 1999). EBV titres following treatment are used to monitor patients for disease recurrence. Patients infected with the human immunodeficiency virus (HIV) are at higher risk of developing HNSCC and Kaposi's sarcoma.

Among environmental factors, chronic sun exposure induces skin and lip cancer. Occupational factors have been implied in HNSCC development. Working in industries associated with higher exposure to aromatic amines and phenoxy herbicides confines an elevated risk for all sites. A specific strong association has been repeatedly described between specific industries and the development of sinonasal cancer. The rate of development of SCC of the sinonasal tract is increased 250 times in workers exposed to nickel (Pedersen et al. 1973).Working with wood in environments without an aspiration system for dust particles results in a 500–1,000 fold increase in the baseline incidence of sinonasal "intestinal type" adenocarcinoma and has led in several countries to the recognition of this cancer as an occupational disease and to stringent safety precautions to minimize dust exposure (Acheson et al. 1968).

1.2.2 Risk Factors for Development of Glandular Neoplasms

Radiation exposure is the only firmly established environmental risk factor for the development of thyroid carcinoma. The information comes from scrutinized follow-up of atomic bomb survivors in Japan and atomic disaster survivors in Chernobyl (UNSCEAR 2000). Typically, a low-dose exposure (e.g. about 3 Gy) results in the development of mainly papillary thyroid carcinoma, some 5–10 years later. The risk follows a linear dose–effect relationship and the incidence can be increased by more than 30 times (Drozdovitch et al. 2010).

Radiation exposure also results in an increased incidence of both benign (Warthin's tumour) and malignant (mucoepidermoid carcinoma) salivary gland tumors in follow-up studies in the same cohorts (Saku et al. 1997). For Warthin's tumor, also a doubled incidence has been observed in smokers versus non-smokers (Gallo and Bocciolini 1997). Epstein–Barr Virus has been implicated in the genesis of bilateral Warthin's tumors and undifferentiated carcinoma of the salivary gland (Gallo 2001).

2 Pathology and Natural History of Frequent Benign and Malignant Head and Neck Neoplasms

In tumor pathology, tumor typing is the first important subject. Within different tumor types, the second subject is detection of features with prognostic significance, such as grading, perineural, or vascular invasion, and radicality of resection margins. Regarding histological typing of head and neck neoplasms, it has already been mentioned that a far majority consists of HNSCC. A detailed discussion of all tumor types encountered in the head and neck is beyond the scope of this chapter and for this the reader is referred to the surgical and pathological literature. What follows is an overview of the clinical course and pathological specificities for the most frequent tumor types.

2.1 Epithelial Neoplasms of the Mucous Membranes

2.1.1 Tumor Typing and Clinical Behavior

2.1.1.1 Benign Lesions

Benign papillary lesions are less frequently a reason for seeking medical attention than malignant and premalignant lesions. Oral, pharyngeal, and laryngeal sites can display squamous papillomas, which are white lesions with a wart-like appearance with no signs of deeper invasion. Part of these lesions (e.g. juvenile laryngeal papillomatosis) have been ascribed to HPV, type 6 and 11. Sinonasal papillomas are also called Schneiderian papillomas and can be exophytic, endophytic (inverted), or oncocytic in presentation. Especially the inverted papilloma is considered premalignant (Fig. 3). Most symptomatic epithelial neoplasms of the mucous

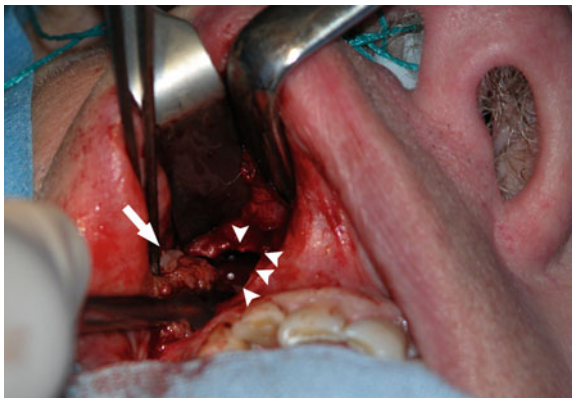

Fig. 3 Inverted papilloma (*arrow*) of the maxillary sinus being removed by Caldwell–Luc approach (antrostomy:*arrowheads*)

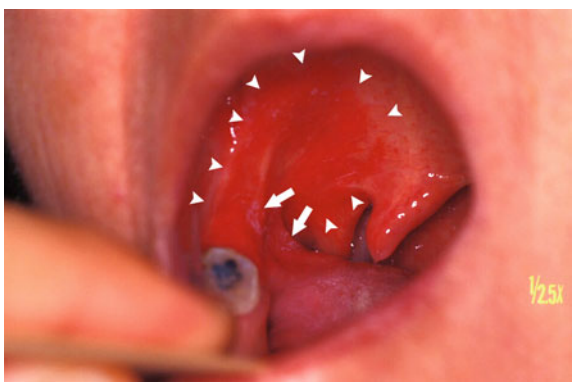

Fig. 4 Erythroplakia (*arrowheads*) with areas of nodular leukoplakia (*arrows*) of the tonsil, glossotonsillar sulcus, anterior tonsillar pillar, and hard and soft palate

membranes of the upper aerodigestive tract that bring patients to the doctor will turn out premalignant or malignant.

2.1.1.2 Premalignant Lesions

Premalignant lesions will often not be visualized on routine imaging studies. Macroscopically, we consider leukoplakia and related lesions: homogeneous leukoplakia versus non-homogeneous leukoplakia (nodular leukoplakia, erythroplakia, proliferative verrucous leukoplakia; Fig. 4). On the microscopical level epithelial hyperplasia, dysplasia, and carcinoma in situ can be discerned.

Leukoplakia is a descriptive clinical term used to describe "a white plaque or patch that cannot be characterized, clinically or histopathologically, as any other disease"(World Health Organization Collaborating Centre for Oral Precancerous Lesions 1978). Furthermore, in order to be designated as leukoplakia, the lesion should not be associated with any known physical (frictional keratosis, candidal leukoplakia) or chemical agent, except tobacco. It should also be impossible to scrape off the lesion.

Homogeneous leukoplakia is histologically either hyperortho- or hyperpara-keratosis and rarely shows dysplasia. Less frequent is non-homogeneous leukoplakia (nodular leukoplakia, erythroplakia, proliferative verrucous leukoplakia), mostly associated with dysplasia and thus much more at risk for becoming really malignant (Batsakis 2003). Dysplasia can be "mild", meaning that there is an increased number of mitotic figures and an abnormal cytologic appearance (loss of an orderly nuclear mosaic pattern, decreased nuclear/cytoplasmatic ratio, and an irregular random nuclear placement) only in the basal epithelial layer, whereas suprabasal mitosis and cytologic abnormality indicates "moderate" dysplasia. In "severe" dysplasia the atypical cells with mitotic activity can be observed everywhere from the basal to the superficial layers. The yearly malignant transformation rate of homogeneous leukoplakia is between 2 and 6% and is higher as the patient is older, female, and as the lesion persists for a longer time. The malignant transformation rate in non-homogeneous (speckled) leukoplakia and erythroplakia is more than 50% (Silverman et al. 1996).

2.1.1.3 Malignant Lesions

Less frequent specific clinical entities are verrucous carcinoma, papillary SCC, basaloid squamous cell carcinoma, and sarcomatous SCC, increasingly aggressive in that order. Verrucous carcinoma is an exophytic papillomatous low grade SCC, very well differentiated, without potential for regional or distant metastasis (Medina et al. 1984). Papillary SCC displays an exophytic growth with a poorly differentiated cell layer lining a central fibrovascular core. Its behavior is more aggressive than verrucous carcinoma, wherein metastasis is observed. Basaloid SCC and sarcomatoid SCC are highly aggressive SCC variants.

Most HNSCC are simply called "invasive squamous cell carcinoma" and can be graded into well, moderately, and poorly differentiated, paralleling the amount of keratin formation by cells. SCC cells by definition produce intercellular bridges. (Figs. 5, 6) Absence of these bridges is one of the features of undifferentiated SCC. This type of tumor occurs most frequently in the nasopharynx and is often diagnosed

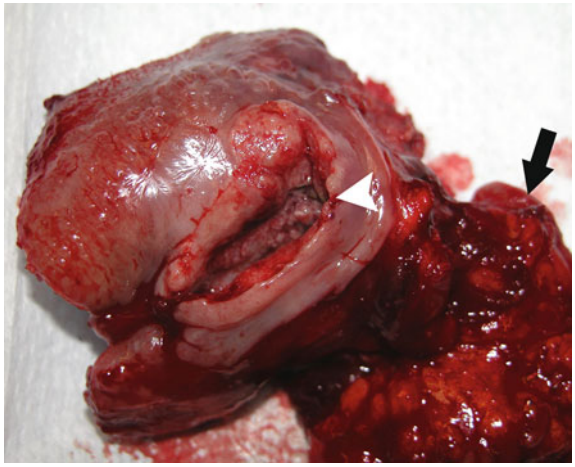

Fig. 5 Hemiglossectomy for ulcerative and deeply invasive well-differentiated squamous cell carcinoma of the lateral tongue (*arrowhead*). Specimen in continuity with radical neck dissection (*arrow*)

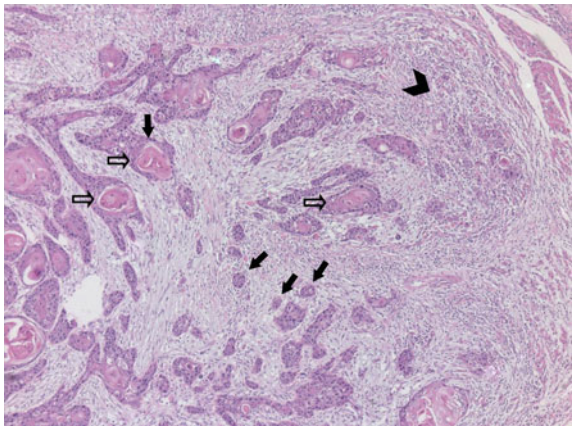

Fig. 6 Microscopical appearance of the same tumor. Note the diffuse infiltrative aspect of the tumor islets (*arrows*), the dense mononuclear inflammatory reaction (*arrowhead*), and the formation of keratin pearls (*hollow arrows*) Picture courtesy of Prof. Raf Sciot

because of massive neck lymph node metastasis already present at initial diagnosis, frequently bilaterally, and involving the posterior neck (region V).

2.1.2 Natural History Before and at Diagnosis

The presenting symptoms of HNSCC depend very much on the site of origin within the head and neck and the functions that thus are interfered with. Table 1 lists the typical alarming symptoms that

Table 1 Alarming symptoms and signs urging specialist referral

Symptoms
Throat pain
Hoarse voice
Swallowing impairment
Neck lump
Unilateral ear pain—hearing loss
Stridor
Epistaxis—haemoptoe
Unilateral nasal obstruction
Signs
Cranial nerve palsy (recurrent laryngeal, abducens, sympathetic chain, facial,…)
Red or white patch on oral mucosa
Ulceration of mucous membranes
Swelling
Unilateral serous otitis
Prooptosis
Neck lump
Skin infiltration
Hypoesthesia (mental nerve, infraorbital nerve,…)

demand urgent specialist referral. Many patients with oral and pharyngeal cancer will present at an advanced disease stage, because of the late occurrence of symptoms and the social situation with more difficult medical access. Patients with glottic cancer tend to present at earlier stages, given the rapid voice disturbance of even a small vocal cord lesion. Early glottic cancer is also not likely to result in regional metastasis and thus often has a good prognosis following radiotherapy or surgery, with 5-year survival rates of 70–100% (Lydiatt and Lydiatt 2001). Advancing stage, and origin of SCC in other anatomical subsites of the upper aerodigestive tract, are associated with lesser chances for successful treatment, and for the specifics the reader is referred to the specific head and neck oncological literature.

2.1.3 Natural History Following Diagnosis and Successful Treatment of Malignant HNSCC

The annual incidence of second primary cancer following successful treatment of an index HNSCC is 3–7%. A known feature in HNSCC is field

cancerization of the upper aerodigestive tract: several synchronous and also metachronous primary carcinomas and areas of moderate to severe dysplasia—carcinoma in situ are observed with areas of normal mucous membranes in between. This is caused by exposure of the entire upper aerodigestive tract to the same carcinogens—usually combined alcohol and tobacco. Patients are especially at risk of developing lung cancer, esophageal and gastric cancer, and a new localization of HNSCC. A change in lifestyle is essential to decrease the incidence of second primaries, but this is often complicated by the social context of the patient.

2.1.4 Microscopical Negative Prognostic Findings

Table 2 lists the important findings to routinely determine during microscopical analysis following resection of a primary HNSCC and its regional lymph nodes. These features carry a worse prognosis and thus contribute to the decision making on the need for further therapy, c.q. postoperative (chemo) radiotherapy. Many of these parameters (cTNM classification, perineural growth, tumour thickness, extracapsular spread in metastatic lymph nodes) can already be strongly suspected on a preoperative high quality imaging study.

Table 2 Histopathological negative prognostic factors in HNSCC

(p)TNM classification (Size of primary tumor, number/laterality of positive nodes, size of largest node)
Vascular invasion
Perineural growth
Resection margins (e.g. <5mm is considered "close margins" in oral cancer)
Thickness
Invasive front
Differentiation
Exophytic versus endophytic growth pattern
Field cancerization
Mitotic index
Presence of extracapsular spread in metastatic lymph nodes

2.2 Glandular Neoplasms

2.2.1 Thyroid Neoplasia

2.2.1.1 Benign Disease: Multinodular Enlargement

Benign multinodular goitre affects almost one in three persons worldwide (Delange 2000). Iodine deficiency is the most frequent contributory factor. In areas where iodine supply is sufficient, the prevalence of clinically detectable goitres is less than 4%, and results from elevated Thyroid Stimulating Hormone (TSH) levels or from elevated stimulation of the TSH receptor (such as in Graves' disease and nonatrophic Hashimoto's goitres). Most patients with multinodular goitre are asymptomatic. Medical concerns arise when compressive symptoms appear (Fig. 7), when autonomous hyperfunction appears, or when malignancy is feared. The latter is feared in rapidly enlarging goitres, enlarging lymph nodes, especially in patients with prior radiotherapy to the neck, or when fine needle aspiration cytology (FNAC) of dominant nodules indicates

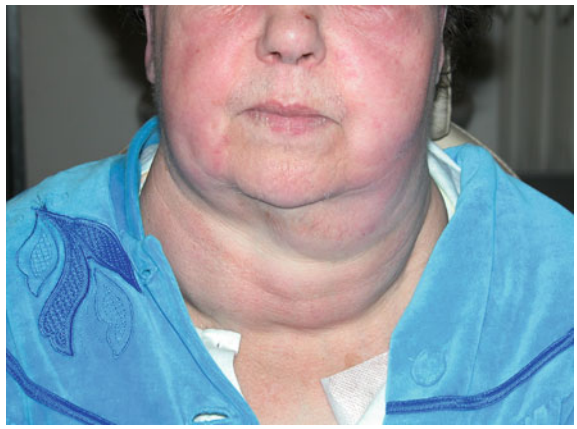

Fig. 7 Large multinodular goitre with pharyngeal, esophageal, and tracheal compression

papillary carcinoma or a microfollicular lesion. A microfollicular lesion can be follicular carcinoma in about one in ten patients. Ultrasound is crucial in determining which nodule in a multinodular goitre merits evaluation by FNAC (Cooper et al. 2006; Frates et al. 2005) (see " Thyroid and Parathyroid Neoplasms").

Macroscopically, following thyroidectomy, we usually see a polynodular, soft, and globally enlarged thyroid gland (Fig. 8). There may be one or more larger nodules which deserve subsequent microscopical analysis. Up to 70% of hyperplastic nodules are clonal, neoplastic proliferations (Kopp et al. 1994). Microscopically, within the nodules, there is a varied pattern of large and small follicles, usually with

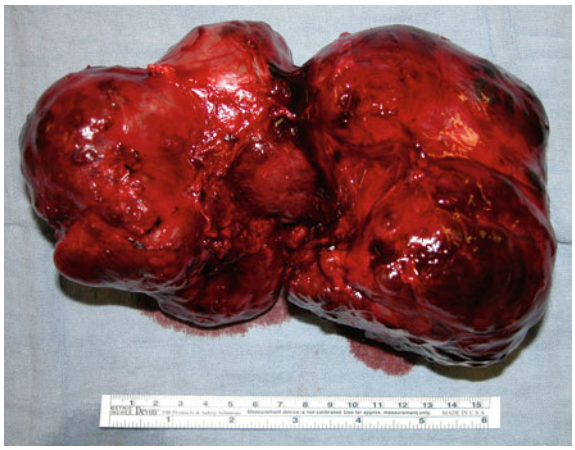

Fig. 8 The same goitre following resection

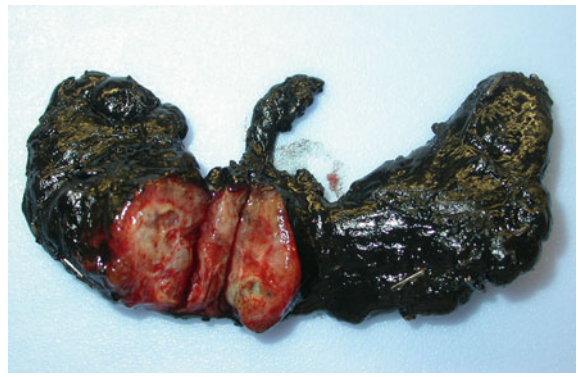

Fig. 9 Thyroidectomy specimen showing papillary carcinoma on cut surface in the left lobe and the isthmus. *Posterior view*. The specimen is inked to assess resection margins

abundant colloid. There is an often oedematous stroma with fibrosis, macrophages, hemosiderin, and calcifications.

2.2.1.2 Benign Disease: Uninodular Enlargement—the Solitary Thyroid Nodule

Any clinically visible or palpable nodule, and "any discrete macroscopic intrathyroidal lesion clearly distinguishable from the adjacent normal thyroid parenchyma" on ultrasonography or Technetium scanning should lead to actions to estimate the chance of malignancy (Hay and Klee 1993). As for multinodular goitre, the next step will be an ultrasound guided FNAC in any nodule showing worrisome features. A solitary thyroid nodule can be a degenerative lesion such as a cyst or a degenerative colloid nodule, or a benign or malignant neoplastic lesion. The global incidence of cancer in patients with a thyroid nodule is 10%, increasing for women or men older than 50 to 30 and 45% respectively (Tezelman and Clark 1995). The rest will be benign, where nine out of ten will be follicular adenomas, the remainder being mostly Hürthle cell adenomas. Macroscopically, adenomas are well demarcated from the adjacent parenchyma, and fleshy and pale, sometimes cystic or hemorrhagic on cut surface. The microscopic appearance of a solitary adenomatous nodule displays large and small follicles with a lot of colloid and a stromal component with hemosiderin, macrophages, fibrotic changes, and often calcifications. A Hürthle cell variant displays oncocytic cells, with an intensely eosinophylic cytoplasm due to a lot of abnormal mitochondria, and large vesicular nuclei.

2.2.1.3 Malignant Disease

An important issue in suspected malignant thyroid disease is the avoidance of iodine containing contrast medium in imaging studies for thyroid lesions. "Differentiated thyroid cancer" (see below) are tumors concentrating iodine due to preserved expression of the sodium–iodine symporter (NIS). They hence can be effectively and selectively treated with radioactive iodine. This treatment, however, will be delayed by about 3 months following an imaging study using iodine contrast medium, due to saturation of the iodine binding capacity of the targeted thyroid cancer cells.

Generally, a distinction is made between "differentiated thyroid cancer" with a relatively good (papillary, follicular, mixed papillary follicular carcinoma) to intermediate (Hürthle cell carcinoma) prognosis, and cancers with worse (medullary thyroid cancer) to fatal prognosis (anaplastic thyroid cancer). Of malignant tumors, the thyroid harbors both the tumors with the best (papillary) and the worst (anaplastic carcinoma) prognoses.

2.2.1.4 Papillary Thyroid Cancer

Papillary cancer is the most frequent thyroid cancer (85% belong to this group) (Sipos and Mazzaferri 2010). Overall women are affected three times more frequently than men. The clinical picture is usually a symptomless thyroid swelling, although enlarged lymph nodes may be the presenting feature (Fig. 9). Indeed, regional metastasis to the paratracheal (level VI–VII) and cervical (level II, III, and IV) lymph nodes is observed in one out of two patients at

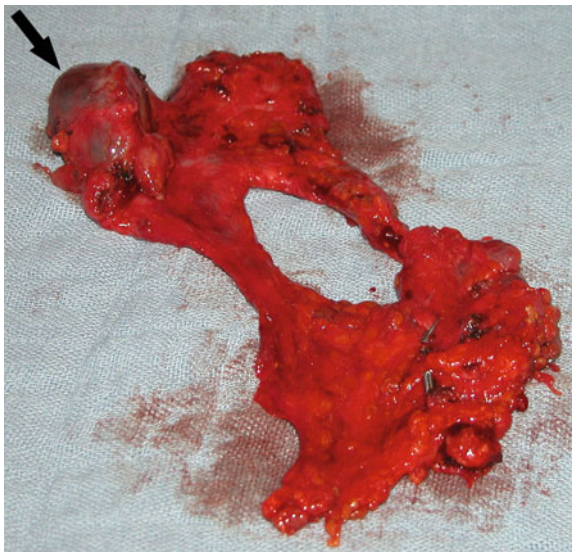

Fig. 10 Functional neck dissection specimen showing a typical *black* cystic metastatic neck node of papillary thyroid carcinoma (*arrow*)

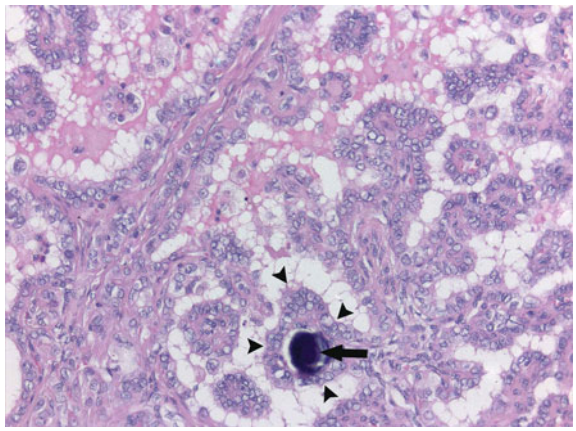

Fig. 11 Microscopical appearance of papillary thyroid cancer. Psammomabody (*arrow*) and papillary growth pattern (*arrowheads*). Picture courtesy of Prof. Raf Sciot

presentation (Fig. 10). Distant metastasis usually occurs late in the disease course.

Following thyroidectomy, macroscopically typical features are multifocality and bilaterality, occuring in up to 87% of specimens (Russell et al. 1963). Lymph node metastasis is often cystic and dark bluish in appearance (Fig. 10).

Microscopically only 3% is true papillary carcinoma and 97% is "follicular variant of papillary carcinoma". Both forms have an equally good prognosis, with overall up to 95% of patients surviving 20 years following treatment (Hay and Klee 1993).

Essential for the diagnosis are the papillae with a central fibrovascular core and an epithelial lining showing the typical nuclear features with overlapping nuclei and nuclear grooves, making an FNAC diagnosis possible. Psammoma bodies, calcific concretions with concentric laminations, are observed in about 1 in 2 of these tumors, mostly already on FNAC. (Fig. 11).

Genetically, about 39% of papillary cancers display a *BRAF* proto-oncogene mutation. This aspect was extensively studied by many authors and found associated with extrathyroidal extension, multicentricity, advanced stage, nodal metastasis, advanced age at presentation and higher frequency of recurrent or persistent disease. Other authors, however, were not able to confirm this negative prognostic effect of a *BRAF* mutation.

Rare subforms of papillary cancer with definite worse prognosis are the "tall cell" and "insular" variants (Sipos and Mazzaferri 2010).

2.2.1.5 Follicular Thyroid Cancer

About one in ten thyroid malignancies are follicular carcinomas. These are macroscopically solitary, encapsulated tumors. The features discriminating them from their benign follicular adenoma counterparts are microscopical vascular invasion and full thickness capsular invasion into the adjacent normal thyroid parenchyma. To be able to search the entire capsule for areas of invasion, all solitary nodules where FNAC suggests a "follicular lesion", should be excised with capsule and surrounding thyroid tissue. A minimal capsular invasion defines a subgroup of minimally invasive follicular carcinomas, behaving essentially as follicular adenomas. The tendency for vascular invasion in invasive follicular carcinoma explains that metastasis is primarily haematogenous to the lungs and the bones, rather than to the cervical lymph nodes, as observed in papillary cancer. Prognosis is somewhat less than for papillary carcinoma, with an overall 20-year survival of 81% (Shaha et al. 1995).

2.2.1.6 Hürthle Cell Carcinoma

Hürthle cell carcinomas are also solitary, encapsulated tumors that are distinguished from their benign counterparts by the presence of capsular and vascular invasion. They have an intermediate prognosis of about 65% 20-year survival (Shaha et al. 1995).

2.2.1.7 Medullary Carcinoma

Somewhat less than one in ten are medullary thyroid carcinomas (MTC). MTC is a malignant tumor of the calcitonin-secreting parafollicular C cells. These cells are embryologically maximally located in the upper two-thirds of the thyroid and this explains that tumors are usually found in that upper part of the gland. The tumors can occur in a usually unifocal sporadic form presenting in the age group of 40–60 years and constituting about 80% of MTC. An autosomal dominant hereditary form, due to a mutation in the Retinoblastoma (RET) proto-oncogen, can occur within the framework of Multiple Endocrine Neoplasia syndromes (MEN 2a: MTC, phaeochromocytoma, and parathyroid hyperplasia and MEN 2b: MTC, phaeochromocytoma and multiple mucosal neurinomas) or as familial medullary thyroid cancer (FMTC) without associated endocrinopathy. These hereditary forms usually occur earlier in life and are often multifocal in both thyroid lobes. In patients with MTC, lymph node metastasis, often bilateral, is frequently present at diagnosis and has a negative prognostic impact.

Microscopically, the diagnosis is suggested by the presence of amyloid and confirmed by immunostaining for calcitonin, chromogranin an carcino embryonic antigen (CEA). The 20-year survival following adequate treatment of MTC is about 65% (Moley 1995).

2.2.1.8 Anaplastic Carcinoma

About 5% of thyroid cancers are anaplastic carcinomas. This is a highly lethal variant which is rapidly progressive and almost universally fatal. Patients are usually 60–75 years old and present with a rapidly enlarging mass in the neck. Frequently, at presentation there are already signs of invasion of the surrounding structures: hoarseness due to recurrent laryngeal nerve paralysis, respiratory obstruction following tracheal compression or invasion, dysphagia due to esophageal invasion. Surgical treatment is almost never satisfactory and can only exceptionally be considered in the rare patient where disease is still intrathyroidal. Most patients are treated with radiotherapy with or without chemotherapy and survival is measured in months (Fig. 12).

The clinical diagnosis can sometimes be confirmed by FNAC, but often an incisional biopsy is performed to rule out thyroid lymphoma. Macroscopically, the surgeon performing an incisional biopsy sees a gray, hard, necrotic, and hemorrhagic tumor. Microscopically, there is a high mitotic index, marked cellular pleomorphism, necrosis, and tumor extension in blood vessels.

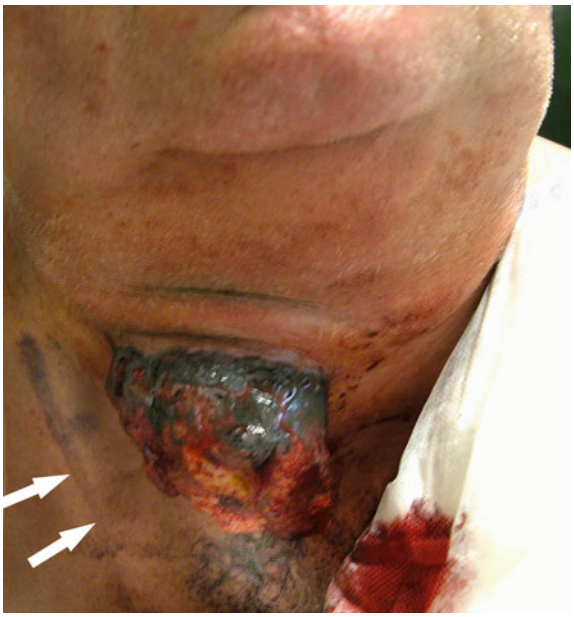

Fig. 12 Anaplastic thyroid carcinoma, growing through the dehiscent incision of the previous biopsy, during the radiotherapy. Note the tattoo on the skin of the patient demarcating the radiation field (*arrows*)

2.2.2 Salivary Gland Neoplasia

A distinction is made between the paired major salivary glands (parotid, submandibular, and sublingual) and the minor salivary glands. The latter are the 500–1,000 seromucous glands that are found throughout the entire upper aerodigestive tract, located in the oral cavity including lips, floor of mouth, cheek mucosa, tongue, soft and posterior hard palate, but also the nasal cavity, paranasal sinuses, nasopharynx, middle ear, Eustachian tube, oropharynx, hypopharynx, and even trachea (Ellis and Auclair 1996a). The majority of tumors (64–80%) arise in the parotids, 15–32% of which are malignant. Seven to 11% arise in the submandibular glands, 41–45% being malignant. Less than 1% of salivary gland tumors occur in the sublingual gland, most of these (70–90%), however, are malignant. Minor salivary gland tumors form 9–23% of the entire group, one in two being malignant (Ellis and Auclair 1996b). This observation results in the didactic rule "the smaller

the salivary gland, the less frequent a tumour arises in it, but the more frequently malignancy is involved".

2.2.2.1 Tumor Typing and Clinical Behavior

The extensive list of salivary gland tumor types is listed in Table 3, which is based on the 2005 World Health Organization Classification (Barnes et al. 2005). The key features of the most frequent benign and malignant types are briefly presented.

2.2.2.2 Benign Tumors

Pleomorphic Adenoma

Pleomorphic adenoma is definitely the most frequent salivary gland tumor and accounts for up to 70% of parotid tumors, 50% of submandibular salivary gland tumors, 35% of the minor salivary gland tumors, and 6% of sublingual tumors (Ellis and Auclair 1996b). Patients typically present with a long-standing, painless swelling (Fig. 13). Macroscopically, the tumor is well delineated from the normal salivary tissue, and this explains the old bad surgical practice to "shell the tumour out". The tumor is gray to white and lobulated on cut surface (Fig. 14). Microscopy shows a "mixture" of epithelial and mesenchymal (stromal) components in a varying combination and this explains the name "pleomorphic" adenoma or "mixed" tumor (Fig. 15). The tumor is notorious for recurring, often in a multinodular way, following inadequate surgery. A 2–23% rate of becoming malignant, the so-called carcinoma ex pleomorphic adenoma, has been reported (Gnepp 1993). The rate of malignant degeneration increases with time of presence of the lesion (Eneroth and Zetterberg 1974).

Warthin's Tumor

Warthin's tumor is the second most frequent benign salivary gland tumor. It occurs exclusively in the parotid gland and the adjacent level II lymph nodes. Between 6 and 10% of parotid tumors are Warthin's tumors (Ellis and Auclair 1996b). There is a male to female preponderance of 5 to 1. Warthin's tumors can occur bilaterally in about 10% of patients (Heller and Attie 1988). Microscopically, there is typically a two-layered eosinophylic epithelium and a lymphoid stroma, hence the name adenolymphoma.

Table 3 The WHO 2005 histologic classification of benign and malignant salivary gland tumors (Barnes et al. 2005)

Adenomas
1. Pleomorphic adenoma
2. Myoepithelioma (myoepithelial adenoma)
3. Basal cell adenoma
4. Warthin's tumor (adenolymphoma)
5. Oncocytoma (oncocytic adenoma)
6. Canalicular adenoma
7. Lymphadenoma
7.1. Sebaceous
7.2. Non-sebaceous
8. Ductal papilloma
8.1. Inverted ductal papilloma
8.2. Intraductal papilloma
8.3. Sialadenoma papilliferum
9. Cystadenoma
Carcinomas
1. Acinic cell carcinoma
2. Mucoepidermoid carcinoma
3. Adenoid cystic carcinoma
4. Polymorphous low grade adenocarcinoma
5. Epithelial myoepithelial carcinoma
6. Clear cell carcinoma, not otherwise specified (NOS)
7. Basal cell adenocarcinoma
8. Sebaceous carcinoma
9. Sebaceous lymphadenocarcinoma
10. Cystadenocarcinoma
11. Low grade cribriform cystadenocarcinoma
12. Mucinous adenocarcinoma
13. Oncocytic carcinoma
14. Salivary duct carcinoma
15. Adenocarcinoma NOS
16. Myoepithelial carcinoma
17. Carcinoma in pleomorphic adenoma
18. Carcinosarcoma
19. Metastasizing pleomorphic adenoma
21. Small cell carcinoma
22. Large cell carcinoma
23. Lymphoepithelial carcinoma
24. Sialoblastoma

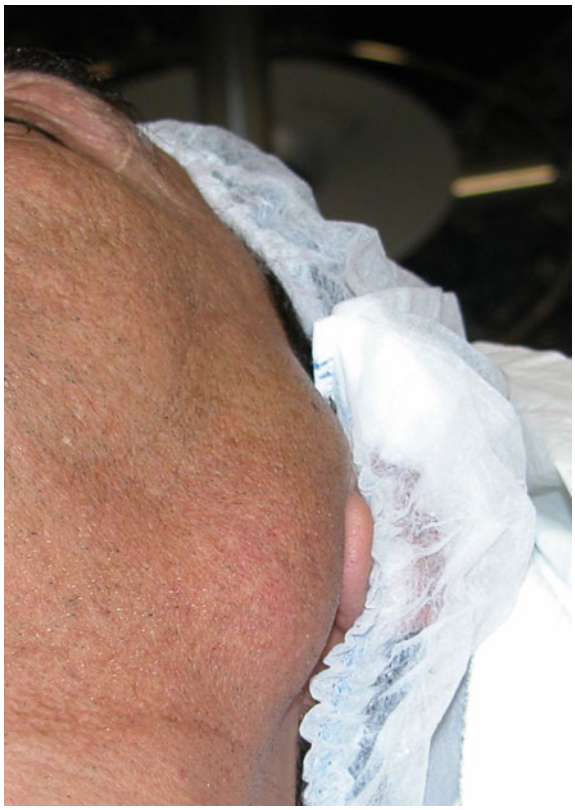

Fig. 13 Typical picture of a long-standing symptomless swelling in the *left* parotid region, following excision the diagnosis of pleomorphic adenoma was confirmed

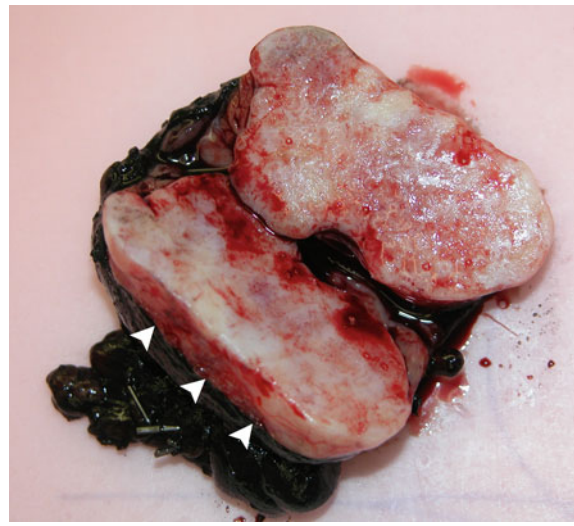

Fig. 14 Pleomorphic adenoma of the submandibular gland with a mainly mesenchymal-chondroid differentiation. *Grey* to *white* and lobulated on cut surface. Specimen inked for assessment of resection margins. Note the tumor looks easy to "shell out" (*arrowheads* demarcating the normal submandibular gland parenchyma that spontaneously retracts upon bisection of the gland)

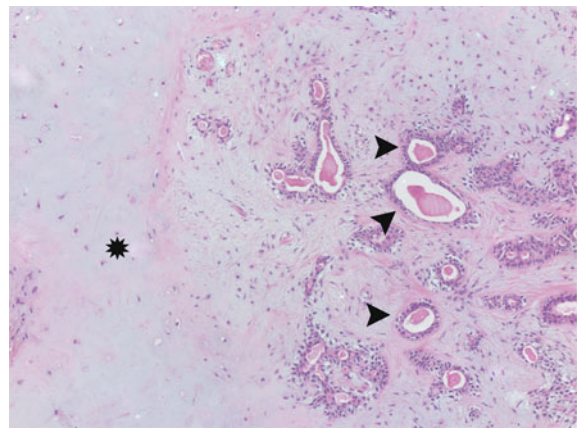

Fig. 15 Microscopical appearance of the same pleomorphic adenoma. Note the chondromyxoid matrix (*asterisk*), in which ductal structures (*arrows*) can be noted. Picture courtesy of Prof. Raf Sciot

2.2.2.3 Malignant Tumors

Mucoepidermoid Carcinoma

About one in six (Vander Poorten et al. 2003) to one in three (Spiro 1986) salivary gland cancers are mucoepidermoid carcinomas. Macroscopically, the cut surface is solid but can contain cysts. Microscopically, the tumor consists of a variable combination of glandular cells lining cystic spaces and epidermoid basaloid type cells forming solid areas (Fig. 16). A histological grading system is based on the relative proportion of mucinous versus epidermoid cells. Tumors containing 90% solid area made up of epidermoid cells are designated high grade (Seifert and Sobin 1992) and are associated with a 72% disease-specific death rate versus only 6–8% disease specific death rate in low grade, more mucus containing, low grade tumors (Healey et al. 1970).

Adenoid Cystic Carcinoma

Adenoid cystic carcinoma accounts for about one out of six parotid carcinomas (Vander Poorten et al. 2003). It occurs more frequently in other sites with about 45% of submandibular and minor salivary gland carcinomas being of this type (Vander Poorten et al. 1999a; Vander Poorten et al. 2000).

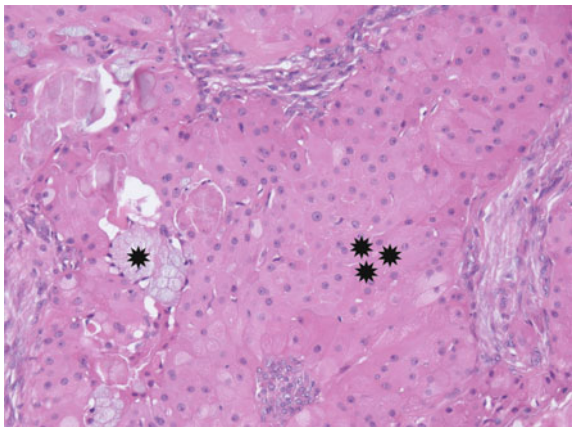

Fig. 16 Intermediate grade mucoepidermoid carcinoma of the parotid gland. Epithelial solid tumor (*3 asterisks*) with some islands of mucinous cells (*asterisk*). Picture courtesy of Prof. Raf Sciot

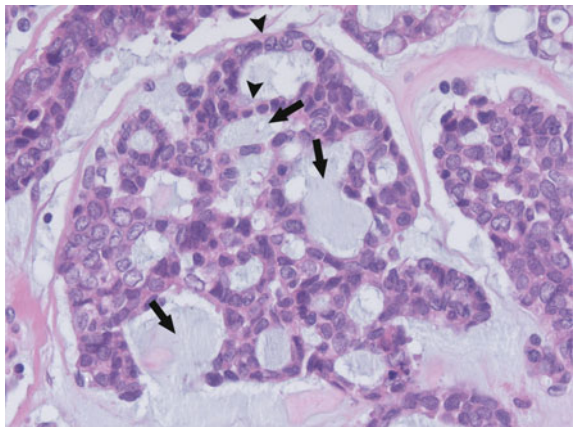

Fig. 18 Adenoid cystic carcinoma of the tongue base. Strands of tumor cells (arrowheads) grow in a cribriform pattern on a mucinous background (*arrows*) thus shaped as pseudolumina. Picture courtesy of Prof.Raf Sciot

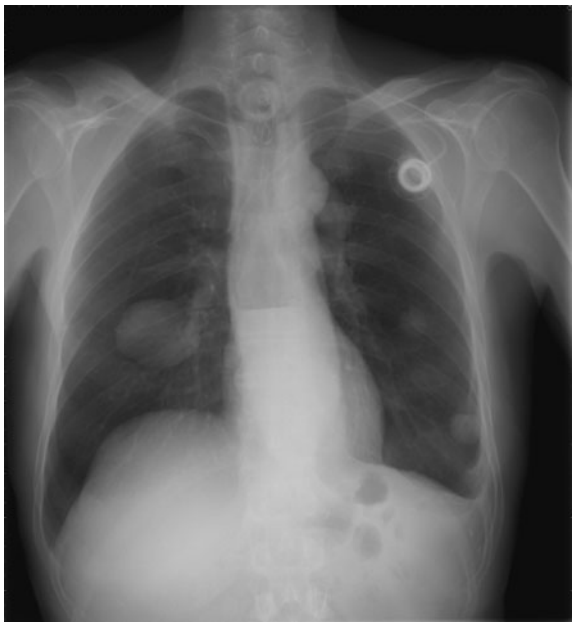

Fig. 17 Diffuse lung metastasis in a patient diagnosed with subglottic adenoid cystic carcinoma 10 years earlier

Macroscopically, it is an often infiltrating rather hard tumor with an irregular extension pattern. The tumor tends to extend via major cranial nerves and in this respect MR imaging is often essential to determine the real anatomical extent. It also has a well-known capacity for distant metastasis in about 40% of patients, (Spiro and Huvos 1992) mostly to the lungs (Fig. 17), and in these patients a protracted clinical course can result in disease-related deaths even after more than 10 years following the initial diagnosis (Spiro and Huvos 1992; Vander Poorten et al. 1999b). Microscopically, the tumor is often composed of cylindrical cystic spaces separated by solid septae of tumor cells, and this is called the "cribriform pattern" (Fig. 18).

Acinic Cell Carcinoma

About one in five parotid carcinomas is diagnosed as acinic cell carcinoma (Vander Poorten et al. 2003). The majority of these tumors have a clinically low grade course, and following adequate resection, low stage tumors are not considered to need additional radiotherapy (Armstrong et al. 1990). Macroscopically acinic cell carcinomas are solitary, well circumscribed, multilobular masses. Microscopically, typical acinar cells with cytoplasmic Periodic Acid Schiff's reagent positive glycogen granules are the main components. A more aggressive (papillocystic (Spiro et al. 1978), microcystic (Colmenero et al. 1991) subgroup is increasingly being distinguished, making up about 15% of acinic cell carcinomas (Hoffman et al. 1999) and requiring a more aggressive treatment.

Adenocarcinoma Not Otherwise Specified (NOS)

Quite frequently a salivary gland adenocarcinoma lacks specific features allowing the pathologist to make a more specific diagnosis. About one in four salivary gland carcinomas cannot be accommodated in the other specific subtypes (Vander Poorten et al. 2003).

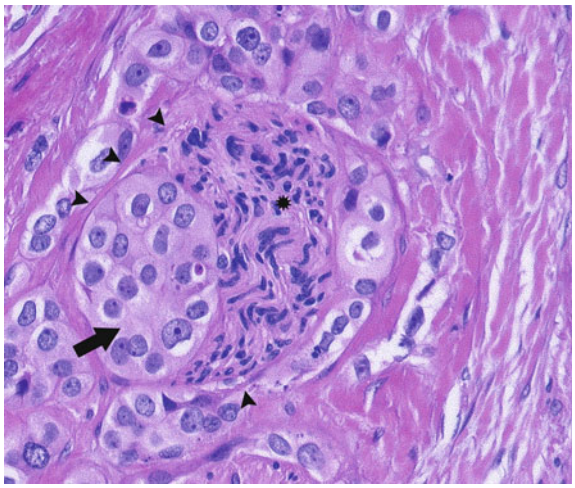

Fig. 19 Perineural growth in a high grade adenocarcinoma NOS of the parotid gland. *Arrowhead* demarcate perineurium, extended by tumor cells (*arrow*), compressing the nerve bundles (*asterisk*) Picture courtesy of Prof. Raf Sciot

Microscopically, they range from well-differentiated and low grade to high grade, invasive lesions, displaying perineural growth (Fig. 19).

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