ELSEVIER
SAUNDERS

Dent Clin N Am 49 (2005) 143–165

THE DENTAL
CLINICS
OF NORTH AMERICA

Oral cancer: leukoplakia and squamous cell carcinoma

Nelson L. Rhodus, DMD, MPH

Division of Oral Medicine, Oral Diagnosis, and Radiology, Department of Diagnostic and Social Services, School of Dentistry, University of Minnesota, 7-536 Moos Health Science Tower, 515 Delaware Street Southeast, Minneapolis, MN 55455, USA

Cancer is the second leading cause of death in the United States. In 2004, more than 563,000 people will die of cancer, and there will be more than 1.3 million new cases (Table 1). Cancer of the mouth and pharynx accounts for nearly 30,000 cases of cancer (incidence of 10/100,000) and approximately 7200 deaths per year in the United States and is the sixth most common cancer worldwide [1]. Oral cancer is more common than leukemia, Hodgkin's lymphoma, brain, stomach, or ovarian cancer. More than 90% of these oral-pharyngeal cancers are squamous cell carcinomas. The other 10% are salivary gland tumors, lymphoma, sarcoma, and others. The 5-year survival rate from these carcinomas has not significantly improved in the past 30 years and remains at approximately 50%. For whites the 5-year survival rate is approximately 55%; for African Americans it is only 31% [1].

The ratio of males to females diagnosed with oral cancer is 2:1 over lifetime, although the ratio comes closer to 1:1 with advancing age (perhaps influenced by the relationship of human papillomavirus to oral cancer). Approximately 96% of oral cancer is diagnosed in persons older than 40 years, and more than 50% of all cancers occur in persons over the age of 65 years [2]. The average age at the time of diagnosis is 63 years [1]. Recently, however, evidence has emerged indicating that oral cancers are occurring more frequently in younger persons (under 40 years) [3,4]. The overall incidence of oral cancer has remained stable, relative to the occurrence of newly diagnosed cancers of all sites, with absolute numbers only slightly increasing each year [5].

The observation that oral cancer generally occurs with advancing age indicates that over time certain sequenced alterations in the biochemical-

E-mail address: rhodu001@umn.edu

doi:10.1016/j.cden.2004.07.003 dental.theclinics.com

Table 1
Incidence of head and neck cancer (38,000/year in 2003)

Location	Incidence	%[a]	%[b]
Oral	17,900	48	2.4
Oropharynx	3500	10	0.8
Nasopharynx	2500	9	0.5
Larynx	9800	25	1.4
Maxillary sinus	1100	3	0.2
Nose	400	1	0.1
Esophagus	800	2	0.2
Ear	300	1	0.2

[a] % of all head and neck cancers.
[b] % of all cancers.
From Jemal A, Tiwari R, Murray T, et al. Cancer statistics, 2004. CA Cancer J Clin 2004;54(1):8–25.

biophysical processes (nuclear, enzymatic, metabolic, immunologic) of aging cells with a particular genetic predisposition undergo and accumulate mutations, resulting in carcinogenic transformation. These carcinogenic changes may be influenced by oncogenes, carcinogens, and mutations caused by chemicals, viruses, irradiation, drugs, hormones, nutrients, or physical irritants. An imbalance between abnormal cell proliferation and apoptosis (programmed cell death) may be modified by factors that alter cellular production of growth and suppressor proteins [6,7].

These malignancies of the oral cavity often begin as preneoplastic lesions in the form of inflammatory lesions such as leukoplakia, erythroplasia, and erythroleukoplakia. Leukoplakia is associated with tobacco and alcohol use and chronic inflammation with the risk of malignant transformation to squamous cell carcinoma of approximately 5% to 17% (Fig. 1) [7,8]. Alterations in host immunity, inflammation, angiogenesis, and metabolism have been noted as prominent clinical features in oral cancer [8,9]. These

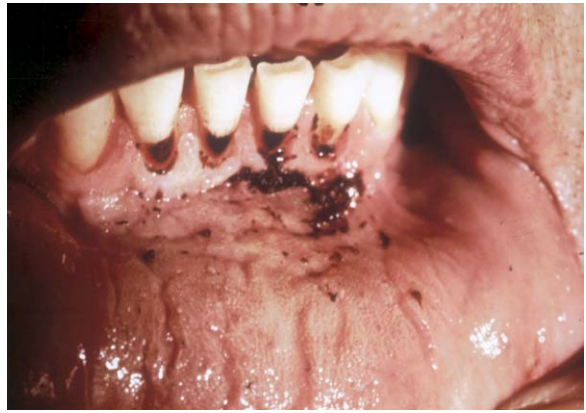

Fig. 1. Leukoplakia in the anterior labial vestibule associated with smokeless tobacco use.

tumor-induced T-lymphocyte, granulocyte, and neoangiogenic responses in the local tumor microenvironment have been associated with increased tumor growth and metastasis and decreased survival rates [10,11]. Pathologic changes in systemic responses have also been observed, including induction of antibody and other acute-phase inflammatory protein responses [12,13].

This article reviews the epidemiology, etiologic risk factors, clinical presentation, recognition, and diagnosis of oral precancer and cancer. The actual treatment and complications from treatment of oral cancer are discussed only briefly.

Anatomic sites

The tongue is the most common site for oral cancer in both American men and women (Table 2). The most recent data (2004) indicate that about 37% (7320/20,010) of all oral cancer (excluding the pharynx) occurs on the tongue [1]. There are some differences in the most common oral sites in other areas of the world. In Southeast Asia nasopharyngeal cancer is more common, and in India buccal mucosa carcinomas are the most common oral cancers. Data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute demonstrate that 30% of all oral cancers diagnosed in the United States between 1985 and 1996 occurred in the tongue, followed by the lip and floor of the mouth [4,5]. Oral tongue malignancies (located in the anterior two thirds of the tongue) accounted for 53% of tongue cancers [5,6]. The other oral anatomic sites, in decreasing order, are lip (22%), floor of mouth (13%), salivary glands (12%), buccal mucosa (6%), gingiva (6%), and palate (4%) [14].

Stage at diagnosis and survival

Approximately half of all patients with oral and pharyngeal cancers survive the disease 5 years following treatment (Table 3). Theses figures are

Table 2
The incidence of oral cancer ranked by anatomic location

Oral location	Incidence	%
Tongue	7300	37
Lip	4200	22
Floor of mouth	2300	13
Salivary glands	2000	12
Buccal mucosa	1100	6
Gingiva	1100	6
Palatal	800	4

From Jemal A, Tiwari R, Murray T, et al. Cancer statistics, 2004. CA Cancer J Clin 2004;54(1):8–25.

Table 3
The 5-year survival rate (%) of oral cancer based upon TMN staging

Site	Localized	Nodes	Distant metastasis	Total
Lip	89	57	40	86
Floor of mouth	65	31	14	44
Other	61	29	18	44
Tongue	52	22	7	33

From Landis S, Murray T, Wingo DS, et al. Cancer statistics. CA Cancer J Clin 1998;48: 6–29.

less favorable for squamous cell carcinoma of the tongue (33%) [5–7]. In the United States, the outcomes are more favorable for whites than for African Americans (5-year survival rates of 58% versus 34%, respectively). Genetics certainly is significantly involved in the predisposition to cancer, but socioeconomic status, education, and access to the health care system also have an influence [5–7]. Obviously, the survival rates are much loserfor advanced tumors than for earlier-detected, localized cancers. At the time of diagnosis, nearly 50% of all carcinomas of the tongue have already metastasized [14]. An additional 35% to 40% metastasize within 5 years. If all cases of oral cancer were diagnosed and treated early as localized tumors, almost 80% of all patients would survive 5 years [13,14]. Unfortunately, little progress in early diagnosis has been made during the past 40 years. Additionally, based on more than 25,000 Surveillance Epidemiology and End Rescue (SEER) program oral/pharyngeal cases for which there was adequate information, localized/early oral cancers were outnumbered by advanced tumors 59% to 41%. The lip was the only major site where localized cancers were found more frequently than more advanced cancers [4–6]. Advances in the treatment of oral cancer have not led to significantly improved survival; therefore, earlier diagnosis is obviously the most important factor in improving oral cancer control and reducing morbidity and mortality [5–7].

Tumor metastasis node staging

Head and neck cancer is staged by the tumor metastasis node (TMN) classification, usually when a malignancy is strongly suspected and before an incisional biopsy. The TMN classification is based upon tumor size, regional lymph node involvement, and distant metastasis. Most often a chest radiograph is used to determine distant metastasis [15,16]. A patient with a suspicious 2.5-cm oral lesion with ipsilateral lymphadenopathy of 2 cm and a negative chest radiograph will be classified as T2N1M0. This classification is useful for determining the severity and prognosis of the cancer and for the choice of therapy (excisional surgery, modified or radical lymph node dissection, radiation, or chemotherapy) [15,16].

Etiology and risk factors

The etiology of oral cancer is almost certainly multifactorial and involves many alterations in host immunity and metabolism, angiogenesis, and exposure to chronic inflammation in a genetically susceptible individual. The carcinogenic changes may be influenced by oncogenes, carcinogens, and mutations caused by chemicals, viruses, irradiation, drugs (tobacco and alcohol), hormones, nutrients, or physical irritants [7,16,17].

Immune system

Multiple studies have shown that the risks of cancer increase in individuals whose immune systems are either congenitally defective or have been suppressed or altered by disease or medications. Furthermore, immune competence and immune cell surveillance diminish with age. These facts undoubtedly contribute to the association between age and malignancy [6,17,18].

Tobacco use

Tobacco smoking is a worldwide epidemic, contributing to serious health problems and systemic diseases of immense proportions. Reports from the US Surgeon General and others conclude that cigarette smoking is the main cause of cancer mortality in the United States, contributing to an estimated 30% of all cancer deaths and substantially to cancers of the head and neck [4,7,18].

The association between cigarette use and oral carcinoma has been firmly established from epidemiologic studies, revealing that there are more than twice as many smokers among oral cancer patients as among control populations [18]. One study of more than 400 patients with oral cancer found that 72% were smokers and 58% smoked more than one pack daily, demonstrating the high risk for tobacco users [19,19a].

Tobacco use also increases the already high risk for developing recurrences of oral cancer as well as second primary oral and pharyngeal cancers [18–20]. The combined effects of tobacco and alcohol use are illustrated in another study of more than 350 patients who had oral cancer and a mortality rate of 31% within 5 years [21].

Certain hydrocarbons isolated from tobacco products have been shown to induce carcinomas in animals under certain experimental conditions [18,19]. Benzo[a]pyrene, one of the most potent of these carcinogens, binds to nucleo-proteins and is mutagenic as well as carcinogenic. The association between tobacco use and oral malignancies also seems to include cigars, pipes, and smokeless preparations [18,19].

Alcohol intake, especially long-term, excessive use, has also been associated with the incidence of oral cancer. One group of investigators found that 44% of 108 patients with cancer of the tongue and 59% of 68 patients

with cancer of the floor of the mouth, palate, or tonsillar fossa had unequivocal evidence of alcoholic cirrhosis. Approximately 75% drank alcohol excessively [21].

Definitive associations between alcohol-containing mouthrinses and the development of oral cancer have not been established [18].

Oral lichen planus

Oral lichen planus (OLP) is a complex, chronic, inflammatory disease. The cause of OLP is unknown, but it is thought to be an immunopathologic disease. Although OLP can occur in any oral site, the buccal mucosa is by far the most common location. OLP can usually be recognized by the unique clinical features of reticular, annular, or punctate keratotic (white) patterns on the mucosal surface [18,22]. Diagnosis should always be confirmed by biopsy.

A summary of the results from several studies performed in seven different countries since 1981 indicates that 0.4% to 5.6% of oral lichen planus lesions transformed to squamous cell carcinoma [18,22–24].

Nutrition

Although some studies indicate a potential association of dietary factors and cancer in general, no clear dietary characteristics (deficiencies or excesses of nutrients) have been recognized that directly correlate with cancer of the oral cavity [18,25].

Viruses

The role of viruses in development of oral cancer has been a matter of speculation for a long time. Although viruses are not known to cause oral squamous cell carcinoma, other head and neck cancers have a defined relationship with viruses. Of the viruses that infect oral tissues, those having oncogenic potential are from two groups: the herpesviruses and the papillomaviruses [26–28].

Clinical examination

A comprehensive oral examination of every patient is essential to dental practice. The standard-of-care examination includes thorough examination of every intraoral mucosal surface and of the extraoral head and neck tissues including lymph nodes [15,18]. Any mucosal abnormality requires some action plan; whether the plan involves treatment, biopsy, referral, or recall examination depends on the nature of the lesion [15]. Many oral lesions are ill-defined, variably appearing, controversial, and poorly understood lesions that fortunately are benign but may present changes that can easily be

confused with malignancy. Conversely, an early malignancy may quite often be mistaken for a benign lesion. Some lesions are considered premalignant because they are statistically correlated with subsequent associated cancerous changes [18]. A considerable amount of clinical uncertainty is involved in the early detection of malignancy as well as in the understanding that many of these lesions may not always remain benign.

Clinically, oral cancer may clinically present with different colors and morphologies. Oral cancer may appear as leukoplakia (white) (Fig. 2), erythroplasia (red), or, most commonly, erythro-leukoplakia (red and white) (Fig. 3) and as plaques, macules, ulcers, exophytic papules, nodules, or tumors, or as granular or verrucous lesions (Fig. 4). Often, squamous cell carcinomas present with pleomorphic characteristics combining several of these features and may or may not be fissured, indurated, and bleeding [15,18,29–31].

Delay in diagnosis

The failure of affected patients to seek professional consultation obviously accounts for much of the delay in the diagnosis of oral cancer. In a considerable number of cases, however, diagnosis has been delayed because a clinician did not suspect the malignant nature of the lesion and either failed to treat it or treated it inadequately [18,29,30].

A retrospective study found that only 14.1% of dentists who had diagnosed a patient with epithelial dysplasia (considered premalignant) followed that lesion with a second biopsy during a 3-year period (Box 1) (Rhodus et al, submitted for publication, 2003).

Most reports reveal that patients usually delay seeking professional advice for more than 3 months after having become aware of an oral sign or

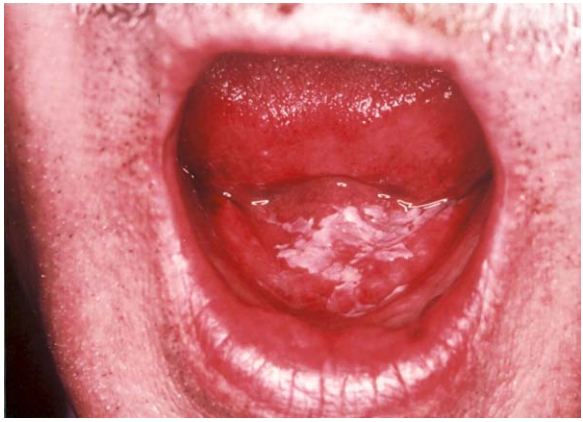

Fig. 2. Leukoplakia in the anterior floor of the mouth in an immunocompromised patient. This lesion was subsequently diagnosed as oral squamous cell carcinoma.

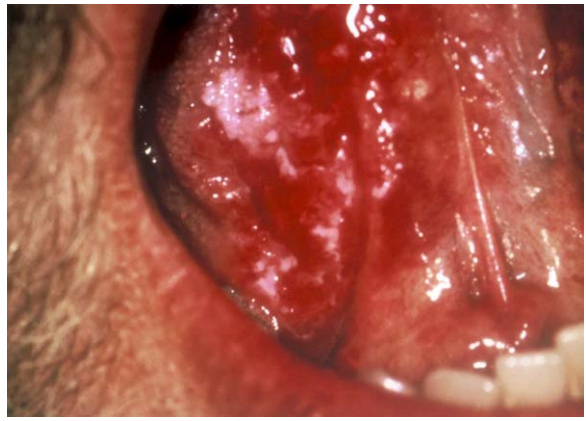

Fig. 3. Erythroleukoplakia on the mid-lateral ventral tongue in a patient with heavy alcohol and tobacco use. This lesion was subsequently diagnosed as oral squamous cell carcinoma.

symptom. Such delays in diagnosis can only lead to local extension of a lesion and increase the risk of metastatic spread of the cancer [15,18,29].

Signs and symptoms

During the earliest stages, oral cancer is usually painless or may present with only mild irritation. Pain usually occurs when the lesion becomes more advanced and ulcerated. Ulceration indicates that the lesion has penetrated through the lamina propria into the connective tissue. Rarely, a patient may seek initial consultation because of a swelling in the neck that represents

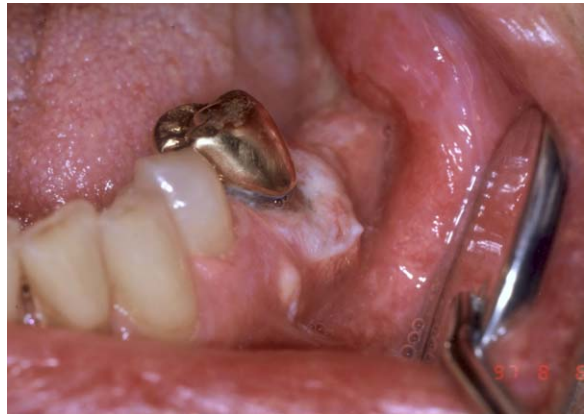

Fig. 4. Proliferative verrucous leukoplakia on the attached gingival of the left mandibular first molar. This lesion was subsequently diagnosed as oral squamous cell carcinoma.

Box 1. Minnesota dentists' follow-up of oral dysplasia

- 285 respondents reported 141 patients with "dysplasia." Patient characteristics: 58.8% male; 41.2% female; mean age, 64.3 ± 5.6 years
- 76.5% of dentists (108/141) said they "followed-up."
- 14.1% of patients (20/141) were biopsied on follow-up.
- 11.3% of lesions (16/141) became cancerous; 7/20 were diagnosed on second biopsy.
- 85.8% of lesions without diagnosis (121/141) were lost to follow-up
- 42.8% of severe dysplasias became cancerous

a metastasis from an oral lesion of which the patient may be completely unaware [15,18,29]. The following are common presenting signs of oral carcinoma [18]:

- Erythema—redness of the mucosa, which reflects inflammation, thinness and irregularity of epithelium, and lack of keratinization
- Ulceration or erosion—occurs with the destruction of epithelial integrity resulting from discrepancy in cell maturation and disruption of basal lamina (basement membrane).
- Induration—mucosal firmness or hardness caused by an increase in the number of epithelial cells secondary to an inflammatory infiltrate
- Fixation—abnormally dividing cells invading to deeper areas of muscle and bone
- Chronicity—failure of lesions to heal. Cancer is not a spontaneously reversible disease. Therefore, a malignant lesion normally will not disappear in the absence of definitive antitumor therapy.
- Lymphadenopathy—hardening or enlargement of regional nodes resulting from engorgement with neoplastic cells that spread by lymphatic vessels. Nodes are usually painless and often become fixed because of capsular erosion and local infiltration. Tumors that involve marked induration, fixation, and lymphadenopathy are signs of advanced cancer.
- Leukoplakia—a white patch on the mucosal surface, reflecting excess epithelial keratin production. Hyperkeratosis is often associated with well-differentiated carcinomatous lesions. Excess keratin also may be produced within the stratified squamous epithelium and can appear as "keratin pearls."
- Erythroplakia—a red macule, plaque, or exophytic lesion that may appear similar to trauma or inflammation but may in fact represent early angiogenic activity and premalignancy. The most common clinical presentations of oral precancerous lesions include some erythema.

- Erythroleukoplakia (mixed)—lesions that present with some combination of both red and white color changes represent the most common clinical appearance of oral precancerous lesions as well as squamous cell carcinomas.

Dysplasia and malignant transformation

Typically, in the early stages, oral carcinomas may appear as small, innocuous, harmless, minor mucosal changes, to which the unsuspecting clinician may not respond aggressively. An extended period of watching and empiric treatments may allow the lesion to expand and potentially metastasize. In the premalignant and early cancerous stages, slow cellular proliferation may obscure clinical recognition of neoplastic activity in some cases [18]. Obviously, this failure to pursue the nature of the lesion aggressively often leads to delays in diagnosis and early intervention, adversely affecting prognosis and eventual outcomes. All lesions of the oral cavity that persist or do not respond to the usual therapeutic measures must therefore be considered precancerous or malignant until proven otherwise [18].

An insight into the histopathogenesis of carcinoma may give the clinician a better understanding of presenting signs [32,33].

The risk of subsequent malignant transformation increases when a biopsy specimen reveals an associated epithelial dysplasia. Current scientific consensus is that this transformation occurs in a stepwise fashion through stages of increasingly severe epithelial dysplasia accompanied by the loss of cell-cycle control, apoptosis, and various genetic aberrations [32–37]. Specific data regarding the correlation among degrees of oral epithelial dysplasia, time-related progression, and the influences of a variety of cofactors remain uncertain, however [32–36].

Oral carcinogenesis

In oral epithelial tissues, accumulating mutations (ie, genetic progression), chromosomal damage, and loss of cellular control functions are observed during the course of sequential histologic changes that culminate in oral cancer [32–37]. These changes are manifested as the transition from normal histology to early intraepithelial dysplasia and preneoplasia, increasingly severe intraepithelial neoplasia, superficial cancer, and finally, invasive disease.

Although the carcinogenic process can be relatively aggressive (eg, in the presence of a DNA-repair -deficient genotype or viral transformant such as human papillomavirus), these changes generally occur over decades [26,32–37]. Carcinogenesis is characterized by progressive loss of proliferation and apoptosis controls and increasing cellular disorganization, aneusomy (DNA content), and heterogeneity [32–37]. The appearance of specific molecular and more general genotypic damage is associated with increasingly severe

dysplastic phenotypes. In many cases, crucial early steps include inactivation of tumor suppressor genes (eg, mutation of the *p53* gene) or activation of oncogenes (eg, *ras*). Carcinogenesis may follow multiple paths and be multifocal; not all cancers in a given tissue nor all cells in a given cancer may ultimately contain the same lesions. Progression to cancer may also be influenced by factors specific to the host's tissue environment [17,32–37].

Molecular progression

Neoplasms arise clonally from transformed cells that have undergone specific genetic alterations in proto-oncogenes or tumor suppressor genes [32–37]. As just one example, loss of chromosomal region 9p21 is a common genetic change that occurs early in tumor progression. This loss leads to an inhibition of cyclin-dependent kinase that is important in cell-cycle regulation. Additionally, a large number of malignant cells express a mutation of the suppressor *p53* gene, which, in turn, diminishes cell senescence and indirectly promotes growth [38–41]. Activation of proto-oncogenes or loss of tumor suppressor genes can result in the stimulation of cell division [18,32–41]. Another phenomenon, telomeres, composed of repeating sequences of six nucleotides, are situated at the end of chromosomes. They influence the longevity of cells and regulate their biologic clock by progressive shortening. When activated by telomerase, telomere growth may prevent cell senescence by maintaining chromosomal integrity. Thus, telomeres may be a potentially important target in controlling cancer. The complexity and multifactorial aspects of explaining neoplasia are evident [18,32–41].

Once the diagnosis of dysplasia is made, there is really no way of determining which dysplasias will transform into carcinoma and which will not. Usually, it may be safely assumed that severe epithelial dysplasia will most likely proceed to carcinoma in situ, intraepithelial carcinoma, or frank malignancy over time.

When the dysplasia of the entire epithelium involves disruption of the basal lamina and subsequent invasion of the adjacent connective tissue, the diagnosis of malignancy is certain.

Precancerous classification

Because a risk of transformation to carcinoma exists, oral leukoplakia is a premalignant lesion. This conclusion is based on the following factors: (1) a large number of oral carcinomas have been associated with leukoplakic changes, and (2) in prospective studies, occurrences of malignant transformations in oral leukoplakias exceed the number of oral cancers expected in the general population. The incidence of malignant transformations in oral leukoplakias ranges from approximately 5% to 17% [7,8,18]. Most longitudinal studies of oral leukoplakia patients focus on habits, dysplastic and malignant transformations, and classification. The possibility of

spontaneous regression of oral leukoplakia has been confirmed in several reports, however [7,8,18].

According to Mashberg [42], the following conclusions regarding the clinical recognition and diagnosis of oral leukoplakia, the development of epithelial dysplasia, and subsequent malignant transformation, may be made:

1. In oral leukoplakia, the occurrence and time of dysplastic changes are uncertain. De novo transformation from hyperkeratosis to carcinoma may occur without recognizable dysplasia.
2. An erythematous component and discomfort should raise suspicion of dysplastic or malignant transformation.
3. Because epithelial dysplasia increases the risk of the development of a malignant tumor, surgical removal of dysplastic lesions is indicated. This treatment limits prospective follow-up studies.
4. Proliferative verrucous forms of leukoplakia have a high risk of dysplasia and malignant trans-formation and should be treated aggressively.
5. Although the severity of the degrees of dysplasia has clinical significance regarding neoplasia, patients with mild dysplasia, or even without should be followed carefully. This advice holds true even after surgical intervention, because recurrences are common.
6. Reproducible interexaminer agreements in diagnosing oral epithelial dysplasia are difficult to achieve, adding to the confusion regarding treatment approaches and aggressiveness. Therefore, the development of biologic markers (eg, monoclonal antibodies, DNA/RNA probes, special stains) emerges as extremely important, and even critical, in producing fundamental advances in the diagnosis, prognosis, and treatment parameters of precancerous lesions [7,8,18,42].

Genomics

Many studies are presently being conducted regarding the role of chromosomes and genes in influencing the development and progression of oral leukoplakia to malignancy. DNA-microarray studies of gene expression are now being used to determine the differential profile of genes that are expressed in both oral cancer and precancerous (leukoplakia) lesions. Ginos and colleagues [43] at the University of Minnesota have found that 2891 genes were differentially expressed in tissues of patients with oral cancer. The categories of genes included those involved in the host immune response, angiogenesis, apoptosis, and cell differentiation, among others [43]. The same group is now using microarrays to analyze tissues from premalignant lesions and is also using cytologic smears. Results from these studies will aid in identifying risks and prognoses.

In a recent study by Sudbo and colleagues [44] of nuclear DNA content (ploidy) in 150 Norwegian patients with dysplastic leukoplakia, there was

a direct risk association between chromosome ploidy and progression to malignancy. Lesions that demonstrated a diploid nuclear DNA content had only a 3% association with cancer, whereas 84% of aneuploid lesions were cancerous.

Erythroleukoplakia and erythroplasia

Leukoplakia that clinically has an erythematous or red component (erythroleukoplakia) is far more likely to undergo dysplastic or malignant epithelial changes than other forms of leukoplakia [7,18,42]. Because red lesions without a white component may also represent either dysplasia or carcinoma, such lesions must be carefully evaluated. Carcinogenic progression in patients with erythroleukoplakia has been shown to be almost fourfold that of the patients with homogeneous leukoplakia [45]. Therefore, all patients with chronic white or red lesions, whether treated or not, should have periodic diagnostic biopsies. In a representative study of 257 patients, 58% of the patients with leukoplakia had an associated erythematous area, whereas 84% of the patients who eventually developed a carcinoma demonstrated a red component. Other studies have confirmed this association [30,32,42,45,46].

With these findings in mind, clinicians should take biopsy specimens that include erythematous areas because of the increased risk of representing dysplasia or neoplasia [47].

In Mashberg and Samit's [42] prospective study of 222 asymptomatic oral carcinomas, 28% were red only; 62% were red and white; 97% occurred in the mouth floor, oral tongue, and oropharynx; and 84% were less than 2 cm at their largest diameter.

Erythroplasia with ulceration

Another rare but high-risk premalignant lesion is the chronic erythematous change associated with constantly recurring erosive changes. These lesions are often mistaken for ''recurrent aphthous stomatitis of the herpetiform variety'' or ''nonspecific inflammatory immunopathologic vesiculoerosive disease'' [18,42].

Proliferative verrucous leukoplakia

Silverman and colleagues [48] first described a unique form of leukoplakia found in 30 patients. This group of lesions has a high risk of malignant transformation. The name proliferative verrucous leukoplakia (PVL) results from the characteristic appearance–an expanding, exophytic/fissured white lesion. PVL is a precancerous lesion with high transformation and mortality rates, women with PVL outnumber men; less

than one-third of PVL patients smoke; and there is usually multisite oral involvement [49].

Candidiasis (candidosis), leukoplakia, and erythroplasia

Some studies indicate that candidiasis may add a potential risk factor for malignant transformation of leukoplakia. As many as 53% of the leukoplakia patients who developed carcinomas were Candida positive before tumor formation [18,49]. Other reports have demonstrated a higher prevalence of Candida in speckled leukoplakia than in homogeneous (all-white) leukoplakia [46].

Diagnosis and management

Patients with leukoplakia are usually asymptomatic [30,46,49]. The lesion is usually discovered by a clinician during a routine examination or by patients themselves because of a feeling of roughness in their mouths. There are really no reliable clinical signs and symptoms associated with oral leukoplakia that relate to an accurate prediction of a premalignant or early malignant change [7,18,30]. Even mild symptoms are often suggestive of a dysplastic epithelial change or even an early invasive tumor. Because the clinical appearance of oral leukoplakia—thick or scant, large or small—does not reliably indicate its biologic potential, clinicians should be suspicious of all white lesions and should carefully evaluate and observe these patients [7,18,30,49]. The diagnosis of these lesions must be made by histopathologic evaluation (Fig. 5).

The first step in management of leukoplakia is the removal of all irritants. If the leukoplakia is not reversible, excision is the most effective treatment [30,46,49].

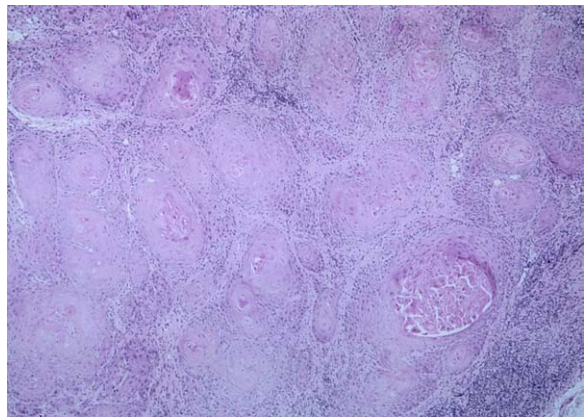

Fig. 5. Histologic examination of oral squamous cell carcinoma.

Excisional biopsy with subsequent histopathologic examination is the criterion for diagnosis for oral lesions [18,46,49]. Because these lesions may spread over a large area, they cannot always be surgically excised. In many cases, incisional biopsies must be taken and multiple-site biopsies may be required in the areas of the lesion that are phenotypically most suspicious for oral cancer [48]. In addition, recurrence after excision is common, possibly because of continuation of an irritant or the biologic potential in adjacent tissue that appears normal morphologically (field cancerization). Some areas of the lesion may be cancer, whereas others may not. Therefore, representative sampling is important in making the diagnosis. The use of the carbon-dioxide laser has proved extremely useful and effective [48,50].

There is always some degree of risk for recurrence and for the development of squamous cell carcinoma at the surgical site. Therefore, close follow-up must be emphasized. To help limit recurrences, adjunctive chemotherapy using antiviral drugs and antioxidants is being studied [51,52].

Although there might be a "field keratinization," genomic susceptibility for hyperkeratosis, there is some evidence of clonal derivation. This clonal derivation is seen at times when a portion of a leukoplakic lesion is removed, and the residual clinical lesion disappears [33,43].

Cytology and brush biopsy

It is not practical or appropriate to biopsy every oral lesion often, even after it has been diagnosed with epithelial dysplasia [48,53]. A simple, reliable, and acceptable technique to support the health professional's clinical judgment in differentiating benign lesions from early malignant neoplasia is highly desirable.

This need is especially strong when the clinician has already obtained a nondiagnostic biopsy and wishes to follow-up the lesion by a noninvasive technique. Exfoliative cytology serves this purpose, but cytology is an adjunct to, not a substitute for, a scalpel biopsy [18,48]. Exfoliative cytology is a technique by which individual epithelial cells (ideally including basal cells) are obtained from a lesion, spread on a slide, fixed and stained, and then examined by microscopy [48,53]. The entire oral cavity is lined with stratified squamous epithelium that varies in thickness and keratinization according to anatomic and functional sites. Transepithelial sampling using a specially designed brush to obtain representative cells from all epithelial layers of a specimen can be accomplished with the proper brush and technique [48,53]. The brush biopsy technique and oral cytology examination can provide a significant adjunct in the evaluation of questionable lesions by giving clinicians an initial screening tool and indicating the use of scalpel incisional biopsy of lesions that did not clinically appear to be oral cancer. Results from these brush biopsies have indicated the early diagnosis of malignancies that would otherwise have remained unsuspected. A thorough

examination of the cell sample is made by an automated microscopic system or by a trained cytologist and certified by a pathologist [48,53].

Classification of benign oral diseases from exfoliative cytologic studies is not yet possible; tissue patterns as seen in biopsies are necessary. There is a possibility of false-positive and false-negative results, but reports of those have been few. These errors, although undesirable, are manageable because of the manner in which cytologic reports are used and interpreted [48,53]:

1. If clinical suspicion remains in the face of a negative or atypical report, a biopsy should be performed in any case.
2. A suspicious report indicates a definite need to establish a definitive diagnosis immediately.
3. When smears contain cells consistent with or suspicious for malignancy, biopsy is mandatory.

Fine-needle aspiration

Fine-needle aspiration (FNA) biopsy is a highly acceptable and accurate technique for differentiating benign from malignant lesions involving lymph nodes [54]. Use of this minimally invasive technique accelerates diagnosis and treatment and improves overall management. This technique also has greatly aided the evaluation of salivary gland lesions and leukemic infiltrates. Thus, FNA biopsy is a safe, quick, and reliable procedure that can immediately differentiate inflammatory, reactive, cystic, and neoplastic processes [54].

Toluidine blue

Because epithelial dysplasia and early squamous cell carcinoma vary considerably in appearance and often resemble certain benign lesions, clinical identification is difficult, and biopsy is frequently delayed by attempts at empiric remedies. Vital staining with toluidine blue has been shown to aid early recognition and accelerate biopsy, diagnosis, and treatment [55,56]. Toluidine blue is a metachromatic dye of the thiazine group that has been effectively used as a nuclear stain because of its binding to DNA. Overall accuracy of the toluidine blue uptake was 93% [55,56]. It can be concluded that toluidine blue staining is a useful adjunct to careful examination, clinical judgment, and biopsy (Fig. 6). There is abundant evidence that toluidine blue dye used in this diagnostic manner is neither mutagenic nor carcinogenic [55,56].

Monoclonal antibodies

Some monoclonal antibodies for use in the detection of oral cancer have been developed, studied, and reported [57–59]. The techniques have not yet

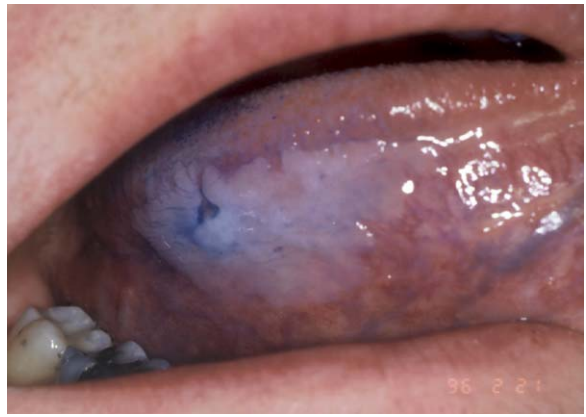

Fig. 6. Dysmorphic leukoplakia on the mid-lateral, ventral tongue stained with toluidine blue. Note the area (ulcerated) with the greatest uptake of toluidine blue. This lesion was subsequently diagnosed as oral squamous cell carcinoma.

been perfected, however, and questions regarding specificity have limited large studies and use in diagnostic laboratories. No matter what diagnostic technique is used, the possibility of a false-negative response exists. The development of monoclonal antibodies that have high sensitivity and specificity for epithelial dysplastic and malignant cells would enhance accuracy of diagnosis in some cases in which the usual or typical cellular characteristics of precancer or cancer are not apparent. Numerous biomarkers now being developed and studied will yield additional information regarding cellular neoplastic potential and even the risks of metastases [57–61].

Imaging

Most commonly, neoplasms of the oral cavity and oropharynx are discovered by clinical examination and confirmed by biopsy or FNA [18,42]. Imaging studies may then be used to map the extent of disease, detect bone invasion and cervical adenopathy, and evaluate adherence of tumor to the carotid artery [62–66]. Occasionally, a patient may present with cervical nodal metastases without a clinically evident primary lesion. In this setting, cross-sectional imaging obtained before panendoscopy and biopsy is useful to locate submucosal tumor and direct biopsies to possible targets. Cross-sectional imaging may also facilitate the detection of recurrent disease following therapy [62–66]. The advanced imaging techniques presently available include CT, MRI, and positron emission tomography (PET) [62–66]. Ultrasonography, often in conjunction with FNA biopsy, may also be useful.

Chemoprevention

Several clinical trials with pharmacologic agents such as retinoids aimed at the prevention of the progression of leukoplakia to frank carcinoma have been performed without real long-term success [67–72]. Although some data have shown that 13-cis-retinoic acid may reverse oral leukoplakia, a common premalignant lesion in the mouth, the data are inconclusive, and there is considerable concern about the toxicity of some of the particular retinoids used in these trials. Patients receiving these agents have had a dropout rate of up to 10%/year secondary to toxicity [67–72]. Additionally, patients who have received prior chemotherapy and have hepatic disease have been excluded from these trials. There is a reasonably high likelihood that a head and neck cancer patient may have either or both of these exclusion criteria. Because the duration of delivery for chemopreventive agents for head and neck cancer has not been determined, the use of compounds with unacceptable long-term adverse toxicity profiles is questionable [67–72].

Therefore, chemoprevention of oral leukoplakia remains experimental [72,73]. Because of the high potential of treating oral leukoplakia effectively and preventing progression to oral cancer, multiple clinical trials are currently underway with several potentially effective chemoprevention agents such as ketorolac, celecoxib, and piogliozone [73].

Follow-up

Because many methods of managing leukoplakia are not always feasible or effective, these patients must be observed periodically [18,42]. The follow-up examination should be frequent (<6 months) depending upon the actual diagnosis and clinical scenario. The follow-up examination includes careful clinical observation and an occasional biopsy [18,42]. Follow-up biopsy is indicated when changes in signs or symptoms occur. These changes may be subtle. Exfoliative cytology using the brush biopsy technique and vital staining with toluidine blue help supplement clinical judgment and serve as an adjunct to biopsy. Because the standard for diagnosis is tissue biopsy with histopathologic examination, the value of adjunctive techniques is to accelerate microscopic evaluation by indicating the need of biopsy in situations in which a biopsy is delayed or not thought to be indicated or necessary. Negative smears or stains must be balanced with good clinical judgment. Therefore, if clinical suspicion persists in a lesion that does not disappear, a standard scalpel biopsy must be considered [18,42].

Treatment

Long-term survival and functional results of treatment depend on the stage of the tumor, histology, and treatment plan [18,42]. The treatment plan is developed at pretreatment conferences (tumor boards) by multi-

disciplinary consultants and subsequent patient/family concurrence. Additional important outcome factors include the patient's nutritional status, general health, tobacco use, alcohol intake, and anticipated compliance with the rigors of therapy [74–79].

Curative treatment modalities include local surgery with wide margins and radiation or a combination of both. Chemotherapy may be used with these modalities to enhance cure rates and to preserve function, which increasingly has led to organ-preservation strategies. If there is a question about survival of the patient, the choice may be to employ measures to ensure palliation, control pain, and maintain quality of life [74–79].

Head and neck surgeons, radiation oncologists, dentists, and rehabilitation specialists all are involved cooperatively in the treatment process. The side effects of treatment are permanent and diminish oral function. Treatment planning is based on careful cancer staging and selection of therapies, which allows for prognostication and facilitates the reporting of outcomes. Physical examination, open biopsy, or FNA biopsy and radiologic imaging studies that include CT, MRI, and PET are used to classify and stage the disease [74–79].

Most of the major functional disabilities following treatment are related to the volume of the disease and to the degree of radiation or chemotherapy required for treatment. The treatment, in turn, is related to the postoperative complications including the extent of mandible (or other tissue) loss, reduction of tongue mobility, caries and loss of dentition, xerostomia, muscle trismus, diminished taste and mastication, risk of osteoradionecrosis, and anesthesia of the oral cavity. To achieve a cure, the treatment plan considers an adequate resection of tumor and surrounding normal tissue and the addition of the lymphatic drainage while attempting to preserve as much normal anatomy and physiology as possible [74–79].

References

[1] Jemal A, Tiwari R, Murray T, Ghafoor A, et al. Cancer statistics, 2004. CA Cancer J Clin 2004;54(1):8–25.
[2] Edwards BK, Howe HL, Ries LA, et al. Annual report to the nation on the status of cancer, 1973–1999, featuring implications of age and aging on US cancer burden. Cancer 2002;94: 2766–92.
[3] Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, et al. SEER Cancer Statistics Review, 1975–2000. Bethesda (MD): National Cancer Institute; 2003.
[4] Myers JN, Elkins T, Roberts D, Byers RM. Squamous cell carcinoma of the tongue in young adults: increasing incidence and factors that predict treatment outcomes. Otolaryngol Head Neck Surg 2000;122:44–51.
[5] Schantz SP, Yu G-P. Head and neck cancer incidence trends in young Americans, 1973–1997, with a special analysis for tongue cancer. Arch Otolaryngol Head Neck Surg 2002; 128:268–74.
[6] Shiboski CH, Shiboski SC, Silverman S Jr. Trends in oral cancer rates in the United States, 1973–1996. Community Dent Oral Epidemiol 2000;28:249–56.
[7] Silverman S Jr. Demographics and occurrence of oral and pharyngeal cancers: the outcomes, the trends, the challenge. J Am Dent Assoc 2001;132:7S–11S.

[8] Silverman S, Gorsky M, Lozada F. Oral leukoplakia and malignant transformation. Cancer 1984;53:563–8.
[9] Young MRI, Wright MA, Lozano Y, Prechel MM, Benefield J, Leonetti JP, et al. Increased recurrence and metastasis in patients whose primary head and neck squamous cell carcinomas secreted granulocyte-macrophage colony stimulating factor and contained CD34 + natural suppressor cells. Int J Cancer 1997;74:69–74.
[10] Gleich LL, Biddinger PW, Duperier FD, Gluckman JL. Tumor angiogenesis as a prognostic indicator in T2–T4 oral cavity squamous cell carcinoma: a clinical-pathologic correlation. Head Neck 1997;19:276–80.
[11] Pak AS, Wright MA, Matthews JP, Collins SL, Petruzelli GJ, Young MRI. Mechanisms of immune suppression in patients with head and neck cancer: presence of CD34 + cells which suppress immune functions within cancers that secrete granulocyte-macrophage colony-stimulating factor. Clin Cancer Res 1995;1:95–103.
[12] Smith CW, Chen Z, Dong G, Loukinova E, Pegram MY, Nicholas-Figueroa L, et al. The host environment promotes the development of primary and metastatic squamous cell carcinomas that constitutively express proinflammatory cytokines IL-1 alpha, IL-6, GM-CSF and KC. Clin Exp Metastasis 1998;16(7):655–64.
[13] Vlock DR, Arnold B, Humpierres J, Schwartz DR, Baker SR, Krause CJ, et al. Serial studies of autologous antibody reactivity to squamous cell carcinoma of the head and neck. Cancer Immunol Immunother 1992;34:329–36.
[14] Landis S, Murray T, Wingo DS, Ries T. Cancer statistics. CA Cancer J Clin 1998;48:6–29.
[15] Little JW, Falace DA, Miller CS, Rhodus NL. Cancer. Dental management of the medically compromised patient. 6th edition. St. Louis (MO): Mosby; 2002. p. 394–412.
[16] Clayman GL, Lippman SM, Laramore GE, Hong WK. Head and neck cancer. In: Holland JF, Frei E, Bast RC Jr, Kufe DW, Morton DL, Weichselbaum R, et al, editors. Cancer medicine. Philadelphia: Williams and Wilkins; 1996. p. 1645–709.
[17] Califano J, van der Riet P, Westra W, Nawroz H, Clayman G, Piantadosi S, et al. Genetic progression model for head and neck cancer: implications for field cancerization. Cancer Res 1996;56(11):2488–92.
[18] Silverman S Jr. Oral cancer. 5th edition. Hamilton, (Ontario, Canada): B.C. Decker; 2003. p. 1–128.
[19] Forastiere A, Koch W, Trotti A, Sidransky D. Head and neck cancer. N Engl J Med 2001; 345:1890–900.
[19a] National Cancer Institute. Risks associated with smoking cigarettes with low machine-measured yields of tar and nicotine. Smoking and tobacco control. National Cancer Institute monograph no. 13. Bethesda (MD): National Cancer Institute; 2001.
[20] Lewin F, Norell SE, Johansson H. Smoking tobacco, oral snuff, and alcohol in the etiology of squamous cell carcinoma of the head and neck. Cancer 1998;82:1367–75.
[21] Mashberg A, Garfinkel L, Harris S. Alcohol as a primary risk factor in oral squamous cell carcinoma. CA Cancer J Clin 1981;31:146–55.
[22] Vincent SD, Fotos PG, Baker KA, Williams TP. Oral lichen planus: the clinical, historical and therapeutic features of 100 cases. Oral Surg Oral Med Oral Pathol 1990;70: 165–71.
[23] Silverman S Jr, Gorsky M, Lozada-Nur F, Giannotti K. A prospective study of findings and management in 214 patients with oral lichen planus. Oral Surg Oral Med Oral Pathol 1991;72:665–70.
[24] Silverman S Jr, Bahl S. Oral lichen planus update: clinic characteristics, treatment responses and malignant transformation. Am J Dent 1997;10:259–63.
[25] Petridou E, Zavras AI, Lefatzis D. The role of diet and specific micronutrients in the etiology of oral carcinoma. Cancer 2002;94:2981–8.
[26] Miller CS, Johnstone BM. Human papillomavirus as a risk factor for oral squamous cell carcinoma: a meta-analysis, 1982–1997. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001;91:622–35.

[27] Shillitoe EJ, Greenspan D, Greenspan JS, Silverman S Jr. Five-year survival of patients with oral cancer and its association with antibody to herpes simplex virus. Cancer 1986;58: 2256–9.
[28] Shillitoe EJ, Gilchrist E, Pellenz C, Murrah V. Effects of herpes simplex virus on human oral cancer cells, and potential use of mutant viruses in therapy of oral cancer. Oral Oncol 1999;35:326–32.
[29] Axell T, Pindborg JJ, Smith CJ, Van der Wa I. Oral white lesions with special reference to precancerous and tobacco-related lesions: conclusions of an international symposium held in Uppsala, Sweden, May 18–21, 1994. J Oral Pathol Med 1996;25:49–54.
[30] Lummerman H, Freedman P, Kerpel S. Oral epithelial dysplasia and the development of invasive squamous carcinoma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1995; 79:321–9.
[31] Mashberg A, Samit A. Early diagnosis of asymptomatic oral and oropharyngeal squamous cancers. CA Cancer J Clin 1995;45:328–51.
[32] Forastiere A, Koch W, Trotti A, Sidransky D. Head and neck cancer. N Engl J Med 2001; 345:1890–900.
[33] Smith BD, Haffty BG, Sasaki CT. Molecular markers in head and neck squamous cell carcinoma: their biological function and prognostic significance. Ann Otol Rhinol Laryngol 2001;110:221–8.
[34] Hong WK, Sporn MB. Recent advances in chemoprevention of cancer. Science 1997;278: 1073–7.
[35] Kelloff GJ. Perspectives on cancer chemoprevention research and drug development. Adv Cancer Res 2000;278:199–234.
[36] Kelloff GJ, Sigman CC, Johnson KM, Boone CW, Greenwald P, Crowell JA, et al. Perspectives on surrogate end-points in the development of drugs that reduce the risk of cancer. Cancer Epidemiol Biomarkers Prev 2000;9:127–34.
[37] Ondrey FG, Dong G, Van Waes C. Constitutive expression of AP-1 and NF IL-6 in squamous carcinoma of the head and neck. Proc Am Assoc Cancer Res 1998;39:3081.
[38] Das S, Khanna N. In vivo and in vitro observation of cellular immune parameters in squamous cell carcinoma of the oral cavity and its correlation with tumor load and prognosis. Cancer Invest 1986;4:207–16.
[39] Schatzkin A, Freedman LS, Dorgan J, McShane L, Schiffman MH, Dawsey SM. Using and interpreting surrogate end-points in cancer research. In: Toniolo P, Boffetta P, Shuker DEG, Rothman N, Hulka B, Pearce N, editors. Application of biomarkers in cancer epidemiology (IARC Scientific Publications No. 42). Lyon (France): International Agency for Research on Cancer; 1997. p. 265–71.
[40] Smith CW, Chen Z, Dong G, Loukinova E, Pegram MY, et al. The host environment promotes the development of primary and metastatic squamous cell carcinomas that constitutively express pro-inflammatory cytokines IL-1 alpha, IL-6, GM-CSF, and KC. Clin Exp Metastasis 1998;16(7):655–71.
[41] Stein GS, Montecino M, van Wijnen AJ, Stein JL, Lian JB. Nuclear structure-gene expression inter-relationships: implications for aberrant gene expression in cancer. Cancer Res 2000;60:2067–71.
[42] Mashberg A, Samit A. Early diagnosis of asymptomatic oral and oropharyngeal squamous cancers. CA Cancer J Clin 1995;45:328–51.
[43] Ginos MA, Page GP, Michalowicz BS, Patel K, Volker S, Pambuccian SE, et al. Identification of a gene expression signature associated with recurrent disease in squamous cell carcinoma of the head and neck. J Cancer Res 2003;64:55–63.
[44] Sudbo J, Kildal W, Risberg B, et al. DNA content as a prognostic marker in patients with oral leukoplakia. N Engl J Med 2001;344:1270–80.
[45] Silverman SJ, Gorsky M, Lozada F. Oral Leukoplakia and malignant transformation: a follow-up study of 257 patients. Cancer 1984;53:563–8.

[46] Waldron CA, Shafer WG. Leukoplakia revisited. A clinicopathologic study or 3,256 oral leukoplakias. Cancer 1975;36:1386–92.
[47] Hansen LS, Olson JA, Silverman S. Proliferative verrucous leukoplakia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1985;60:285–9.
[48] Silverman S Jr. Oral cavity. In: Bibbo M, editor. Comprehensive cytology. 2nd edition. Philadelphia: WB Saunders; 1997. p. 403–12.
[49] Silverman S Jr, Gorsky M. Proliferative verrucous leukoplakia. A follow-up study of 54 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1997;84:154–7.
[50] Chu FWF, Silverman S Jr, Dedo HH. CO2 laser treatment of oral leukoplakia: a follow-up of 70 patients. Laryngoscope 1991;109:950–63.
[51] Shaheen NJ, Straus WL, Sandler RS. Chemoprevention of gastrointestinal malignancies with non-steriodal anitinflammatory drugs. A review. Cancer 2002;94:950–63.
[52] Lippman SM, Spitz M, Zoltan T. Epidemiology, biology, and chemoprevention of aerodigestive cancer. Cancer 1994;74:2719–25.
[53] Christian DC. Computer-assisted analysis of oral brush biopsies at an oral cancer screening program. J Am Dent Assoc 2002;133:357–62.
[54] Scher RL, Oostingh PE, Levine PA. Role of fine-needle aspiration biopsy in the diagnosis of lesions of the oral cavity, oropharynx, and nasopharynx. Cancer 1988;62:2602–6.
[55] Portugal LC, Wilson KM, Biddinger PW, Gluckman JL. The role of toluidine blue in assessing margin status after resection of squamous cell carcinomas of the upper aerodigestive tract. Arch Otolaryngol Head Neck Surg 1996;122:517–9.
[56] Warnakulasuriya KAAS, Johnson NW. Sensitivity and specificity of Orascan toluidine blue mouthrinse in the detection of oral cancer and precancer. J Oral Pathol Med 1996;25: 97–103.
[57] Chen Z, Colon I, Oritz N, Callister M, Dong G, Pegram MY, et al. Effects of interleukin-1α, interleukin-1 receptor antagonist, and neutralizing antibody on proinflammatory cytokine expression by human squamous cell carcinoma lines. Cancer Res 1998;58:3668–76.
[58] Chen Z, Malhotra PS, Ondrey F, Duffy DC, Smith CW, Enamorado I, et al. Expression of proinflammatory and proangiogenic cytokines in human head and neck cancer patients. Head Neck 1998;20:450.
[59] Dong G, Loukinova E, Smith CW, Chen Z, Van Waes C. Genes differentially expressed with malignant transformation and metastatic tumor progress on of murine squamous cell carcinoma. J Cell Biochem Suppl 1997;28/29:90–100.
[60] Van Waes C, Chen Z, Cheng L, Kirby M, Smith CS, et al. Cytokines in the immune pathogenesis and therapy of head and neck cancer. Head Neck 1998;20(5):153.
[61] Boone CW, Kelloff GJ. Biomarker end-points in cancer chemoprevention trials. In: Toniolo P, Boffetta P, Shuker DEG, Rothman N, Hulka B, Pearce N, editors. Application of biomarkers in cancer epidemiology (IARC Scientific Publications No. 142). Lyon (France): International Agency for Research on Cancer; 1997. p. 273–80.
[62] Hsu I-C, Phillips TL. Oral cavity cancer. In: Leibel SA, Phillips TL, editors. Textbook of radiation oncology. Philadelphia: WB Saunders; 1998. p. 457–77.
[63] Curtin HD, Ishwaran H, Mancuso AA. Comparison of CT and MR imaging in staging of neck metastases. Radiology 1998;207:123–30.
[64] Braams JW, Pruim J, Freling NJM. Detection of lymph node metastases of squamous cell cancer of the head and neck with FDG-PET and MRI. J Nucl Med 1995;36:211–6.
[65] Harnsberger HR. Head and neck imaging. St. Louis (MO): Mosby Yearbook; 1990.
[66] Schaefer SD, Maravilla KR, Suss RA. Magnetic resonance imaging vs. computed tomography. Comparison in imaging oral cavity and pharyngeal carcinomas. Arch Otolaryngol 1985;111:730–4.
[67] Lippman SM, Benner SE, Hong WK. Cancer chemoprevention. J Clin Oncol 1994;12: 851–73.
[68] Lippman SM, Lee JS, Lotan R, Hittelman W, Wargovich MJ, Hong WK. Biomarkers as intermediate end points in chemoprevention trials. J Natl Cancer Inst 1990;82:555–60.

[69] Hong W, Endicott J, Itri LM, Doos W, Batsakis JG, Bell R, et al. 13-cis retinoic acid in the treatment of oral leukoplakia. N Engl J Med 1986;315:1501–5.
[70] Lippman SM, Batsakis JG, Toth BB, Weber RS, Lee JJ, Martin JW, et al. Comparison of low-dose 13cRA with beta carotene to prevent oral carcinogenesis. N Engl J Med 1993;328: 15–20.
[71] Hong WK, Lippman SM, Itri LM, Karp DD, Lee JS, Byers RM, et al. Prevention of second primary tumors with 13cRA in squamous-cell carcinoma of the head and neck. N Engl J Med 1990;323:795–801.
[72] Benner SE, Pajak TF, Lippman SM, Earley C, Hong WK. Prevention of second primary tumors with 13cRA in squamous cell carcinoma of the head and neck: Long term follow-up. J Natl Cancer Inst 1994;86:140–1.
[73] Sporn MB, Suh N. Chemoprevention of cancer. Carcinogenesis 2000;21:525–30.
[74] Fu KK, Pajak TF, Trotti A, Chapman D, Cooper J, Forastiere A, et al. A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyper-fractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003. Int J Radiat Oncol Biol Phys 2000;48:7–16.
[75] Schuchter LM, Hensley ML, Meropol NJ, Winer EP. 2002 update of recommendations for the use of chemotherapy and radiotherapy protectants: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 2002;20:2895–903.
[76] Puthawala A, Nisar Syed AM, Gamie S. Interstitial low-dose-rate brachytherapy as a salvage treatment for recur-rent head-and-neck cancers: long-term results. Int J Radiat Oncol Biol Phys 2001;5:354–62.
[77] Krakoff IH. Systemic treatment of cancer. CA Cancer J Clin 1996;46:134–41.
[78] Kramer AM. The role of chemotherapy in head and neck malignancy. Oral Maxillofac Surg Clin North Am 1993;5:303–17.
[79] Merlano M, Vitale V, Rosso R, Benasso M, Corvo R, Cavallari M, et al. Treatment of advanced squamous cell carcinoma of the head and neck with alternating chemotherapy and radiotherapy. N Engl J Med 1992;327:1115–21.