Oral Cancer

9

Introduction

Oral cancer imposes a significant burden on public health in the USA and many parts of the world. The morbidity of the disease and its treatment can be quite substantial, resulting in disfigurement, pain, impaired speech and swallowing, and overall decreased quality of life. Research into the molecular biology of carcinogenesis has provided greater insight into the etiology and pathogenesis of oral cancer, which has translated into new and potentially more effective strategies for diagnosis and treatment. In addition to alcohol and tobacco, traditionally recognized as the two major known causative agents of oral cancer, human papilloma virus (HPV) associated oropharyngeal cancer accounts for a growing proportion of cases. Education and prevention are therefore of high priority in the overall management of this problem.

Epidemiology

The incidence of oral and oropharyngeal cancer in the USA is approximately 30,000 cases per year, accounting for 2–4 % of all cancers diagnosed annually. Worldwide, it ranks as the sixth leading cause of cancer. The vast majority of cancers are epithelial in origin, with *squamous cell carcinoma* (SCCA) being the most common. Unfortunately, overall 5-year survival is only about 50 %, which has not improved significantly over time despite technological advances in treatment. Survival is much higher for localized disease, with a survival rate 5 years after treatment of about 80 % for patients with early disease versus approximately 20 % for those with advanced stage disease. Only about one-third of oral cancer, however, is detected at an early stage, underscoring the importance of early diagnosis. Cancer screening in the community by physicians, nurses, dentists, hygienists, and other healthcare professionals is of critical importance in gaining ground against this disease.

The majority of oral cancer occurs in patients over the age of 40 with the average age at diagnosis between 60 and 65 years. Men are affected more than women by a factor of two, which is presumably related to differences in tobacco usage. This gender gap has been closing steadily over the past 50 years and is likely to continue. The incidence is higher in African-Americans than whites, with African-Americans also exhibiting a higher mortality rate from the disease. Patients diagnosed with oral cancer have an increased incidence of developing additional malignancies (*second primary tumors*) of the upper aerodigestive tract, particularly in smokers who continue the habit following treatment.

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Risk Factors

There are a number of known risk factors for oral SCCA, with tobacco and alcohol being the most notable. Others have been implicated but are not as well characterized. It is important to remember that many cancers arise in the absence of identifiable risk factors and any patient who presents with suspicious signs or symptoms must be fully evaluated.

Tobacco

Tobacco in all forms is a major risk factor for oral SCCA. A large number of carcinogens have been identified in tobacco and its combustion products, the most important of which are polycyclic aromatic hydrocarbons containing benzene, tobacco-specific nitrosamines, and aromatic amines. These compounds result in damage to epithelium in a dose-dependent fashion, with disruption of DNA repair mechanisms and potentially critical genetic mutations leading to malignant transformation. Smokers have about a five- to tenfold risk of developing oral cancer over nonsmokers. This will decrease by approximately half over a 5-year period if they stop smoking and will reach the risk of a nonsmoker after about 10 years. Cigar and pipe smokers experience a risk profile similar to that of cigarette smokers. Oral cancer risk associated with use of electronic cigarettes remains unknown, but is likely to be low due to the absence of tobacco-associated carcinogens in the inhaled vapor.

Smokeless tobacco is associated with a considerably lower risk of oral cancer than smoked tobacco, however, it should not be considered "safe" to use or an acceptable substitute for cigarettes. Risk varies with the composition of the particular product that is used and can be up to fourfold higher than that of a non-user. It is thought that tobacco-specific nitrosamines induce dysplastic changes in the epithelium, which is probably intensified with prolonged surface contact.

Alcohol

Alcohol consumption by itself imparts an increased risk for oral cancer in "moderate to heavy" drinkers; this is variably defined but roughly equivalent to five to eight drinks per day (with one drink containing 1.5 oz or 10–15 g of alcohol). Importantly, the combined use of alcohol and tobacco produces a *synergistic effect*, in which the presence of one substance enhances the effect of the second. This results in a much greater risk than would be expected by a simple summation of the individual responses. It is thought that ethanol may alter the permeability of the oral mucosa to various substances, including carcinogens, thereby enhancing their penetration into the tissues.

Sun Exposure

Sun exposure is a risk factor for lip cancer due to the cumulative effects of ultraviolet damage. The lower lip is more commonly affected, as it tends to receive relatively more direct exposure to the sun than the upper lip. Sun exposure is not a risk factor for intraoral SCCA or mucosal melanoma.

Betel

Betel products, derived from the nut of the areca palm, are commonly used in parts of the world such as Southeast Asia and the Indian subcontinent, and are believed to be carcinogenic. Preparations usually consist of a mixture of areca nut, betel leaf, tobacco, and slaked lime (calcium hydroxide). Addition of lime enhances the euphoric effect, although it may also potentiate carcinogenicity. Long-term use is associated with the development of *submucous fibrosis* (see below). Clinicians should be aware that certain immigrant populations to the USA may continue to use these products and should be screened for cancer.

Viral

A number of viruses have been associated with benign and malignant neoplasia of the head and neck. *Epstein-Barr Virus* (EBV) has long been linked to nasopharyngeal carcinoma, Burkitt lymphoma, and other lymphomas. A strain of *human herpesvirus* (HHV-8) is believed to be associated with development of Kaposi sarcoma (see Chap. 6) in HIV-infected patients. *Human papillomavirus* (HPV) is well known to cause benign proliferative epithelial lesions throughout the head and neck region, including *squamous papilloma* and *condylomata* (see Chap. 7). High-risk strains of HPV (particularly 16 and 18; associated with cancer of the uterine cervix) have been identified in tumors of the posterior oral cavity/oropharynx. HPV associated oropharyngeal malignancies tend to arise in younger patients without traditional risk factors and exhibit overall improved prognosis and treatment outcomes.

Immunosuppression

Immunosuppressed individuals are at increased risk for malignancy in the oral cavity and elsewhere in the body. HIV-infected patients in particular can develop oral SCCA, Kaposi sarcoma, and non-Hodgkin lymphoma. Transplant patients are at risk for multiple malignancies including lip and mouth cancer. Patients with *dyskeratosis congenita*, which is a very rare inherited condition of progressive bone marrow failure leading to aplastic anemia, present with skin hyperpigmentation, dystrophic nail changes, and *leukoplakia* (see below). Leukoplakic lesions in these patients exhibit a particularly high risk of malignant transformation (Fig. 9.1). Patients with *Fanconi anemia*, a similarly rare bone marrow failure syndrome, are also at high risk for developing oral SCCA.

Nutrition

Nutritional factors, such as vitamin and mineral deficiencies, are thought to play some role in carcinogenesis, although no specific causative pathway has been elicited. This is possibly related to loss of an antioxidant mechanism and formation of damaging free radicals. Patients with *Plummer–Vinson syndrome*, which is a rare condition presenting with dysphagia, esophageal webs, and iron-deficiency anemia in middle-aged women, are thought to be at increased risk for esophageal and oral carcinoma.

Sanguinaria

Extract derived from the common bloodroot plant *Sanguinaria canadensis*, has been used commercially in oral rinses and toothpaste as an antibacterial agent to reduce plaque and gingivitis. It has been linked to development of leukoplakia occurring particularly in the region of the maxillary vestibule. Monitoring of patients who have used these products is advised, although the risk of malignant change in these lesions is unclear and is probably not high. The main commercial marketer in the USA has removed sanguinaria from its products; however, dentifrices containing this herbal supplement may still be available in some parts of the world and their use should be discouraged.

Other

Marijuana smoking has been implicated as a potential risk factor for oral cancer; however, this has not been clearly substantiated to date. *Hyperplastic candidiasis* (see Chap. 7) may be associated with premalignancy, as invasion of fungal elements has been demonstrated in some thick or nodular leukoplakias, however, this relationship is unclear with respect to development of cancer. Historically, *syphilis* has been linked to an increased incidence of tongue cancer, although no definite causative relationship has been established.

High-Risk Sites

Tongue

The tongue is the most common location for oral cancer in the USA, with more than half of lesions presenting on the *oral tongue*, and the remainder

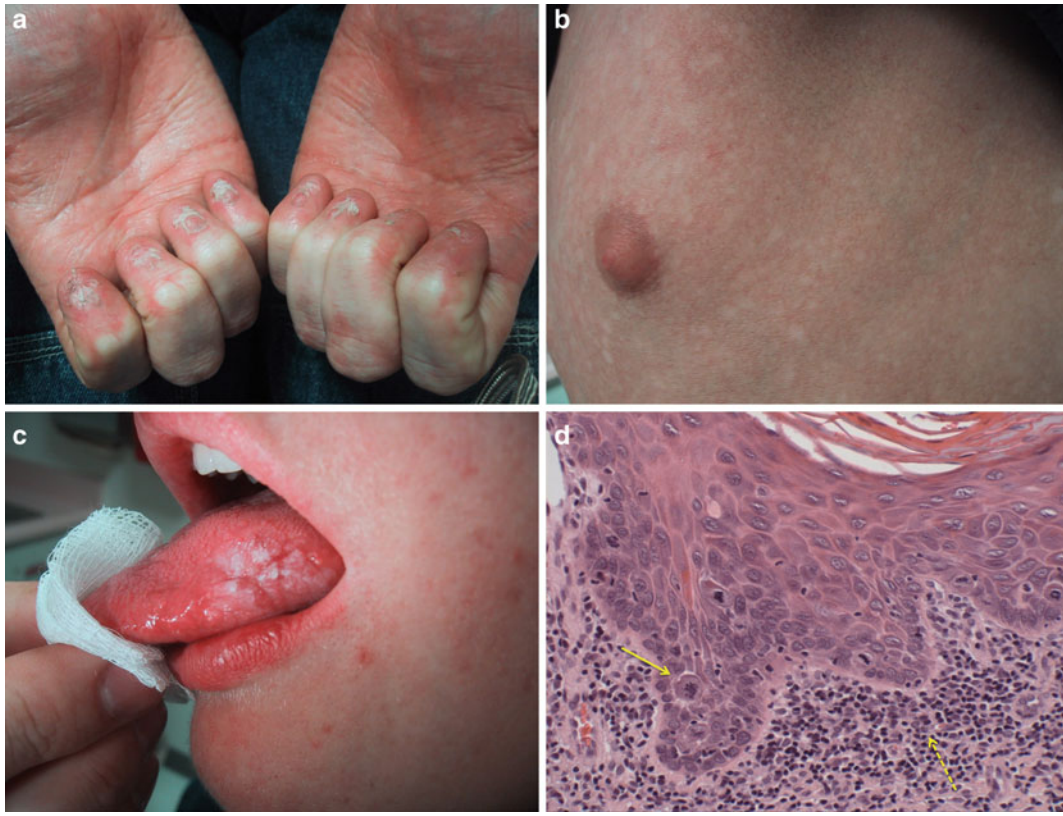

Fig. 9.1 Dyskeratosis congenita. (**a**) Dystrophic nails and leathery, cracked palms. (**b**) Hypo- and hyperpigmentation of the skin. (**c**) Diffuse lateral tongue leukoplakia. (**d**) Biopsy of the tongue demonstrated dysplasia with maturational disarray and large mitotic figures (*solid arrow*) with an inflammatory infiltrate (*broken arrow*). Reprinted from Treister et al. (2004), with permission from Elsevier

occurring in the *tongue base*. In the oral cavity proper, lesions are most frequently seen on the lateral and ventral surfaces, and these areas are considered particularly high-risk sites. The overall incidence of tongue cancer has been rising, with some concern for increasing frequency at this site in patients under the age of 40 who do not have a history of tobacco use or other known risk factors. In general, malignancies of the tongue base tend to be more advanced at the time of diagnosis, with up to three-fourths already exhibiting metastasis to regional lymph nodes at presentation. This may be partly due to greater difficulty in visualizing and palpating the area on examination, causing these lesions to remain "hidden" longer.

Lip

The vermillion of the lip is the second most common site for oral cancer, and this has been decreasing in incidence over time. The majority of labial carcinomas occur on the lower lip, more frequently in men than women. Ultraviolet radiation exposure is the major risk factor for this area, and increased occupational and/or recreational sun exposure in men is thought to account for the gender difference. Use of lipstick and other topical protectants may also contribute to the lower incidence in women. Cancer can arise in pipe smokers where the pipestem contacts the lip repeatedly over a long period of time.

Lip cancers in general are diagnosed at an early stage due to their relatively high visibility, and can usually be treated surgically with an overall 5-year survival rate of 90 %. Poorer prognosis is associated with lesions on the upper lip or commissure region. From an epidemiologic standpoint, lip cancers are often grouped with skin cancers, as they have a distinctive risk factor profile and prognosis compared to intraoral mucosal carcinomas.

Floor of Mouth

Pooling of secretions in the floor of mouth is thought to potentiate contact of carcinogens with the tissues. In addition, the very thin, nonkeratinized mucosa in this area may provide less of a barrier for penetration of toxic substances than might be found in other parts of the oral cavity. Cancers in this area can be quite aggressive and present with early lymph node involvement due to the rich lymphatic supply.

Signs and Symptoms

Squamous Cell Carcinoma

The clinical presentation of oral SCCA is quite varied, and necessitates a high level of awareness and vigilance during the oral examination. Lesions may appear flat (*macular*; Fig. 9.2), raised (*plaque-like*; Fig. 9.3), *exophytic* or *endophytic* (growing outward or inward; Fig. 9.4), or *ulcerated* (showing surface erosion; Figs. 9.5 and 9.6). The surface texture can range from smooth to irregular. *Induration* (firmness or hardness; Fig. 9.7) and *fixation* (immobility or palpable adherence to underlying structures) indicate infiltration of cancer cells into deeper tissues. These lesions have the potential for local bone destruction and nerve invasion as well as more distant spread via the lymphatics and bloodstream. Pain is a worrisome symptom, although lack of pain does not exclude malignancy.

Any nonhealing ulcer or extraction socket, as well as any white or red patch that cannot be rubbed off or induced to resolve, should be

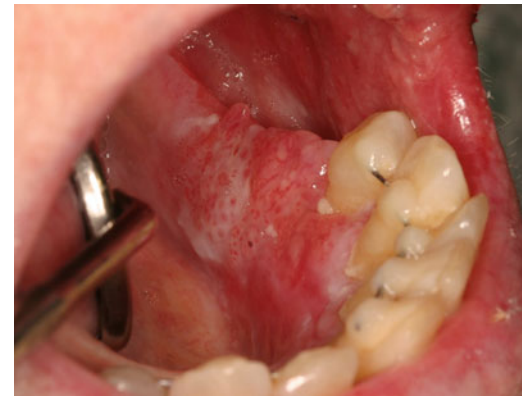

Fig. 9.2 Squamous cell carcinoma of the mandibular ridge with erythroleukoplakia and focal areas of ulceration. This patient developed multifocal involvement, suggestive of a *field cancerization* effect

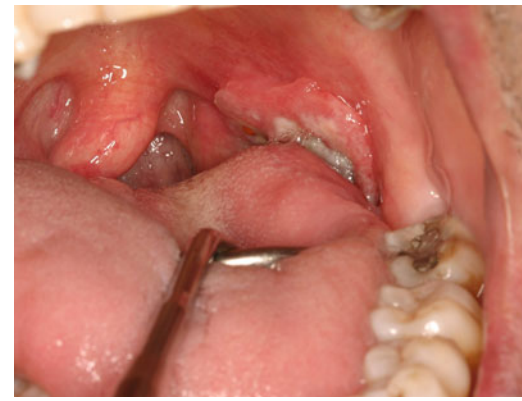

Fig. 9.3 Squamous cell carcinoma of the left soft palate presenting as an exophytic mass with central ulceration

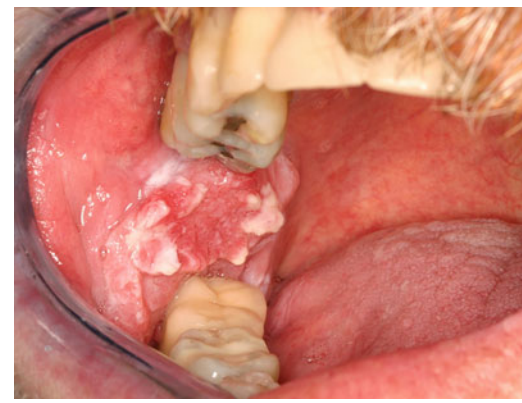

Fig. 9.4 Large exophytic squamous cell carcinoma of the buccal mucosa with heavy keratinization and induration

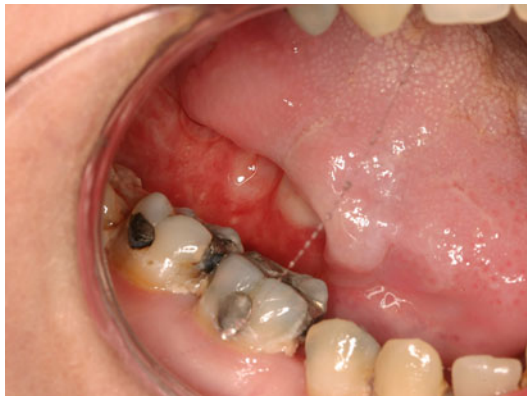

Fig. 9.5 Large squamous cell carcinoma of the right lateral tongue with ulceration and induration

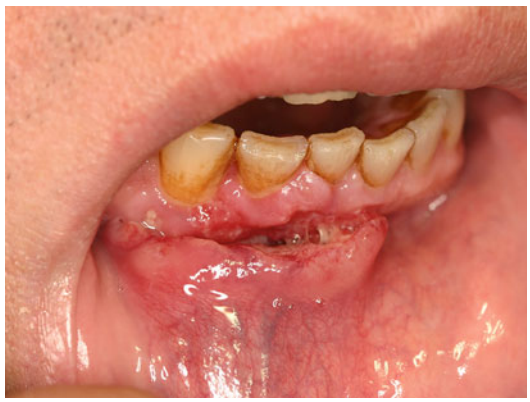

Fig. 9.6 Squamous cell carcinoma of the mandibular labial vestibule presenting as a clefted, indurated mass with central ulceration and necrosis

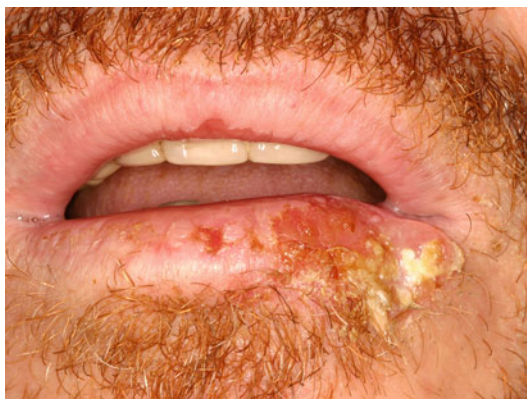

Fig. 9.7 Squamous cell carcinoma of the left lower lip with crusting, ulceration, and induration

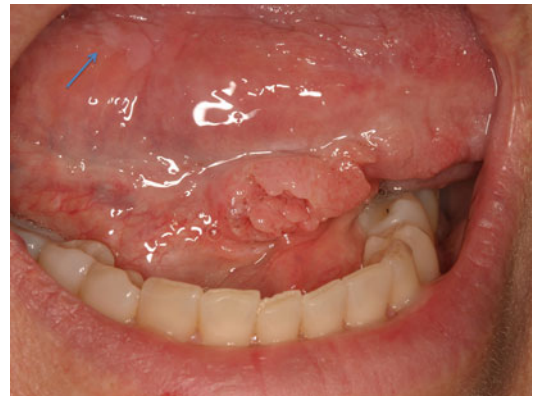

Fig. 9.8 Papillary verruciform squamous cell carcinoma of the ventral tongue. This lesion developed in the context of leukoplakic changes that can be partly seen on the superior aspect of the lateral tongue (*arrow*)

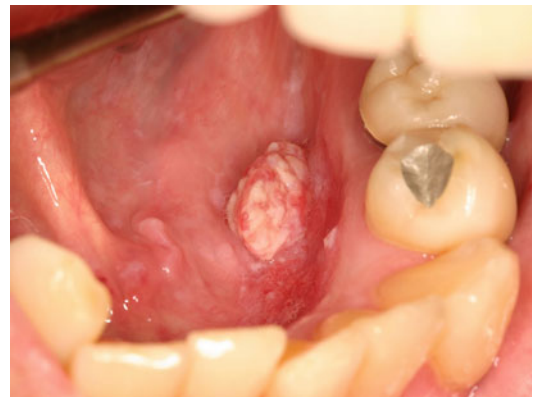

Fig. 9.9 Verrucous carcinoma of the floor of the mouth with surrounding erythroleukoplakia

biopsied. The following can all be warning signs for cancer: difficulty or pain with chewing or swallowing (*dysphagia*, *odynophagia*), ear pain (*otalgia*), limitation of mouth opening (*trismus*), alteration of speech (*dysarthria*), alteration of sensation such as numbness or tingling (*paresthesia*), cervical lymph node enlargement (*adenopathy*), tooth mobility, or change in the fit of a denture.

Verrucous Carcinoma

Verrucous carcinoma is a low-grade variant of SCCA with a distinctive exophytic and papillary, or warty, appearance (Fig. 9.8). Heavy keratinization causes a typically whitish or gray color (Fig. 9.9);

common sites are the buccal mucosa, gingiva, and vestibule. The prognosis is usually more favorable than that of conventional SCCA due to its slow growth, high degree of differentiation, and minimal propensity for metastasis. Treatment consists of local surgical excision without use of radiation or chemotherapy.

Histopathology

Terminology and Definitions

Epithelial *dysplasia* represents a disruption of the normal orderly growth and maturation process of oral mucosa, which may then progress to *carcinoma in situ* or *invasive carcinoma*. Normally, cell division occurs in the deep *basal layer* of the epithelium (see Chap. 1), which is separated from the underlying connective tissue by a *basement membrane*. New cells migrate upward through the layers of epithelium to replace those that are shed regularly from the surface. Cell maturation and differentiation take place in the process, with mature cells ultimately acquiring their flattened (*squamoid*) shape and ability to make keratin. Keratin production and deposition occurs only in the superficial layers of keratinized tissues. The entire process of epithelial regeneration and turnover is well organized and regulated, with distinct maturational layers (*stratification*) visible histologically (Fig. 9.10).

Cell alteration and *atypia* are seen in dysplastic epithelium, with evidence of abnormal cell division, hyperplasia of the basal cell layer, cell crowding, and loss of the usual stratification pattern (Fig. 9.11). Cell maturation is disordered, with appearance of keratin producing cells or clumps of keratin (*keratin pearls*) in the deeper layers and immature cells more superficially (Fig. 9.12). Dysplasia is a histological diagnosis, and the severity is determined according to the proportion of epithelium that exhibits these abnormal features.

Mild dysplasia involves the deeper layers only, generally estimated at no more than 1/3 of the total thickness of the epithelium. *Severe dysplasia* involves the entire thickness of epithelium without disruption of the basement membrane, and is considered equivalent to *carcinoma in situ*. Once the barrier basement membrane between epithelium and connective tissue has been breached by abnormal cells, the lesion is labeled *invasive carcinoma* and possesses the potential for spread (*metastasis*) through the lymphatic or vascular systems (Fig. 9.12). Not all dysplastic lesions will progress to invasive carcinoma, and in some cases they may actually regress; however the underlying mechanisms for this remain poorly understood.

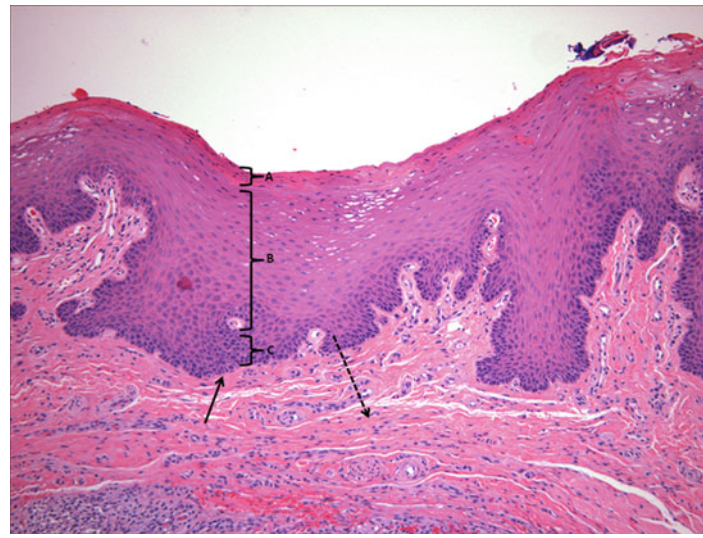

Fig. 9.10 Histology of normal keratinized oral mucosa showing the keratin (**a**), spinous (**b**), and basal (**c**) layers, basement membrane (*solid arrow*), and underlying connective tissue (*broken arrow*). Photomicrograph courtesy of Mark Lerman, D.M.D., Boston, MA

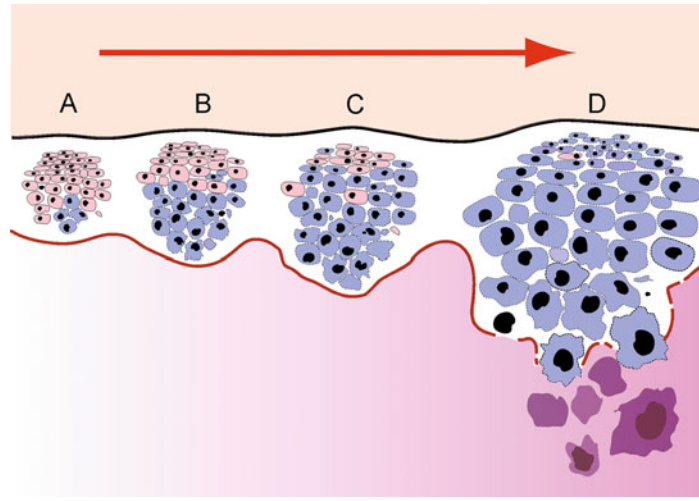

Fig. 9.11 Progression of cellular atypia and dysplasia to invasive squamous cell carcinoma: (**a**) mild dysplasia, (**b**) moderate dysplasia, (**c**) severe dysplasia (*carcinoma in situ*), and (**d**) invasive carcinoma; note breach of basement membrane

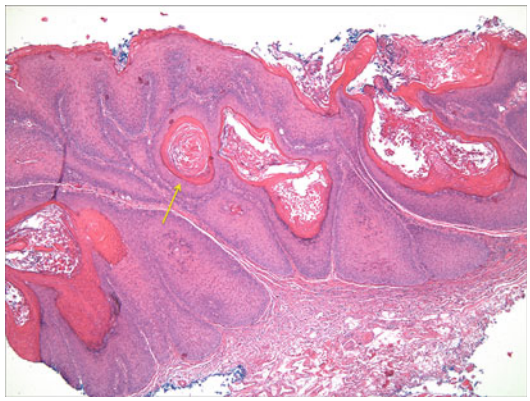

Fig. 9.12 Squamous cell carcinoma histopathology demonstrating dysplastic surface epithelium and invasive tumor islands with keratin pearl formation (*arrow*). Photomicrograph courtesy of Mark Lerman, D.M.D., Boston, MA

Biopsy Considerations

To adequately diagnose invasive carcinoma or determine the degree of dysplasia present, the biopsy specimen must include the full thickness of epithelium with adjacent basement membrane and connective tissue interface. This is obtained by either *incisional* or *excisional biopsy* (see Chap. 3). In general, small lesions are excised fully via excisional biopsy if possible. Incisional biopsy is preferred for larger lesions in order to initially establish the diagnosis and facilitate treatment planning, as a subsequent major resection may be required in conjunction with other treatment modalities.

Exfoliative cytology and brush biopsy techniques (see Chap. 3) can be useful for detecting abnormal appearing cells in a specimen. However, as only individual cells are obtained, these tests do not provide information regarding epithelial architecture or basement membrane integrity. Therefore, the pathologist cannot make a determination regarding dysplasia or carcinoma. These methods may help to guide the practitioner in deciding whether formal biopsy should be performed, but clinical judgment in favor of biopsy should prevail if any suspicion for malignancy remains. *Vital stains*, such as toluidine blue, which bind to DNA and indicate areas of high cell turnover, can also be used as adjuncts for biopsy and monitoring of suspicious lesions.

Potentially Malignant Lesions

The term potentially malignant, or "premalignant" or "precancerous," implies that there is a known potential for the lesion to transform into malignancy at a rate high enough to warrant preemptive action or close observation. As there is no way to predict whether a given lesion will undergo malignant change in a particular individual, a high level of vigilance is necessary.

Actinic Cheilitis (Sailor's Lip; Solar Cheilitis)

This is a type of *actinic keratosis* which classically occurs on the lower lip and is directly related to long-term sun exposure. It is most frequently seen in white males over age 40. The vermilion appears atrophic and pale, with a glossy surface and loss of demarcation at the vermilion border. With progression, fissuring and ulceration can occur along with crusting or scaling (Fig. 9.13). Epithelial atrophy and elastosis are seen histologically and these changes are irreversible. Areas of persistent ulceration should be biopsied due to a 6–10 % rate of malignant transformation. Treatment of malignancy is primarily surgical; however, topical chemotherapy with 5-fluorouracil can be used with early lesions. Prophylactic laser ablation or vermillionectomy may be performed in cases where malignant transformation has not yet occurred. Close long-term follow-up is indicated, as these patients are at risk for additional cancers associated with solar damage.

Leukoplakia

The term leukoplakia is derived from Greek, meaning literally a "white patch," and is defined by the World Health Organization as a white plaque that cannot be rubbed off or clinically identified as another named entity (such as described in Chap. 4). It is therefore strictly a *clinical* label rather than a *histological* diagnosis. These lesions should be biopsied, after which a more definitive diagnosis can be assigned. Most prove to be histologically benign (usually hyperkeratosis or chronic inflammation), however, up to 20 % may exhibit histological changes consistent with dysplasia or carcinoma. They should therefore be regarded with suspicion until proven otherwise, particularly if occurring in a high-risk site such as the ventral or lateral tongue or floor of mouth. The clinical appearance is extremely variable with respect to size, shape, thickness, and homogeneity of color (Figs. 9.14, 9.15, 9.16, 9.17, 9.18, and 9.19). They are usually asymptomatic.

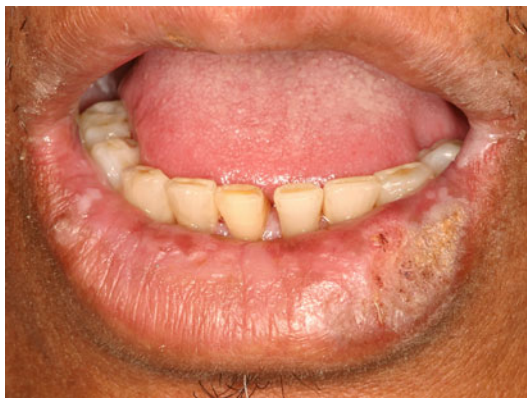

Fig. 9.13 Actinic cheilitis of the lower lip showing crusting, atrophic changes, and loss of vermillion border definition

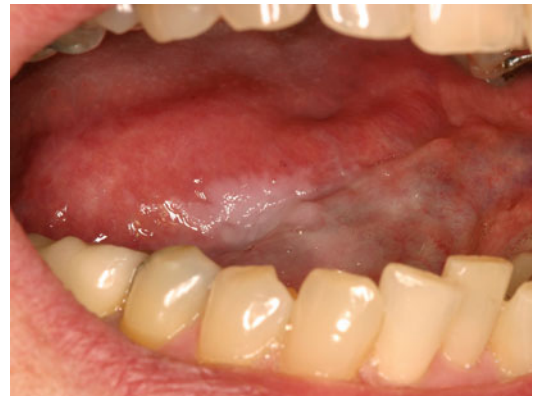

Fig. 9.14 Well-defined, smooth, and homogeneous leukoplakia of the right lateroventral tongue

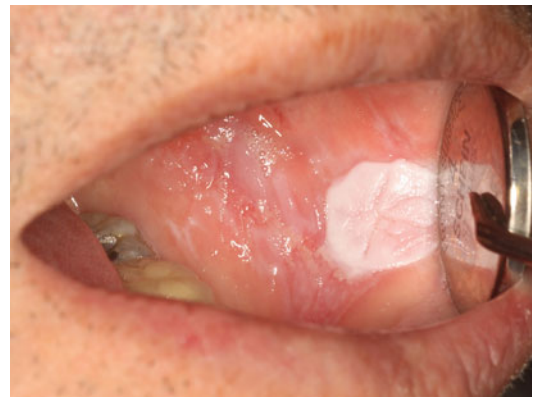

Fig. 9.15 Well-defined thick and slightly wrinkled appearing leukoplakia of the left buccal mucosa arising within the context of longstanding oral lichen planus

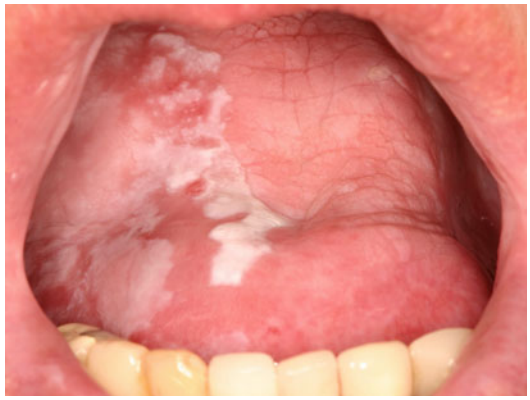

Fig. 9.16 Proliferative leukoplakia involving most of the tongue dorsum, with associated atrophy and depapillation

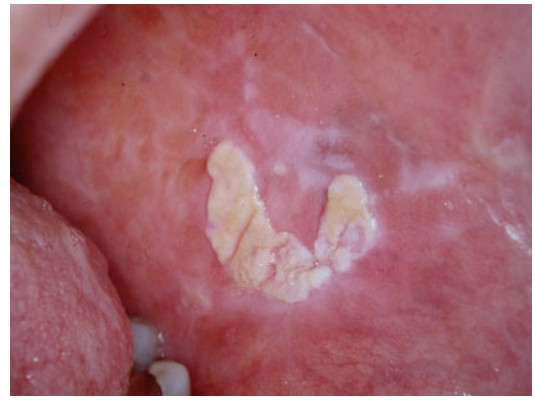

Fig. 9.18 Thick verrucous leukoplakia of the left buccal mucosa in the setting of extensive mucosal changes exhibiting a slightly *lichenoid* appearance. Photograph courtesy of Sook-Bin Woo, D.M.D., D.M.Sc., Boston, MA

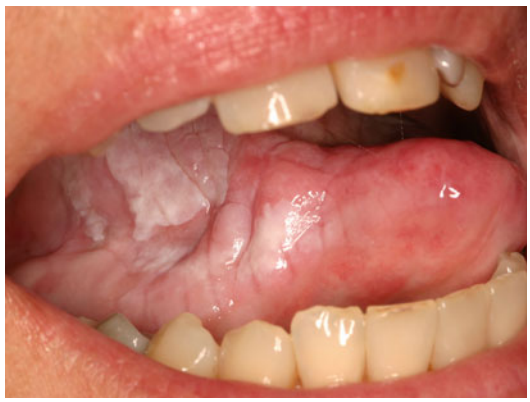

Fig. 9.17 Leukoplakia of the right lateral tongue in a patient previously treated for squamous cell carcinoma of the tongue

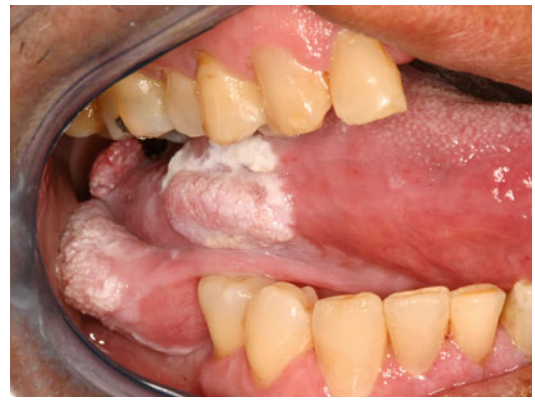

Fig. 9.19 Prominent multifocal, mass-like verrucous leukoplakia of the right lateral tongue in an HIV-positive patient

Proliferative Verrucous Leukoplakia

Proliferative verrucous leukoplakia (PVL) is an uncommon but specific type of leukoplakia that is known for a very high rate of malignant change. It is typically thick and exophytic in appearance, although may appear flat in the early stages (Fig. 9.20). Lesions often develop on the buccal mucosa and gingiva; this is in contrast to conventional leukoplakia which is more commonly seen on the ventral/lateral tongue and floor of mouth. There is an unusual predisposition for women over the age of 50 for unknown reasons. Specific risk factors have not been identified, and tobacco use does not appear to be related. It is generally slowly progressive and often multifocal. The treatment of choice is surgical resection, although the extensive and "creeping" nature of these lesions can make definitive therapy extremely challenging. The recurrence rate is high and patients with PVL must be monitored closely.

Tobacco Pouch Keratosis

Tobacco pouch keratosis, also referred to as *snuff dipper's keratosis*, is a unique form of leukoplakia related to the direct effect of smokeless tobacco on the oral mucosa. Lesions occur at the

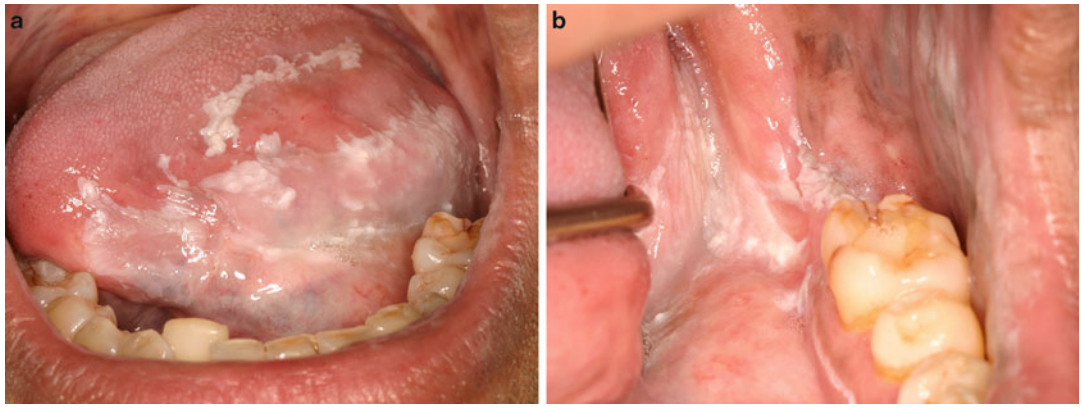

Fig. 9.20 Proliferative verrucous leukoplakia. (**a**) Extensive involvement of the tongue and (**b**) floor of mouth with a thick, wrinkled appearance. Photographs courtesy of Sook-Bin Woo, D.M.D., M.M.Sc., Boston, MA

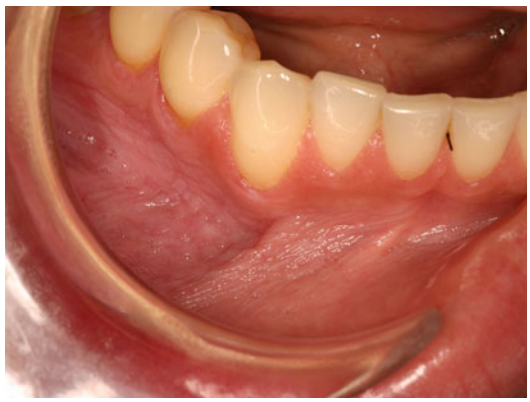

Fig. 9.21 Smokeless tobacco keratosis with thickened, corrugated appearing mucosa in the area where the tobacco is placed

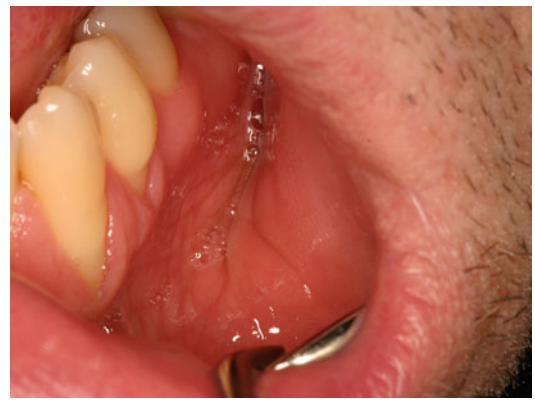

Fig. 9.22 Smokeless tobacco keratosis with deeply wrinkled and fissured appearance

site of contact, which is usually in the mandibular anterior labial vestibule or more posteriorly in the buccal vestibule. The mucosa is gray to whitish in color and wrinkled, and there may be an associated pouch-like depression secondary to stretching of the tissue from the mass of tobacco (Figs. 9.21 and 9.22). The lesion becomes increasingly white over time, as well as more leathery or nodular in texture. The neighboring gingiva is commonly inflamed or receded. The risk of malignant transformation is less than that of conventional leukoplakia, and most lesions will resolve several weeks after use of the product is discontinued. Lesions that show ulceration or erythema or that persist despite tobacco cessation, must be biopsied.

Oral Submucous Fibrosis

This represents chronic inflammation with atrophy and fibrosis of the oral mucosa secondary to habitual use of betel products and is seen mainly in areas of the world where this practice is endemic. Development of this condition may also be influenced by nutritional and/or genetic factors. Mucosal stiffening occurs over time with formation of fibrotic bands, particularly in the buccal region and soft palate, with gradual onset

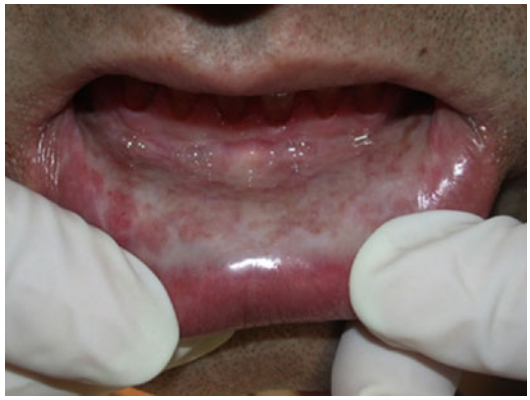

Fig. 9.23 Submucous fibrosis of the lower labial mucosa with loss of vestibule depth in a user of betel product. Photograph courtesy of Ross Kerr, D.D.S., M.S.D., New York, NY

of trismus (Fig. 9.23). This is progressive and irreversible, with a reported malignant transformation rate ranging from 4 to 13 %. Treatment consists of local steroid injection and surgical disruption (*lysis*) of fibrous bands, however, outcomes are generally poor

Erythroplakia

Erythroplakia is derived from Greek, meaning "flat red area," and is a clinically descriptive term without specific histologic definition. Lesions frequently exhibit a bright red, velvety appearance and are usually asymptomatic. The incidence of severe dysplasia or carcinoma in these lesions is very high (80–90 %), and biopsy is mandatory. Areas of erythroplakia may also coexist with leukoplakia in the so-called mixed or speckled lesions (*erythroleukoplakia*; Figs. 9.24, 9.25, and 9.26). Care must be taken to obtain a representative biopsy specimen in such cases, with sampling of multiple areas within the lesion, as carcinoma may be present only focally.

Oral Lichen Planus

Development of cancer within an existing area of lichen planus (see Chap. 5) has long been a topic of controversy and no definite answer is

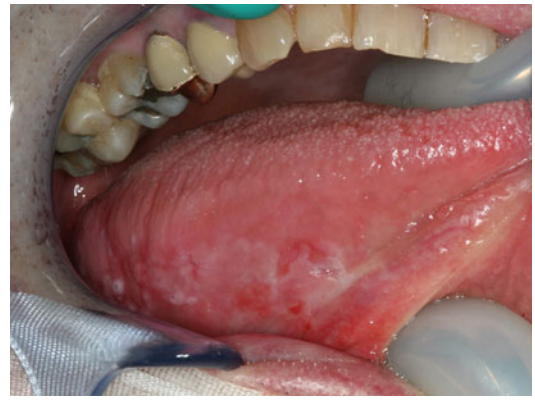

Fig. 9.24 Erythroleukoplakia of the right lateral tongue

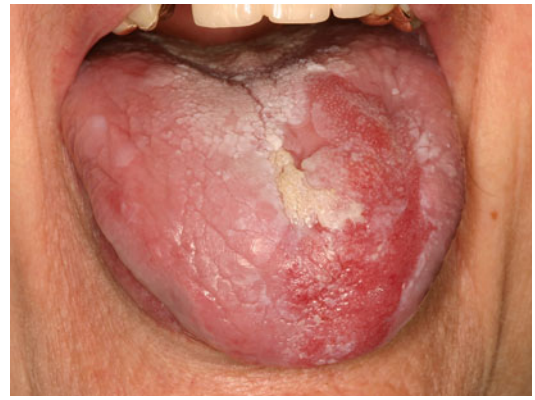

Fig. 9.25 Extensive erythroleukoplakia of the tongue dorsum that initially demonstrated inflammation without dysplasia on biopsy but subsequently transformed to squamous cell carcinoma

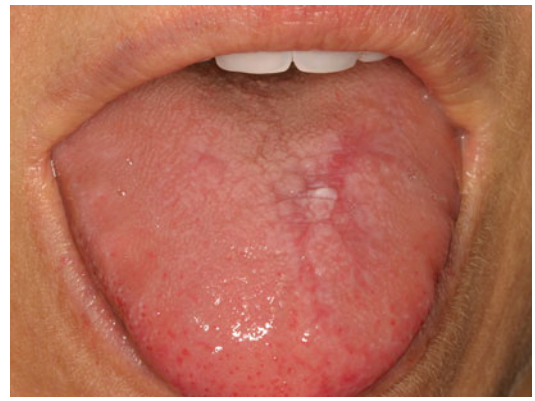

Fig. 9.26 Erythroleukoplakia of the tongue dorsum with thick plaque-like area of leukoplakia

available. Whether the two entities arise coincidentally or the atrophic epithelium seen in the erosive/ulcerative form of lichen planus is rendered more susceptible to carcinogens is unclear. Common wisdom dictates that patients with lichen planus be monitored regularly, with biopsy of any areas that are changing or otherwise appear suspicious.

Cancer Staging

Staging, or defining the extent of cancer, is important with respect to treatment planning and determination of prognosis. Patients in whom cancer is diagnosed at an early stage are generally expected to fare better, and may require less aggressive therapy than patients with more advanced disease. Accurate staging, with consistent use of accepted and uniform terminology, is also necessary to evaluate outcomes of cancer therapy and compare data across different populations.

The staging system for head and neck cancer that is currently in use follows the American Joint Committee on Cancer (AJCC) cancer staging manual, which was most recently revised in 2010 (7th edition). This is based on the clinically determined anatomic extent of the primary tumor and tumor spread. It does not take into account histological or biological features of the lesion. It is referred to as the "TNM system," describing tumor size (T), lymph node involvement (N), and metastasis to distant sites (M). These three parameters taken together determine the stage of disease, with stage IV being the most advanced and carrying the worst prognosis (Tables 9.1 and 9.2).

Oral SCCA metastasizes primarily through the lymphatic system to regional cervical lymph nodes in a relatively predictable pattern. The neck is anatomically divided into "levels," which help to define the extent of lymph node involvement and guide treatment planning (Fig. 9.27). The presence of lymph node involvement at the time of diagnosis dramatically worsens the patient's prognosis. Lymphatic drainage from oral cavity sites (see Chap. 1) is primarily to level I (submental, submandibular) and level II (upper jugular) lymph nodes, however, other levels can be involved. Suspicious clinical signs include nontender node enlargement, very firm or hard consistency of the node on palpation, and fixation (immobility). Fixation indicates penetration of

Table 9.1 TNM classification for oral cancer

Primary tumor (T)	Tx	Primary tumor cannot be assessed
	T0	No evidence of primary tumor
	Tis	*Carcinoma in situ*
	T1	Tumor <2 cm in greatest dimension
	T2	Tumor >2 cm in greatest dimension but <4 cm
	T3	Tumor >4 cm
	T4	Tumor invades deep or adjacent structures (further subdivided into T4a and T4b)
Regional lymph nodes (N)	Nx	Lymph nodes cannot be assessed
	N0	No lymph node metastasis
	N1	Metastasis in a single ipsilateral lymph node measuring <3 cm in greatest dimension
	N2a	Metastasis in a single ipsilateral node measuring >3 cm but <6 cm
	N2b	Metastasis in multiple ipsilateral nodes, none measuring >6 cm
	N2c	Metastasis in bilateral or contralateral nodes, none >6 cm
	N3	Metastasis in a node >6 cm
Distant metastasis (M)	Mx	Distant metastasis cannot be assessed
	M0	No distant metastasis
	M1	Distant metastasis present

Table 9.2 Stage groupings for oral cancer

Stage	TNM classification
0	Tis N0 M0
I	T1 N0 M0
II	T2 N0 M0
III	T3 N0 M0 T1-3 N1 M0
IV (further subdivided into IVA, IVB, and IVC)	T4 N0 M0 T4 N1 M0 Tany N2-3 M0 Tany Nany M1

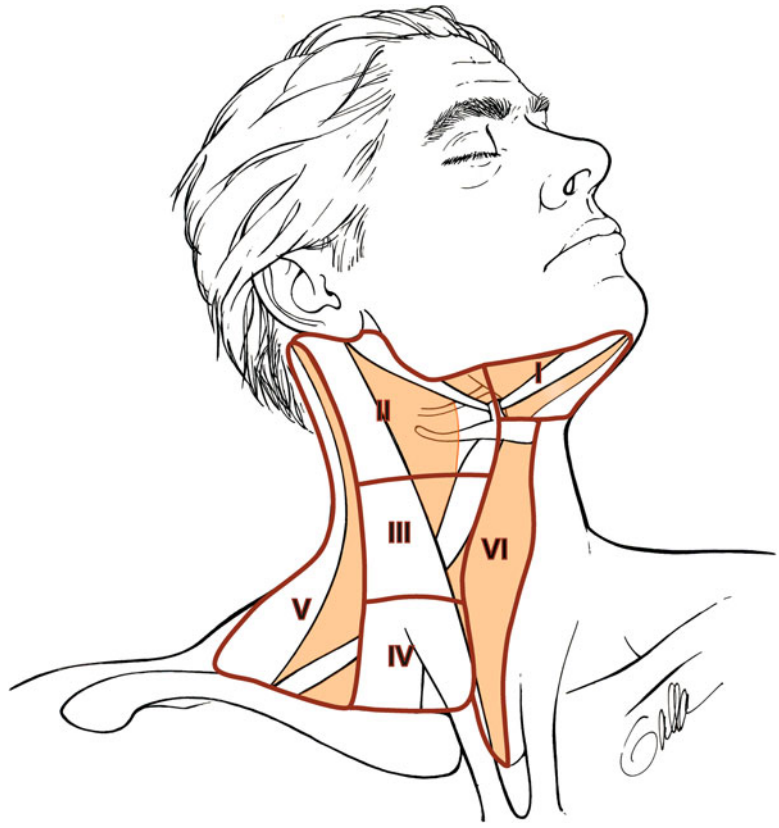

Fig. 9.27 Cervical lymph node groups by levels. (Reprinted with permission from Janfaza (2001); Lippincott Williams & Wilkins)

cancer through the lymph node capsule with spread and adherence of tumor to adjacent tissues (*extracapsular extension*). In contrast, normal lymph nodes responding to an inflammatory insult (*reactive nodes*) are generally enlarged but tender, rubbery in consistency, and mobile.

Metastasis of cancer cells through the bloodstream results in spread to more distant tissues (*distant metastasis*), such as the brain and lungs. Presence of distant metastasis (M1 designation in the TNM system) indicates advanced disease and is classified as stage IV.

Treatment

Treatment is largely determined by location and extent of disease following full workup and staging. Other factors are taken into consideration, including general health and nutritional status of the patient with respect to their ability to tolerate (or wish to pursue) various treatment options. Treatment planning is now frequently carried out in a multidisciplinary fashion, involving a team of practitioners from a range of specialty areas, including surgery (otolaryngology/head and neck or oral/ maxillofacial), radiation oncology, medical oncology, radiology, speech/swallowing pathology, and dentistry. Ancillary and support services are important to help the patient and family through a potentially long, difficult, and often debilitating course of therapy.

Lip cancer, particularly of the lower lip, generally responds very well to surgical excision with a 5-year survival rate of greater than 90 %. Surgical resection is also the primary treatment modality for intraoral SCCA, with 5-year survival varying widely depending on the extent and

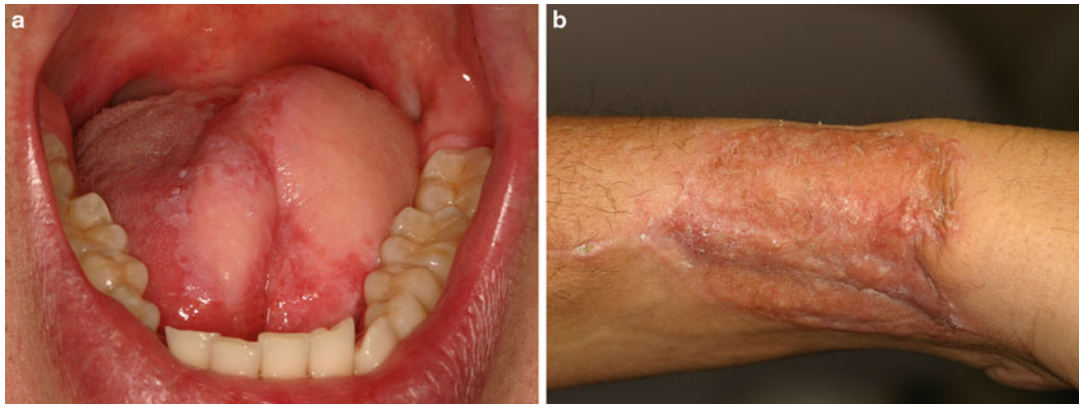

Fig. 9.28 Hemiglossectomy with surgical reconstruction using a free-tissue transfer graft from the forearm. (**a**) The left side of the tongue has a thick, pale, "skin-like" appearance compared with the mucosa on the right. (**b**) Appearance of the healing graft harvest site

location of disease. Surgical removal of regional lymph nodes is indicated when there is evidence of lymph node involvement at the time of diagnosis or significant risk for spread to the lymph nodes. Postoperative chemoradiation therapy (i.e., concurrent platinum-based chemotherapy that renders the tissue more radiosensitive) is recommended for advanced stage cancers in which there is high risk for recurrent disease or metastasis. For tumors located more posteriorly, such as base of tongue, chemoradiation therapy may be chosen as the primary treatment modality with surgery reserved as a secondary option if needed.

All treatment modalities are associated with potentially unpleasant or debilitating side effects. Surgery can result in disfigurement and sensory changes of the mucosa as well as functional deficits in speech, swallowing, and breathing (Figs. 9.28, 9.29, and 9.30). These can lead to poor nutritional intake and social isolation. Radiation therapy causes both acute and chronic side effects; mucositis (Fig. 9.31) and reddening of the skin in the field of radiation are common acute effects. The major late effects include xerostomia (see Chap. 6), hypothyroidism, trismus, and *osteoradionecrosis* (ORN) of the jaws (Fig. 9.32). Radiation-induced xerostomia can lead to rampant severe caries that can be quite problematic to treat and often lead to tooth loss. Aggressive preventive dental care is essential in these patients (see Chap. 8). ORN is a potentially devastating complication of radiation therapy that is often precipitated by trauma to irradiated bone or extraction of teeth within the field of radiation. Fibrosis and compromised blood supply secondary to radiation can lead to poor wound healing and bone necrosis. Surgical debridement and hyperbaric oxygen (used to encourage wound healing through increased oxygen tension and stimulation of vascular proliferation) may be required for treatment for this problem.

Treatment of oral cancer remains challenging despite best efforts, with poor overall survival rates for advanced disease. Research in the field is active, however, and the future will hopefully bring new advances. In the meantime, the clinician should be aware that the best chance for cure lies in detection and treatment of disease in the earliest stages.

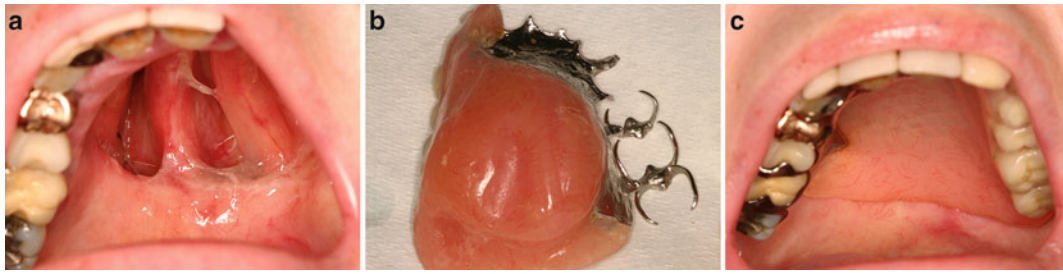

Fig. 9.29 Partial maxillectomy surgical defect functionally restored with a prosthesis. (**a**) Anatomical defect in the hard palate. (**b**) Maxillary prosthesis (obturator) used to seal the opening from the oral cavity into the nasal cavity and maxillary sinus. (**c**) Prosthesis in place allowing patient to eat, swallow, and speak comfortably

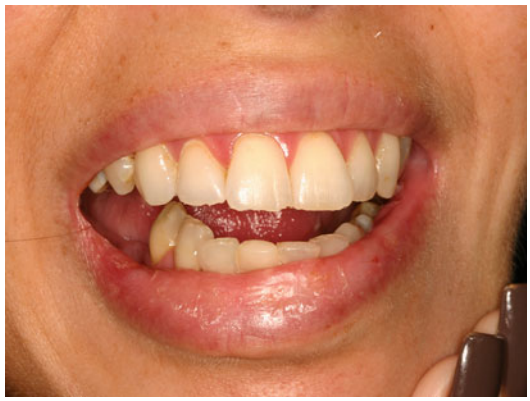

Fig. 9.30 A 22-year-old female with severe trismus following radiation therapy for nasopharyngeal carcinoma. This represents the patient's maximum opening

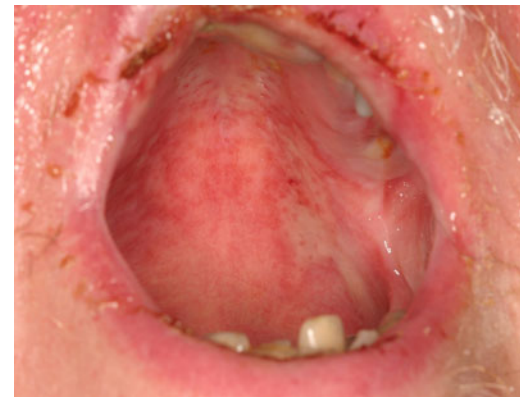

Fig. 9.31 Typical radiation mucositis of the palate with irregularly shaped ulcer and associated erythema. There is also ulceration of the upper labial mucosa

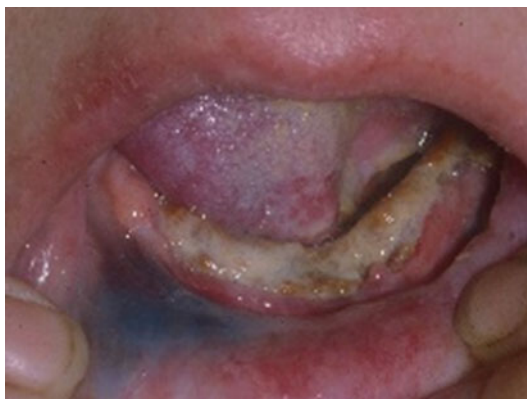

Fig. 9.32 Osteoradionecrosis of the mandible. The necrotic bone appears *yellow* and ragged with edematous surrounding gingiva. Note the large amalgam tattoo in the right labial mucosa. Photograph courtesy of Stephen Sonis, D.M.D., D.M.Sc., Boston, MA

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