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Diagnostic Imaging

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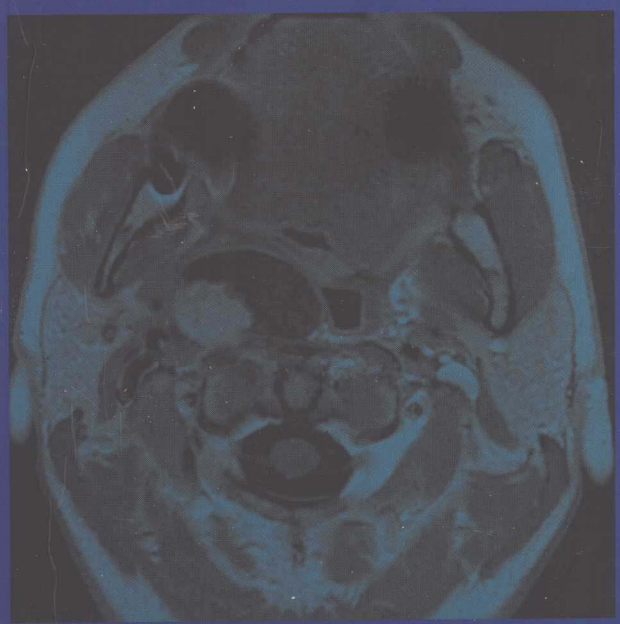
Head and Neck Cancer Imaging

Second Edition



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Head and Neck Cancer Imaging

Foreword by
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To my wife, Isabelle
And our children, Simon, Lies, Thomas and Tim

Bob Hermans

Foreword

Cancer treatment in the very complex head and neck region is largely dependant on the nature of the lesion, its local extension and the stage of the tumor. The rapid technological development of imaging, in recent years, provides us with an increasingly detailed and reliable visualization of these pathological features. For the treatment strategy as well as the management of the patient, the role of the radiologist within the multidisciplinary team becomes more and more important.

With this second edition of Head and Neck Cancer Imaging, we hope to provide the radiologist with detailed clinical background on the head and neck region in order to fully understand the clinical significance of imaging findings. At the same time we hope to inform all other members of interdisciplinary cancer treatment teams on the specific possibilities, advantages and limitations which modern imaging technology provides for the detection, evaluation, treatment, monitoring and follow-up of head and neck malignancies.

This book offers a comprehensive, up-to-date review of state-of-the-art head and neck cancer imaging, including numerous illustrative graphics and images.

The editor, R. Hermans, of the radiological department of the Leuven University, is an internationally recognized expert in head and neck radiology and was already in charge of the very successful first edition of this book. The authors of the individual chapters were invited to contribute because of their outstanding experience and expertise and their major contributions to the radiological literature on the topic.

I would like to thank the editor and all authors for their great efforts which resulted in this excellent volume.

München

Maximilian F. Reiser

Preface

The head and neck is a region of considerable anatomical and functional complexity, making the accurate staging of a head and neck neoplasm a challenging task. Many neoplasms in this region originate from the mucosa, and are detectable by the clinician. However, the submucosal tumor extension, as well as the possible regional and distant disease spread cannot be completely assessed based on the clinical examination alone.

Modern imaging modalities visualize the head and neck structures to an unprecedented level of detail. If carefully performed and interpreted, these techniques allow a comprehensive evaluation of the extent of head and neck neoplasms.

The radiologist is an important member of the multidisciplinary team managing head and neck cancer patients. Recent and ongoing research is enforcing the impact of imaging in oncologic patient care. These new developments are not only focusing on technical advances, such as PET-CT or diffusion-weighted MRI. Also, the impact of existing imaging techniques in treatment choice, in monitoring tumor response and following-up patients after treatment has now been established.

This purpose of this book is to provide a comprehensive review of state-of-the-art head and neck cancer imaging. Several distinguished head and neck radiologists have contributed to this book, fully covering the field of advanced imaging in the head and neck cancer patient.

Compared to the previous edition of this book, several chapters have been rewritten, incorporating recent insights and knowledge. In other chapters, the increasing role of metabolic and functional imaging is included in more detail where appropriate.

Clinical-diagnostic techniques, as well as therapeutic strategies, also have changed significantly over the past years; in this regard I would like to thank my colleague-clinicians from Leuven who contributed to this book. Care has been taken to situate the role of imaging within these developments.

The ultimate goal of all medical actions is to provide our patients with the best possible therapy for their health problems. Hopefully this book contributes to achieving this purpose.

Leuven

Robert Hermans

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Contents

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

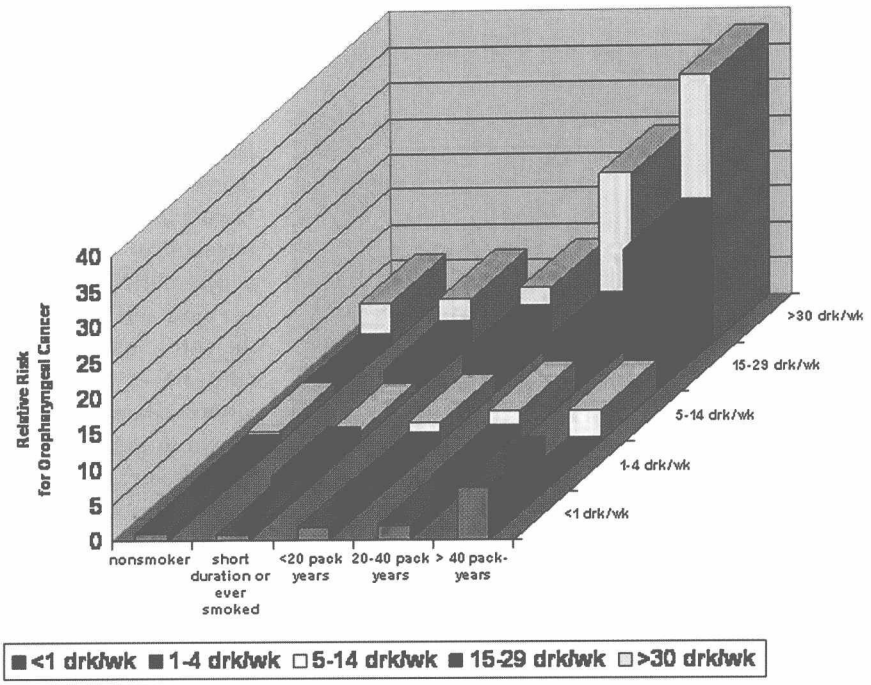

Fig. 2 Relative risk for oropharyngeal cancer for males according to amount of tobacco and alcohol use. (based on data from Blot WJ, et al. Cancer Research 1988; 48:3282–7, with permission)

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

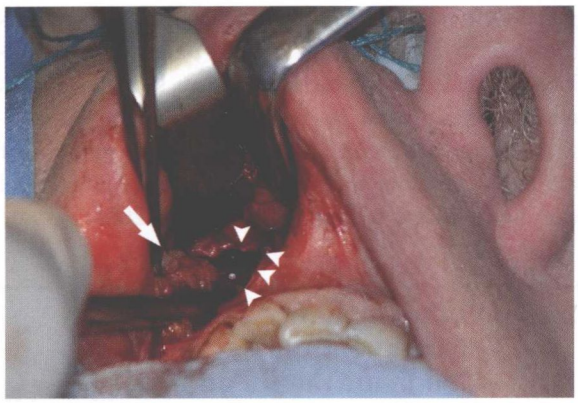

Fig. 3 Inverted papilloma (*arrow*) of the maxillary sinus being removed by Caldwell–Luc approach (antrostomy:*arrowheads*)

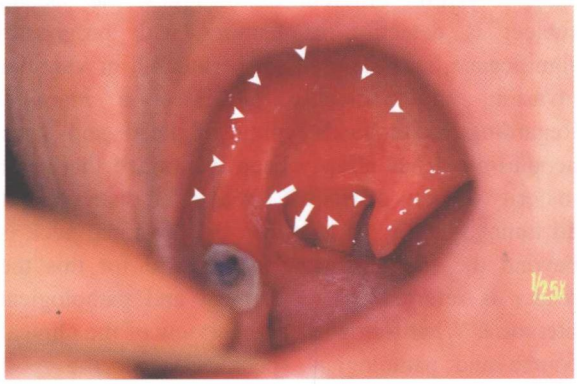

Fig. 4 Erythroplakia (*arrowheads*) with areas of nodular leukoplakia (*arrows*) of the tonsil, glossotonsillar sulcus, anterior tonsillar pillar, and hard and soft palate

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

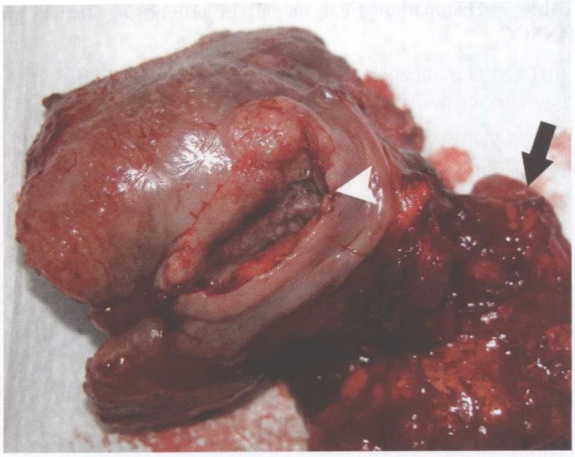

Fig. 5 Hemiglossectomy for ulcerative and deeply invasive well-differentiated squamous cell carcinoma of the lateral tongue (*arrowhead*). Specimen in continuity with radical neck dissection (*arrow*)

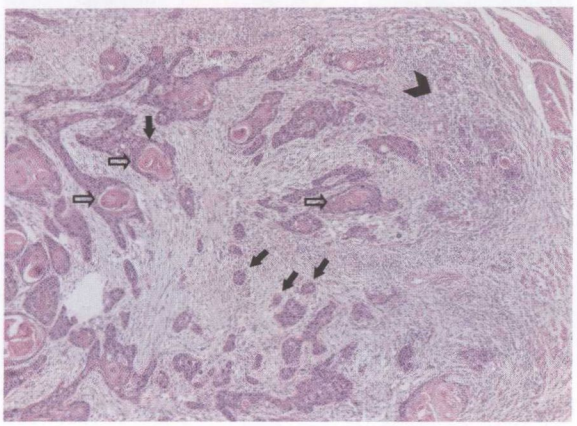

Fig. 6 Microscopical appearance of the same tumor. Note the diffuse infiltrative aspect of the tumor islets (*arrows*), the dense mononuclear inflammatory reaction (*arrowhead*), and the formation of keratin pearls (*hollow arrows*) Picture courtesy of Prof. Raf Sciot

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