If clinically indicated, conservative surgical excision is the treatment of choice for cutaneous blue nevi. Recurrence is minimal with this treatment. Malignant transformation to melanoma is rare but has been reported. Because an oral blue nevus clinically can mimic an early melanoma, biopsy of intraoral pigmented lesions is usually advisable.

**LEUKOPLAKIA (LEUKOKERATOSIS; ERYTHROLEUKOPLAKIA)**

As originally defined by the World Health Organization (WHO), oral leukoplakia (leuko = white; plakia = patch) represents “a white patch or plaque that cannot be characterized clinically or pathologically as any other disease.” The term is strictly a clinical one and does not imply a specific histopathologic tissue alteration.

The definition of leukoplakia is unusual in that it makes the diagnosis dependent not so much on definable appearances as on the exclusion of other entities that appear as oral white plaques. Such lesions as lichen planus, morsicatio buccarum (chronic cheek nibbling), frictional keratosis,
tobacco pouch keratosis, nicotine stomatitis, leukoedema, and white sponge nevus must be ruled out before a clinical diagnosis of leukoplakia can be made. As with most oral white lesions, the clinical color results from a thickened surface keratin layer, which appears white when wet, or a thickened spinous layer, which masks the normal vascularity (redness) of the underlying connective tissue.

Although leukoplakia does not constitute a specific histopathologic diagnosis, it is considered a precancerous or premalignant lesion (see Box 10-3 for definitions of these and other related terms). That is, the frequency of transformation into malignancy is greater than that for normal or unaltered mucosa.

Incidence and Prevalence

Leukoplakia is by far the most common oral precancer, representing 85% of such lesions. In addition, more than one-third of oral carcinomas exhibit leukoplakia in close proximity. Based on pooled, weighted data from previously reported studies, the worldwide prevalence of leukoplakia has been estimated to fall within a range of 1.5% to 4.3%. There is a strong male predilection (70%), except in regional populations in which women use tobacco products more than men. A slight decrease in the proportion of affected males, however, has been noted over the past half century. The disease is diagnosed more frequently now than in the past, probably because of an enhanced awareness among health professionals (rather than because of a real increase in frequency).

Cause

The cause of leukoplakia remains unknown, although hypotheses abound.

**BOX 10-3 Precancer Terminology Used in This Text**

- **Precancerous lesion (precancer, premalignancy).** A benign, morphologically altered tissue that has a greater than normal risk of malignant transformation.
- **Precancerous condition.** A disease or patient habit that does not necessarily alter the clinical appearance of local tissue but is associated with a greater than normal risk of precancerous lesion or cancer development in that tissue.
- **Potentially malignant disorder.** A lesion, disease, or condition associated with a greater than normal risk of developing malignancy.
- **Malignant transformation potential.** The risk of cancer being present in a precancerous lesion or condition, either at initial diagnosis or in the future (usually expressed in percentages). The potential for mucosa without precancerous lesions or conditions is called normal.
- **Relative risk.** A specific epidemiologic measure of the association between exposure to a particular factor and the risk of acquiring a disease, expressed as a ratio of the incidence or prevalence of a disease among those exposed and those not exposed to the factor.

**Tobacco**

Among the various proposed contributory factors, tobacco smoking appears to be the most closely associated with leukoplakia. More than 80% of patients with leukoplakia are smokers, and smokers are much more likely to have leukoplakia than nonsmokers. Heavier smokers have greater numbers of lesions and larger lesions than do light smokers, especially after many years of tobacco use. In addition, leukoplakias often disappear or become smaller within the first year of smoking cessation.

Smokeless tobacco use often causes a clinically distinctive white oral plaque called tobacco pouch keratosis (see page 364). This lesion probably is not a true leukoplakia. In contrast, betel quid use (see page 366)—with or without smokeless tobacco—is associated with true leukoplakia; this habit is common in parts of Asia.

**Alcohol**

Alcohol exerts a strong synergistic effect with tobacco in oral cancer development. Nevertheless, there is conflicting evidence as to whether alcohol is associated independently with leukoplakia. People who excessively use mouth rinses with alcohol content greater than 25% may have grayish buccal mucosal plaques, but these lesions are not considered true leukoplakias.

**Sanguinaria**

Persons who use toothpaste or mouth rinses containing the herbal extract, sanguinaria, may develop a true leukoplakia called sanguinaria-associated keratosis. This lesion usually arises in the maxillary vestibule or on the maxillary alveolar mucosa (Fig. 10-56). More than 80% of individuals with maxillary vestibular or alveolar leukoplakia have a history of using products that contain sanguinaria, compared with 3% of the normal population.

The affected epithelium may demonstrate dysplasia identical to that seen in other leukoplakias, although the potential for cancer development is uncertain. The white plaque may persist for years even after the patient stops using the product.
CHAPTER 10  Epithelial Pathology

Epithelial Pathology

357

or become less severely dysplastic after antifungal therapy. In some cases, tobacco smoking may cause the leukoplakia and also may predispose the patient to develop candidiasis.

The potential role of HPV in the development of oral leukoplakias remains uncertain. Investigators have detected HPV DNA about two to four times more often in oral leukoplakias than in clinically normal oral mucosa. Nevertheless, the presence of HPV DNA alone cannot exclude the possibility of coincidental (or “bystander”) infection. Low viral load and frequent absence of viral integration into the host genome among many HPV-positive oral precancers and cancers bring into question the biological relevance of HPV infection in these lesions. Also problematic is the fact that HPV is found more frequently in homogeneous leukoplakias than in non-homogeneous leukoplakias, whereas non-homogeneous lesions are more likely to undergo malignant transformation (see later).

Trauma

Several keratotic lesions, which until recently had been viewed as variants of leukoplakia, are now considered not to be precancers. Nicotine stomatitis is a generalized white palatal alteration that seems to be a hyperkeratotic response to the heat generated by tobacco smoking (usually a pipe), rather than a response to the carcinogens within the smoke (see page 368). Its malignant transformation potential is so low as to be about the same as that of normal palatal mucosa.

In addition, chronic mechanical irritation can produce a white lesion with a roughened keratotic surface, termed frictional keratosis. Although this lesion clinically appears similar to true leukoplakia, it is now thought to be no more than a normal hyperplastic response (similar to a callus on the skin). Keratoses of this type are readily reversible after elimination of the trauma, and obviously traumatic lesions—such as linea alba (see page 259), morsicatio (see page 259), and toothbrush gingival “abrasion”—have not been documented to transform into malignancy. In addition, the presence of dentures or broken and missing teeth has not been shown to increase cancer risk. Alveolar ridge keratoses (Fig. 10-58)—involving the retromolar pad or crest of an edentulous alveolar ridge—represent another form of frictional keratosis caused by masticatory function or denture trauma. Frictional keratosis should be differentiated from oral precancers.

Clinical Features

Leukoplakia usually affects persons older than 40 years. Prevalence increases rapidly with age, especially for males, and as many as 8% of men older than 70 years are affected (Fig. 10-59). The average age (60 years) is similar to that for patients with oral cancer; however, in some studies, leukoplakia has been found to occur about 5 years earlier (on average) than oral squamous cell carcinoma.

Approximately 70% of oral leukoplakias are found on the lip vermilion, buccal mucosa, and gingiva. Lesions on
Thick leukoplakia may disappear or continue unchanged and seldom shows dysplasia on biopsy. For tobacco smokers who do not reduce their habit, as many as two-thirds of such lesions enlarge and progress to a stage called homogeneous or thick leukoplakia, characterized by a thickened, leathery, distinctly white plaque with deepened fissures (Figs. 10-60 and 10-61). Most remain indefinitely at this stage. However, as many as one-third regress or disappear. Some lesions develop increased surface irregularities and are called granular or nodular leukoplakia (Figs. 10-62). Lesions with sharp or blunt, wartlike projections are called verrucous or verruciform leukoplakia.

A special high-risk form of leukoplakia, proliferative verrucous leukoplakia (PVL), is characterized by the development of multiple, slowly spreading, keratotic plaques with rough surface projections (Figs. 10-63 and 10-64). The relationship of PVL to cases described as verrucous leukoplakia is uncertain. The gingiva frequently is involved, but other sites may be affected as well. Although the lesions typically begin as simple, flat hyperkeratoses that are
despite therapy. PVL is unusual among the leukoplakia variants in having a strong female predilection (1:4 male-to-female ratio) and minimal association with tobacco use.

Leukoplakia may become dysplastic or even malignant, with no change in its clinical appearance. However, some lesions eventually demonstrate scattered patches of redness, called erythroplakia (see page 363). Such areas usually represent sites in which epithelial cells are so immature or atrophic that they can no longer produce keratin. This intermixed red-and-white lesion, called erythroleukoplakia or speckled leukoplakia, frequently exhibits advanced dysplasia on biopsy (Fig. 10-65).

Over the years, several new techniques (such as vital dyes, brush cytology, chemiluminescence, and autofluorescence) have been proposed to aid in the identification or diagnosis of premalignant and malignant oral lesions. However, there

indistinguishable from ordinary leukoplakia, PVL exhibits persistent growth, eventually becoming exophytic and verrucous. As the lesions progress, they may go through a stage indistinguishable from verrucous carcinoma (see page 389), but they later usually develop dysplasia and transform into full-fledged squamous cell carcinoma (often within 8 years of initial PVL diagnosis). These lesions rarely regress

Fig. 10-62 Granular Leukoplakia. Focal leukoplakic lesion with a rough, granular surface on the posterior lateral border of the tongue. Biopsy revealed early invasive squamous cell carcinoma.

Fig. 10-63 Proliferative Verrucous Leukoplakia (PVL). A, Diffuse, corrugated, white lesions of the buccal and palatal mucosa. B, Thickened, corrugated, white lesion involving the palate, alveolar ridge, and lingual marginal gingiva.

Fig. 10-64 Proliferative Verrucous Leukoplakia (PVL). A, An elderly white female developed extensive leukoplakia with rough surface projections on the buccal mucosa and mandibular alveolar ridge. B, After failing to comply with a recommendation for biopsy, the same patient returned 2 years later with a verrucous carcinoma.
is currently insufficient evidence to support the use of such
technologies in routine practice, and careful clinical eval-
uation with directed conventional biopsy remains the gold
standard for assessment of oral leukoplakia (see Fig. 10-98).

Histopathologic Features
Microscopically, leukoplakia is characterized by a thickened
keratin layer of the surface epithelium (hyperkeratosis),
with or without a thickened spinous layer (acanthosis).
Some leukoplakias demonstrate surface hyperkeratosis but
show atrophy or thinning of the underlying epithelium.
Frequently, variable numbers of chronic inflammatory cells
are noted within the subjacent connective tissue.

The keratin layer may consist of parakeratin (hyperpara-
eratosis), orthokeratin (hyperorthokeratosis), or a com-
bination of both (Fig. 10-68). With parakeratin, there is no
granular cell layer and the epithelial nuclei are retained in
the keratin layer. With orthokeratin, the epithelium dem-
onstrates a granular cell layer, and the nuclei are lost in the
keratin layer.

Verrucose leukoplakia has papillary or pointed surface
projections, varying keratin thickness, and broad, blunted
rete ridges. It may be difficult to differentiate from early
verrucous carcinoma.

The microscopic appearance of PVL varies by lesion
stage. Early PVL appears as a benign hyperkeratosis that is

• Fig. 10-65 Erythroleukoplakia. Red and white lesion of the lateral
  border of the tongue. Biopsy revealed carcinoma in situ.

• Fig. 10-66 Leukoplakia. Extensive ventral and lateral tongue
  lesion with areas representing various possible phases or clinical
  appearances (compare with Fig. 10-67).

• Fig. 10-67 Leukoplakia. Composite representation of the various phases or clinical appearances of
  oral leukoplakia, with anticipated underlying histopathologic changes. Lesions have increasing malignant
  transformation potentials as their appearances approach those toward the right. (From Bouquot JE, Gnepp DR:
  Laryngeal precancer—a review of the literature, commentary and comparison with oral leukoplakia, Head Neck
  13:488-497, 1991.)
The grade of epithelial dysplasia refers to its “severity” or intensity. **Mild epithelial dysplasia** refers to alterations limited principally to the basal and parabasal layers (Fig. 10-69). **Moderate epithelial dysplasia** demonstrates involvement from the basal layer to the midportion of the spinous layer (Fig. 10-70). **Severe epithelial dysplasia** demonstrates alterations from the basal layer to a level above the midpoint of the epithelium (Fig. 10-71). Sometimes dysplasia may extend down the duct of a minor salivary gland, especially in lesions of the floor of the mouth (Fig. 10-72); such cases exhibit an increased risk for recurrence.

The diagnosis of PVL requires careful correlation of the variable clinical and microscopic findings.

Epithelial dysplasia or carcinoma is found in only about 5% to 25% of oral leukoplakias. Dysplastic changes typically begin in the basilar and parabasilar portions of the epithelium. The more dysplastic the epithelium becomes, the more the atypical epithelial changes extend to involve the entire thickness of the epithelium. The histopathologic alterations of dysplastic epithelial cells are similar to those of squamous cell carcinoma and may include the following:

- Enlarged nuclei and cells
- Large and prominent nucleoli
- Increased nuclear-to-cytoplasmic ratio
- Hyperchromatic (excessively dark-staining) nuclei
- Pleomorphic (abnormally shaped) nuclei and cells
- Dyskeratosis (premature keratinization of individual cells)
- Increased mitotic activity (excessive numbers of mitoses)
- Abnormal mitotic figures (tripolar or star-shaped mitoses or mitotic figures above the basal layer)

In addition, histomorphologic alterations of dysplastic epithelium are evident at low-power magnification, including the following:

- Bulbous or teardrop-shaped rete ridges
- Loss of polarity (lack of progressive maturation toward the surface)
- Keratin or epithelial pearls (focal, round collections of concentrically layered keratinized cells)
- Loss of typical epithelial cell cohesiveness

The grade of epithelial dysplasia refers to its “severity” or intensity. **Mild epithelial dysplasia** refers to alterations limited principally to the basal and parabasal layers (Fig. 10-69). **Moderate epithelial dysplasia** demonstrates involvement from the basal layer to the midportion of the spinous layer (Fig. 10-70). **Severe epithelial dysplasia** demonstrates alterations from the basal layer to a level above the midpoint of the epithelium (Fig. 10-71). Sometimes dysplasia may extend down the duct of a minor salivary gland, especially in lesions of the floor of the mouth (Fig. 10-72); such cases exhibit an increased risk for recurrence.

**Carcinoma in situ** is defined as dysplasia involving the entire thickness of the epithelium (i.e., extending from the basal layer to the surface or “top-to-bottom” change) (Fig. 10-73). There may or may not be a thin layer of keratin on the surface. The epithelium may be hyperplastic or atrophic. Some authorities consider carcinoma in situ to be a precancerous lesion, whereas others believe that it represents a genuine malignancy discovered before invasion. Regardless, an important feature of carcinoma in situ is absence of invasion, and without invasion, metastasis cannot occur.
In this light, keratin pearl formation is rare in carcinoma in situ and may indicate focal invasive squamous cell carcinoma.

**Treatment and Prognosis**

Because leukoplakia represents a clinical term only, a biopsy is required to obtain a histopathologic diagnosis and to guide the appropriate management. Biopsies should be taken from the clinically most "severe" areas (with features toward the right of Fig. 10-67). Multiple biopsies may be needed for large or multifocal lesions.

Leukoplakia exhibiting moderate epithelial dysplasia or worse warrants complete destruction or removal, if feasible. The management of leukoplakia exhibiting less severe change is guided by the lesion size and the response to more conservative measures, such as tobacco cessation. Some smoking-related leukoplakias with no or minimal dysplasia may disappear or diminish in size within 3 months after the patient stops smoking.

Complete removal can be accomplished with equal effectiveness by surgical excision, electrocautery, cryosurgery, or laser ablation. An advantage of surgical excision is that it allows for optimal tissue preservation for histopathologic analysis, whereas the other methods may be preferable in some cases for limiting procedure-related morbidity.

Even after removal, reported overall recurrence rates range from 10% to 35%, and development of additional leukoplakias is common. In particular, verruciform or granular leukoplakias exhibit an 83% recurrence rate and, thus, often undergo additional removal or destruction. Nevertheless, it is unclear whether surgical excision of leukoplakia significantly reduces the risk for developing malignancy. Therefore, even after removal, long-term follow-up is extremely important.

Although leukoplakia without dysplasia often is not excised, clinical evaluation every 6 months is recommended because of the possibility of disease progression. Additional biopsies are recommended if smoking continues or if the clinical changes increase in severity.

Reported malignant transformation rates for oral leukoplakia vary considerably across studies, although best estimates suggest a malignant transformation rate of less than 2% per year. Some of this variation may be due to patient selection bias, with lower rates typically reported among community-based than hospital-based studies. Additional confounding factors include variations in diagnostic definitions, clinical management, and periods of observation. Typically, the latter extend for 5 to 10 years, but several studies have observed patients for more than 20 years. Carcinomatous transformation usually occurs 2 to 4 years after leukoplakia onset, but it may occur within months or after decades.

Each clinical phase of leukoplakia has a different malignant transformation potential. Thin leukoplakia seldom becomes malignant without demonstrating a clinical change. In contrast, malignant transformation occurs in
approximately 1% to 7% of homogeneous, thick leukoplakias and 4% to 15% of granular or verruciform leukoplakias. Erythroleukoplakia carries an average transformation potential of 28%, but reported rates vary from 18% to 47%.

The transformation potential of the different phases of leukoplakia is related closely to the degree of dysplasia present. Lesions with moderate and severe dysplasia reportedly have malignant transformation potentials of 4% to 11% and 20% to 43%, respectively.

Additional factors associated with an increased risk for malignant transformation of leukoplakia include female gender, older age, nonsmoking status, lesion persistence for several years, extensive lesion size, and involvement of the ventrolateral tongue or floor of mouth. In particular, leukoplakia of the ventrolateral tongue and oral floor exhibits malignant transformation in 16% to 39% of cases and 47% of those occurring in females.

There is much interest in the identification of chromosomal, genetic, and molecular alterations that may aid in predicting the risk of malignant transformation for oral leukoplakia. Cytogenetic studies have suggested that loss of heterozygosity (LOH) of chromosome arms 3p and 9p is associated with increased risk of malignant transformation, and additional LOH at 4q, 8p, 11q, 13q, and 17p further increases this risk. Additional alterations—such as microsatellite instability (insertion or deletion of base pairs in repetitive stretches of short DNA sequences), increased telomerase activity (important for cellular longevity), and changes in expression of various molecular markers (e.g., p53, survivin, and other regulators of apoptosis; p16 and other markers of cell cycle regulation; epidermal growth factor receptor [EGFR]; matrix metalloproteinases; vascular endothelial growth factor receptor [VEGFR])—have exhibited a variable association with histopathologic progression in oral premalignant lesions. Despite these interesting observations, histopathologic grading of dysplasia remains the standard method for predicting the risk of progression to malignancy.

Chemoprevention for oral leukoplakia has been attempted but remains experimental. Retinoid-based therapies (e.g., 13-cis-retinoic acid; vitamin A alone or in combination with beta-carotene) have reduced or eliminated some leukoplakic lesions in short-term studies. Toxic reactions to systemic retinoids are frequent, however, as is lesion recurrence after the conclusion of therapy. Additional potential chemopreventive agents of interest include lycopene, cyclooxygenase-2 (COX-2) inhibitors, epidermal growth factor receptor (EGFR) inhibitors, green tea polyphenols, peroxisome proliferator activator (PPAR)-gamma agonists (traditionally used as oral hypoglycemics for diabetes management), and ONYX-015 (an attenuated adenovirus with selectivity for cells harboring TP53 mutations). However, to date there is insufficient evidence to support the effectiveness of such medical therapies in preventing the progression of oral premalignant lesions to squamous cell carcinoma.

**ERYTHROPLAKIA (ERYTHROPLASIA; ERYTHROPLASIA OF QUEYRAT)**

Similar to leukoplakia, erythroplakia is defined as a red patch or plaque that cannot be clinically or pathologically diagnosed as any other condition. Queyrat originally used the term erythroplasia to describe a precancerous red lesion on the penis. Oral erythroplakia is clinically and histopathologically similar to the genital process. Almost all true erythroplakias demonstrate significant epithelial dysplasia, carcinoma in situ, or invasive squamous cell carcinoma. The causes of erythroplakia are presumed to be the same as those associated with oral squamous cell carcinoma (see page 375).

The estimated point prevalence rate (number of persons with active lesions at a given point in time) of oral erythroplakia is 1 per 2500 adults. The reported prevalence among several large-scale epidemiologic surveys—many of which were conducted in Asia and the United States—ranges from 0.01% to 0.83%. The incidence is unknown, but the estimated annual incidence for microscopically proven oral carcinoma in situ, which represents the great majority of erythroplakias, is 1.2 per 100,000 population in the United States.

Erythroplakia also may occur in conjunction with leukoplakia (see page 355) and has been found concurrently with a large proportion of early invasive oral carcinomas. Although erythroplakia is less common than leukoplakia, it has a much greater potential to be severely dysplastic at the time of biopsy or to develop malignancy later.

**Clinical Features**

Erythroplakia is predominantly a disease of middle-aged to older adults with no significant gender predilection. In the United States, a peak prevalence of 65 to 74 years has been reported. In India, the peak prevalence is in a somewhat younger age range of 45 to 54 years. The floor of mouth, tongue, and soft palate are the most common sites of involvement, and multiple lesions may be present.

The lesion appears as a well-demarcated, erythematous patch or plaque with a soft, velvety texture (Figs. 10-74 and 10-75). It is usually asymptomatic and may be associated with an adjacent leukoplakia (erythroleukoplakia) (see Fig. 10-65). Biopsy typically is required to distinguish erythroplakia from other conditions with a similar clinical appearance, such as nonspecific mucositis, candidiasis, psoriasis, or vascular lesions.

**Histopathologic Features**

According to one large clinicopathologic investigation, 90% of erythroplakic lesions histopathologically represent severe epithelial dysplasia (see page 361), carcinoma in situ (see page 361), or superficially invasive squamous cell carcinoma (see page 385). The epithelium lacks keratin production and
The three main types of smokeless tobacco used in the United States include chewing tobacco, dry snuff, and moist snuff. The latter is most popular, with increasing sales over the past few decades due in part to the convenience of small, inconspicuous, prepackaged pouches. Chewing tobacco often is used by men in conjunction with outdoor activities, and dry snuff is used primarily by women in the southern United States. Smokeless tobacco use also has been referred to as spit tobacco use—a term preferred by the US federal government in its attempt to diminish the appeal of the habit.

In the United States, according to the 2011 National Survey on Drug Use and Health, approximately 3.2% of people (or 8.2 million individuals) 12 years and older use smokeless tobacco. The highest prevalence rates are seen in some Southeastern and Midwestern states. The habit is especially common among young individuals, with approximately 13% of male high school students reporting current smokeless tobacco use. The habit typically is started at around 8 to 14 years of age, and rarely is initiated after 20 years of age. Another national survey detected smokeless tobacco lesions of all types in 1.5% (2.9% in males, 0.1% in females) of US adolescents and teenagers. As part of its Healthy People 2020 objectives, the US Department of Health and Human Services has set a goal to reduce the national prevalence of smokeless tobacco use from 2.3% to 0.3% among adults and from 8.9% to 6.9% among adolescents.

In India and other Asian countries, smokeless tobacco may be combined in a quid with betel leaves, areca nuts, and slaked lime. Oral lesions associated with betel quid use are described separately (see page 366).

**Clinical Features**

Several health and addiction hazards may be associated with smokeless tobacco use because of the ready absorption of nicotine and other molecules through the oral mucosa. A variety of local oral alterations also are found in chronic users. One of the most common local changes is painless gingival recession in the area of tobacco contact (Fig. 10-76), at times accompanied by destruction of the underlying facial alveolar bone. The severity of the defect correlates with the quantity and duration of smokeless tobacco use. Although the association between smokeless tobacco and gingival recession is well known, there is some variability across studies regarding the association between smokeless tobacco and periodontal bone loss. Researchers have suggested that this variability may be related to the specific type...
Smokeless tobacco keratosis usually takes 1 to 5 years to develop. Once it occurs, however, the keratosis typically remains unchanged indefinitely unless the daily tobacco contact time is altered. In some cases, the lesion gradually becomes thickened to the point of appearing leathery or nodular (Fig. 10-78).

**Histopathologic Features**

The histopathologic appearance of smokeless tobacco keratosis is not specific. The squamous epithelium is hyperkeratotic and acanthotic, with or without intracellular vacuolization or “edema” of glycogen-rich superficial cells. Parakeratin chevrons may be seen as pointed projections above or within superficial epithelial layers (Fig. 10-79). Increased subepithelial vascularity and vessel engorgement often are observed. In some cases, an unusual deposition of amorphous eosinophilic material is noted within the subjacent connective tissue and salivary glands (Fig. 10-80). Epithelial dysplasia is uncommon in smokeless tobacco keratosis and, when present, is typically mild. Occasionally,
however, significant dysplasia or squamous cell carcinoma may develop.

Treatment and Prognosis

Chronic use of smokeless tobacco in the United States is considered to be carcinogenic, although the risk is less than that associated with cigarette smoking and alcohol abuse. Fortunately, the clinical appearance of smokeless tobacco keratosis is distinct enough and the malignant transformation potential is low enough that biopsy is needed for only severe or atypical lesions (i.e., those demonstrating an intense whiteness, a granular or verruciform clinical appearance, ulceration, mass formation, induration, or hemorrhage). Treatment depends on the histopathologic diagnosis. Keratoses without dysplasia or malignancy may require only continued monitoring and encouraged tobacco cessation. Alternating the tobacco-chewing sites between the left and right sides will eliminate or reduce the keratotic lesion but may result in epithelial alteration or gingival and periodontal difficulties in two sites rather than one.

Squamous cell carcinoma (see page 376) related to smokeless tobacco use typically develops after a latency period of several decades. Most such cases represent conventional squamous cell carcinoma, although an uncommon low-grade variant known as verrucous carcinoma (“snuff dipper’s cancer”) (see page 389) also is possible. In a review of case control studies performed in the United States and Western Europe, the reported relative risk of developing oral cancer from chronic smokeless tobacco use ranged from less than 2 to 26, with lower risk associated with chewing tobacco and moist snuff and higher risk associated with dry snuff. Recent studies from Sweden, however, have failed to show an increased risk for users of Swedish moist snuff (also known as snus). Many of the early reports of malignant transformation described lesions among female dry snuff users in the southern United States. Only recently have epidemiologic studies tried to separate the various types of smokeless tobacco with respect to their carcinogenic potential.

Significantly, habit cessation leads to a normal mucosal appearance (usually within 2 weeks) in 98% of smokeless tobacco keratoses that are not intensely white (Fig. 10-81). A lesion that remains after 6 weeks without smokeless tobacco contact should be considered a true leukoplakia and should be biopsied and managed accordingly (see page 362).

ORAL SUBMUCOUS FIBROSIS

Oral submucous fibrosis is a high-risk, precancerous condition characterized by chronic, progressive scarring of the oral mucosa. It is seen primarily in the Indian subcontinent, Southeast Asia, Taiwan, southern China, Polynesia, and Micronesia. The condition affects more than 5 million people in India alone. Cases among Asian communities in North America, Europe, and Africa also have been reported.
inflammatory cells may promote fibrosis by inducing fibroblast proliferation, upregulating collagen synthesis, and downregulating collagenase production.

Clinical Features

Oral submucous fibrosis often manifests in young adult betel quid users. Reported gender predilection varies by population. Typical chief complaints include an inability to open the mouth (trismus) and a generalized oral burning sensation (stomatopyrosis) with intolerance to spicy foods. An interincisal distance of less than 20 mm is considered severe; in advanced cases, the jaws may be inseparable.

Vesicles, petechiae, melanosis, xerostomia, and stomatopyrosis are usually the first signs and symptoms. The buccal mucosa, retromolar area, and soft palate are the most commonly affected sites. Subsequently, the mucosa develops a blotchy, marblelike pallor and progressive stiffness (Fig. 10-82). The tongue may become immobile, diminished in size, and devoid of papillae. Submucosal fibrous bands are palpable on the buccal mucosa, soft palate, and labial
mucosa of fully developed cases. Involvement may extend to include the pharynx and upper esophagus. Leukoplakia of the surface mucosa often is noted as well (see page 355).

Betel quid chewers also may exhibit a brown-red discoloration of the mucosa with an irregular surface that tends to desquamate. This particular change, known as betel chewer’s mucosa, is not believed to be precancerous. In addition, some authors have reported betel quid lichenoid lesions, characterized by white, parallel, wavy striae resembling oral lichen planus (see page 729). Other possible sequelae include tooth staining, attrition, and periodontal disease.

**Histopatologic Features**

Oral submucous fibrosis is characterized by juxtaepithelial and submucosal deposition of densely collagenized, hypovascular connective tissue with variable numbers of chronic inflammatory cells (Fig. 10-83). Epithelial changes include subepithelial vesicles in early lesions and hyperkeratosis with marked epithelial atrophy in older lesions. Epithelial dysplasia is found in 10% to 15% of cases submitted for biopsy, and carcinoma is found in at least 6% of sampled cases.

Betel chewer’s mucosa appears histopathologically similar to morsicatio buccarum (see page 259), except the ragged keratinaceous surface is covered by encrusted betel quid ingredients.

**Treatment and Prognosis**

Unlike tobacco pouch keratosis, oral submucous fibrosis does not regress with habit cessation. Mild cases may be treated with intralesional corticosteroids to reduce symptoms and limit progression. Moderate to severe cases may require surgical splitting or excision of the fibrous bands followed by lifelong physiotherapy; however, relapse is common. There is limited evidence for various alternative treatments, such as intralesional injection of interferon-gamma; topical or intralesional proteolytics (e.g., collagenase, hyaluronidase, chymotrypsin, and human placental extract); vitamins and minerals; antioxidants (e.g., lycopene); pentoxifylline; and ayurvedic remedies (e.g., turmeric).

Frequent evaluation for development of oral squamous cell carcinoma is essential because a 17-year malignant transformation rate of 8% has been determined for betel quid users in India. Overall, persons with oral submucous fibrosis are at least 19 times more likely to develop oral cancer than persons without the disease.

**NICOTINE STOMATITIS (NICOTINE PALATINUS; SMOKER’S PALATE)**

Once a common mucosal change of the hard palate, nicotine stomatitis has become less common because cigar and pipe smoking have lost popularity. Although this hyperkeratotic lesion is associated with tobacco smoking, it does not appear to have a premalignant nature, perhaps because it develops in response to heat rather than the chemicals in tobacco smoke. In particular, pipe smoking appears to generate more heat on the palate than other forms of smoking. Similar changes also can be produced by the long-term use of extremely hot beverages.

In some South American and Southeast Asian cultures, hand-rolled cigarettes and cigars are smoked with the lit end held within the mouth. This “reverse smoking” habit produces a pronounced palatal keratosis, or reverse smoker’s palate, which has a significant potential to develop dysplasia or carcinoma.

**Clinical Features**

Nicotine stomatitis most commonly affects men older than 45 years. With long-term exposure to heat, the palatal mucosa becomes diffusely gray or white; numerous slightly elevated papules are noted, usually with punctate red centers (Figs. 10-84 and 10-85). Such papules represent inflamed minor salivary glands and their ductal orifices.

The palatal keratin may become so thickened that a fissured or “dried mud” appearance is imparted. The whiteness also may involve the marginal gingiva and interdental papillae, and hyperkeratosis of the buccal mucosa occasionally is seen. A heavy brown or black tobacco stain may be present on the teeth.

**Histopathologic Features**

Nicotine stomatitis is characterized by hyperkeratosis and acanthosis of the palatal epithelium and mild, patchy, chronic inflammation of subepithelial connective tissue and mucous glands (Fig. 10-86). Squamous metaplasia of the excretory ducts is usually seen, and an inflammatory exudate may be noted within the duct lumina. In cases with papular...
elevation, hyperplastic ductal epithelium may be seen near the orifice. The degree of epithelial hyperplasia and hyperkeratosis appears to correlate positively with the duration and the level of heat exposure. Epithelial dysplasia rarely is seen.

**Treatment and Prognosis**

Nicotine stomatitis is completely reversible, even when it has been present for many decades. The palate usually returns to normal within 1 to 2 weeks of smoking cessation. Although this lesion is not precancerous and does not require treatment, the patient nevertheless should be encouraged to stop smoking (and other high-risk areas should be examined closely). Any white lesion of the palatal mucosa that persists after 1 month of habit cessation should be considered a true leukoplakia and managed accordingly (see page 362).

**ACTINIC KERATOSIS**

**SOLAR KERATOSIS**

Actinic keratosis is a common, cutaneous premalignant lesion that is caused by chronic, high-level exposure to UV radiation. A similar phenomenon, actinic cheilosis, is associated with sun damage to the lower lip vermilion (see page 370). UV light exposure can produce mutations in various genes, such as the tumor suppressor gene TP53. Additional risk factors for actinic keratosis include fair skin, old age, immunosuppression, arsenic exposure, and certain genetic abnormalities (e.g., albinism, Rothmund-Thompson syndrome, Cockayne syndrome, xeroderma pigmentosum [see page 696], and Bloom syndrome). Furthermore, recent studies suggest that HPV infection may be a cofactor in some cases, especially those arising in immunosuppressed individuals.

Actinic keratosis affects more than 50% of white adults with significant lifetime sun exposure. In the United States, reported prevalence rates range from 14% to 27% for men and 6% to 10% for women. According to the National Ambulatory Medical Care Survey, more than 47 million physician office visits were conducted in the United States over a 10-year period for the diagnosis of actinic keratosis. Another study reported that actinic keratosis accounts for more than 5 million physician office visits per year in the United States.

**Clinical Features**

Actinic keratosis seldom occurs in persons younger than 40 years. Common sites of involvement include the face, neck, dorsum of the hands, forearms, and balding scalp. The lesions most often occur in clusters (apparently due to UV-induced field cancerization [see page 389]), although solitary lesions also are possible. The lesions appear as irregular, scaly plaques, which range in color from normal to white, gray, or brown, and may be superimposed on an
Alternatively, cryotherapy may be combined with broader application of topical agents. Recurrence is rare, but additional lesions frequently arise in adjacent sun-damaged skin. Long-term follow-up, therefore, is recommended. The estimated malignant transformation rate for an individual lesion varies considerably (0.025% to 16% per year) but generally is considered low. However, the risk increases significantly for a patient with a large number of lesions over an extended period. The average person initially presents to a dermatologist with six to eight actinic keratoses; a person with this many lesions is estimated to have a 6% to 10% risk of progression to squamous cell carcinoma over a 10-year period. Longitudinal studies suggest that malignancy most often develops within 2 years, and spontaneous regression may occur in up to 26% of cases within 12 months of reduced sun exposure.

ACTINIC CHEILOSIS (ACTINIC CHEILITIS; SOLAR CHEILOSIS)

Actinic cheilosis is a common premalignant alteration of the lower lip vermilion that results from chronic UV light exposure. Its etiopathogenesis is similar to that of actinic keratosis of the skin (see previous topic). The incidence of...
Actinic cheilosis increases with proximity to the equator, and there is a predilection among middle-aged to elderly, fair-complexioned men. Outdoor occupations are associated with this condition, leading to popular terms, such as farmer’s lip and sailor’s lip. In addition, there is increased susceptibility among patients with certain genetic disorders (e.g., xeroderma pigmentosum, albinism, and porphyria cutanea tarda). Furthermore, cofactors—such as immunosuppression and tobacco smoking—may increase the likelihood of progression to squamous cell carcinoma.

Clinical Features

Actinic cheilosis seldom occurs in persons younger than 45 years. There is a strong male predilection (reported male-to-female ratio as high as 10:1), which may reflect more outdoor occupational activity and less frequent use of lip protective agents among men compared to women. The lesion develops so slowly that patients often are unaware of a change. Early clinical findings include atrophy (characterized by smooth, blotchy, pale areas), dryness, and fissures of the lower lip vermilion, with blurring of the margin between the vermilion and the adjacent skin. As the lesion progresses, rough, scaly areas develop on the drier portions of the vermilion. These areas may thicken to form leukoplakic lesions, especially when they extend near the wet line of the lip (Fig. 10-89). The patient may peel off the scale with some difficulty, only to see it reform within a few days. Eventually, chronic ulceration may develop (Fig. 10-90). Such ulcerations may last for months and suggest progression to squamous cell carcinoma (Fig. 10-91).

Histopathologic Features

The surface epithelium exhibits varying degrees of dysplasia. There is usually hyperkeratosis, and the epithelium may be either atrophic or acanthotic. The underlying connective tissue invariably demonstrates a band of amorphous, acellular, basophilic change known as solar elastosis, an UV light–induced alteration of collagen and elastic fibers (Fig. 10-92). A chronic inflammatory cell infiltrate and dilated blood vessels may be present as well.

Treatment and Prognosis

Many of the changes associated with actinic cheilosis are probably irreversible, but patients should be encouraged to reduce sun exposure, wear a wide-brimmed hat, and use sunscreen to prevent further damage. Areas of induration, thickening, ulceration, or leukoplakia should be submitted for biopsy to rule out carcinoma. In clinically severe cases without obvious malignant transformation, a lip shave procedure (vermilionectomy) may be performed. The vermilion mucosa is removed, and either a portion of the intraoral labial mucosa is pulled forward or the wound is allowed to heal by secondary intention. The advantage of this technique is that it provides tissue for histopathologic examination should areas of superficially invasive squamous cell carcinoma be present. Alternative treatments include CO₂ or erbium:YAG (Er:YAG) laser ablation, electrodesiccation,
in certain heritable conditions attributed to defects in DNA repair, including Muir-Torre syndrome (sebaceous neoplasms, keratoacanthomas, and gastrointestinal carcinomas) and xeroderma pigmentosum (see page 696).

Comparative genomic hybridization has shown that keratoacanthomas and squamous cell carcinomas typically exhibit distinct genetic profiles, which suggest different underlying pathogenetic mechanisms.

Clinical Features

Keratoacanthoma shows a male predilection and rarely occurs before 45 years of age. Almost 95% of solitary lesions involve sun-exposed skin, and 8% of all cases involve the outer edge of the vermilion border of the lips, with equal frequency on the upper and lower lips.

Keratoacanthoma appears as a firm, well-demarcated, sessile, dome-shaped nodule with a central plug of keratin (Figs. 10-93 and 10-94), although lesions reported as intraoral keratoacanthoma usually have lacked a central plug. The outer portion of the nodule typically has a normal texture and color but may be erythematous. The central
the stationary phase, which usually is of similar duration as the growth phase. Most lesions regress spontaneously within 6 to 12 months of onset, frequently leaving behind a depressed scar. The regression of keratoacanthomas is a curious phenomenon, which some investigators have theorized is related to a cytotoxic immune response to the tumor or mechanisms similar to those controlling normal cycling of hair follicles. Some authors also have described a subset of lesions (termed abortive keratoacanthoma) that involute after only 4 to 6 weeks.

Several other variants exist, including giant keratoacanthoma (greater than 2 to 3 cm in diameter), keratoacanthoma centrifugum marginatum (characterized by continuous peripheral growth and central scarring), subungual keratoacanthoma (involving the nail bed), and mucosal keratoacanthoma (involving the oral, nasal, genital, ocular, or other regions). These variants often do not regress.

In addition, early onset of multiple keratoacanthomas has been described in association with two rare, heritable conditions: Ferguson-Smith syndrome and Witten-Zak syndrome. The former is characterized by nodular lesions and primarily affects patients of Scottish descent; the latter typically exhibits a mixture of variably sized lesions. In contrast, Grzybowski syndrome manifests later in life as hundreds or thousands of small papules of the skin and upper digestive tract and may be associated with internal malignancy.

Histopathologic Features

Because the overall architectural pattern is crucial for the diagnosis of keratoacanthoma, excisional or large incisional biopsy with inclusion of adjacent, clinically normal epithelium is necessary for proper histopathologic interpretation. The tumor cells appear mature, although considerable dyskeratosis (abnormal keratin production) typically is seen in the form of deeply located individually keratinizing cells and keratin pearls similar to those found in well-differentiated squamous cell carcinoma.

The surface epithelium at the edge of the tumor appears normal; at the lip of the central crater, however, a characteristic acute angle (or "buttress") is formed between the overlying epithelium and the lesion. The crater is filled with keratin, and the epithelium at the base of the crater proliferates downward (Fig. 10-96), often with a pronounced chronic inflammatory cell response. Downward proliferation typically does not extend below the sweat glands in skin lesions or into underlying muscle in vermilion lesions. Late-stage lesions show considerably more keratinization in the deeper aspects of the tumor than do early lesions. Perineural and vascular invasion have been reported rarely; although worrisome, such features do not necessarily indicate a worse prognosis. Migration of eosinophils or neutrophils into the epithelium with resultant microabscess formation is a frequent finding. Regressing lesions tend to flatten, hollow out, and exhibit an underlying band of fibrosis.
Numerous immunohistochemical studies comparing keratoacanthoma and squamous cell carcinoma have been reported, but no reliable marker for discernment between these two lesions has been identified.

Treatment and Prognosis

Because of the difficulty in clinically and histopathologically distinguishing between keratoacanthoma and squamous cell carcinoma, many authorities advocate excision without waiting for spontaneous regression. Also, early treatment may prevent significant scarring. Approximately 4% to 8% of lesions recur after excision. Although conventional surgical excision is preferred, alternative therapies include cryosurgery (reserved for small early lesions), electrodessication and curettage, Mohs micrographic surgery (especially for lesions of the central face), laser therapy, intralesional injection of chemotherapeutic agents (such as, 5-fluorouracil, bleomycin, methotrexate, or interferon alpha), and topical agents (such as, imiquimod or 5-fluorouracil). Systemic retinoids may be used alone or in combination with local treatment for patients with multiple or especially large lesions.

Aggressive behavior and transformation into carcinoma have been reported in a small proportion of keratoacanthomas—particularly those occurring in the setting of immunosuppression. However, the close histopathologic similarities between this lesion and squamous cell carcinoma sometimes make it difficult to rule out the possibility of microscopic misinterpretation.

**SQUAMOUS CELL CARCINOMA**

In the United States, approximately one of every two men and one of every three women will develop a malignancy (other than nonmelanoma skin cancer) at some point. It is estimated that in the United States in 2013, more than 1.6 million new cancer cases will be diagnosed, in addition to around 3.5 million nonmelanoma skin cancers. Although the relative 5-year cancer survival rate is approximately 68%, cancer still causes more than 580,000 deaths each year in the United States and accounts for more than 20% of all deaths. From 1930 to 1991, the annual cancer death rate (excluding nonmelanoma skin cancer) increased and reached a peak of 215 per 100,000 population. This trend reflected an increase in the incidence of lung cancer as well as a decrease in mortality at an early age from other common disorders, such as cardiovascular disease and infection. Since 1991, however, the annual cancer death rate has declined to about 173 per 100,000 population. In part, this decline is related to a decrease in tobacco use and lung cancer deaths; in addition, improvements in detection and treatment have resulted in declines in breast, colorectal, and prostate cancer deaths.

**Squamous cell carcinoma** accounts for more than 90% of oral malignancies. Statistics for oral cancer can be difficult to review, because cancer registries and investigators often report oral and pharyngeal cancers in aggregate. Also, a distinction between intraoral and lip vermilion cancers is not always made. With that said, in the United States oral cancer accounts for less than 2% of all cancers (excluding nonmelanoma skin cancers and *in situ* carcinomas for all sites but urinary bladder). It represents the eleventh most common cancer in males and the sixteenth most common in females. Around 27,000 new cases of oral cancer are diagnosed annually, and approximately 5,500 individuals die of this disease each year.

The risk for oral and pharyngeal cancer increases with age, especially among males. In the United States, according to the Surveillance, Epidemiology, and End Results (SEER) Program, the age-adjusted incidence rate for oral and pharyngeal cancer from 2005 to 2009 was 60 per 100,000 for males aged 65 years and older, compared to 10 per 100,000 for males younger than 65 years. Among those 65 years and older, the incidence was somewhat higher for white males (62 per 100,000) than black males (52 per 100,000), whereas similar incidence rates were seen for black and white males under 65 years. Notably, there was a marked disparity in age-adjusted mortality rates between black and white males (5.7 versus 3.6 per 100,000, respectively) with oral and pharyngeal cancer. This disparity has been explained by socioeconomic factors and differences in access to quality health care. However, recent studies suggest that patient outcomes actually are similar between races for oral and other non-opharyngeal head and neck cancers; instead much of this disparity may be due to racial differences in oropharyngeal cancers. Specifically, white patients are more likely to have HPV-positive oropharyngeal tumors compared to black patients, and these HPV-positive tumors are associated with a better response to treatment and prolonged survival. It is unknown why racial differences exist in the prevalence of HPV-positive oropharyngeal carcinomas, although some investigators have hypothesized that differences in behavior, oral HPV acquisition rates, and/or viral clearance may play a role.

In the United States, females overall have a much lower incidence of oral and pharyngeal cancer than males, with a male-to-female ratio of approximately 2.5:1. However,
among young adults and pediatric patients, recently reported incidence rates for oral and pharyngeal cancers in females have been similar or even slightly higher than that in males. Interestingly, over the past several decades, a significant increase in the incidence of oral tongue cancer has been noted among young individuals, especially white women aged 18 to 44 years. The underlying cause for this trend is uncertain. Such cases often are not associated with the traditional risk factors of tobacco and alcohol use, and the oral tongue—unlike the base of tongue—is an infrequent site for HPV-positive carcinomas.

Carcinoma of the lip vermillion is somewhat different from intraoral carcinoma. It has a pathophysiologic more akin to squamous cell carcinoma of sun-exposed skin. According to recent SEER data, the overall age-adjusted annual incidence rate for lip cancer in the United States is 0.7 per 100,000 population. However, the incidence increases with age, with annual rates among those 75 years and older of approximately 7 per 100,000 for males and 3 per 100,000 for females. White males are affected most commonly, although there has been a considerable decrease in the incidence of lip cancer in this group over the past several decades; this trend may be related to a decline in the number of white males engaged in outdoor occupations. Among women and nonwhite men, lip carcinoma is very infrequent. The low incidence among women may be related to little outdoor occupational activity and prevalent use of lip protective agents. In nonwhites, racial pigmentation may provide protection against sun exposure.

The worldwide incidence of oral cancer is approximately 263,000 cases per year, with an especially high incidence reported in the Indian subcontinent, Taiwan, Hungary, France, Brazil, and parts of southern Africa. Exceptionally wide variations in oral cancer incidence and mortality across regions likely results from differences in population habits, life expectancies, preventive education, and accuracy of disease reporting. Despite the difficulties involved in interpreting such data, these findings have been helpful in identifying potential causative factors.

**Etiology of Oral Cancer**

The cause of oral squamous cell carcinoma is multifactorial. No single causative agent or factor (carcinogen) has been clearly defined or accepted, but both extrinsic and intrinsic factors may be involved. It is likely that more than a single factor is needed to produce such a malignancy (cancerogenesis). **Extrinsic** factors include tobacco smoke, alcohol, and (for vermilion cancers only) sunlight. **Intrinsic** factors include systemic or generalized states, such as malnutrition or iron-deficiency anemia. Heredity does not appear to play a major causative role, although a few heritable conditions (e.g., dyskeratosis congenita [see page 695], Fanconi anemia) have been associated with an increased risk for oral squamous cell carcinoma. Many oral squamous cell carcinomas have been documented to be associated with or preceded by a precancerous lesion, especially leukoplakia (Table 10-2).

**Tobacco Smoking**

Tobacco smoking reached its greatest popularity in the United States during the 1940s, when at least 65% of white men smoked and other population subgroups were beginning to smoke in large numbers. Today less than 20% of US adults, men and women alike, smoke cigarettes. Although an overall decrease in smoking prevalence has been observed over the past decade, intensive efforts will be required to meet the US Department of Health and Human Services’ Healthy People objective to reduce smoking prevalence by the year 2020 to 12% or less.

Tobacco smoke contains more than 70 carcinogens, including nitrosamines, arsenic, benzo[a]pyrene, and benzene. In addition, smoking produces free radicals and oxidants that promote the destruction and counteract the protective effects of endogenous antioxidants (such as, glutathione-S-transferase, glutathione reductase, and superoxide dismutase).

Much indirect clinical evidence implicates tobacco smoking in the development of oral squamous cell carcinoma. The proportion of smokers (80%) among patients with oral carcinoma is about four times greater than that

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**TABLE 10-2**

<table>
<thead>
<tr>
<th>Disease Name</th>
<th>Malignant Transformation Potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proliferative verrucous leukoplakia (PVL)*</td>
<td>★★★★★★★</td>
</tr>
<tr>
<td>Nicotine palatinus in reverse smokers†</td>
<td>★★★★★</td>
</tr>
<tr>
<td>Erythroplakia</td>
<td>★★★★★</td>
</tr>
<tr>
<td>Oral submucous fibrosis</td>
<td>★★★★</td>
</tr>
<tr>
<td>Erythroleukoplakia</td>
<td>★★★</td>
</tr>
<tr>
<td>Granular leukoplakia</td>
<td>★★</td>
</tr>
<tr>
<td>Laryngeal keratosis</td>
<td>★</td>
</tr>
<tr>
<td>Actinic cheilosis</td>
<td>★</td>
</tr>
<tr>
<td>Smooth, thick leukoplakia</td>
<td>★</td>
</tr>
<tr>
<td>Smooth, red tongue of Plummer-Vinson syndrome</td>
<td>★</td>
</tr>
<tr>
<td>Smokeless tobacco keratosis</td>
<td>★</td>
</tr>
<tr>
<td>Lichen planus (erosive forms)‡</td>
<td>★</td>
</tr>
<tr>
<td>Smooth, thin leukoplakia</td>
<td>★</td>
</tr>
</tbody>
</table>


*PVL: High-risk, high-recurrence form of oral leukoplakia affecting multiple sites.
†Reverse smoking: Smoking with the lit end of the cigarette in one’s mouth.
‡Precancer character is controversial.
among the general population. For patients who quit smoking, the risk for developing oral cancer declines over time; approximately 10 years after cessation, the incidence of oral cancer approaches that of individuals who have never smoked. The risk for a second primary carcinoma of the upper aerodigestive tract is two to six times greater for treated patients with oral cancer who continue to smoke than for those who quit after diagnosis.

According to a meta-analysis of observational studies on tobacco smoking and cancer in various regions of the world, the pooled risk for oral cancer is approximately three times greater among smokers than nonsmokers. Moreover, the relative risk (smoker’s risk for oral cancer compared with that of a nonsmoker) is dose-dependent. It is at least five for persons who smoke 40 cigarettes daily, but increases to as much as 17 for persons who smoke 80 or more cigarettes daily. The risk also increases the longer a person smokes. Furthermore, studies suggest that cigar or pipe smoking is associated with a similar or greater risk for oral cancer compared to cigarette smoking.

In India it is common to smoke bidi (small, hand-rolled cigarettes consisting of flaked tobacco rolled in a temburni or tendu leaf), and bidi smoking is associated with an approximately threefold greater risk of oral cancer compared to cigarette smoking. The highest risk of all probably is found in certain Indian and South American cultures in which the practice of reverse smoking is popular, especially among women. In reverse smoking, the burning end of a handmade cigar or cigarette is held inside the mouth. Where reverse smoking is practiced, as many as 50% of all oral malignancies are found on the hard palate, a site usually spared by this disease.

**Smokeless Tobacco**

Smokeless tobacco use in Western cultures may increase a chronic user’s risk for oral carcinoma by a factor ranging from less than two to as high as 26. This variation in reported relative risk may be influenced by the type of smokeless tobacco used, with some studies suggesting a lower risk associated with moist snuff and chewing tobacco and a higher risk associated with dry snuff. This apparent increased risk is supported by clinicopathologic investigations that have found an abnormal male-to-female ratio for oral carcinoma (>1.0:1.5) in geographic areas where the habit is more popular among women than among men. These geographic areas are typically in the southeastern United States, where women use dry snuff. In addition, approximately 50% of all oral cancers in smokeless tobacco users occur at the site where the tobacco is habitually placed.

**Betel Quid (Paan)**

Betel quid (or paan) is a combination of natural substances (i.e., areca palm nuts, betel leaf, slaked lime, and perhaps tobacco leaf) chewed for their psychostimulating effects. The carcinogenicity of betel quid traditionally has been attributed to tobacco, although areca nut alone also appears to be carcinogenic. In addition, commercially freeze-dried betel quid substitutes (e.g., pan masala and gutkha) packaged in convenient sachets have become increasingly popular. Among betel quid users in Asia, the lifetime risk of developing oral cancer is a remarkable 8%. This habit also is associated with development of precancers, such as leukoplakia. As many as 600 million persons worldwide chew these quids on a regular basis.

**Alcohol**

It is well established that alcohol in combination with tobacco is a significant risk factor for oral cancer development, with a reported relative risk of 15 or more among heavy users of both substances. Furthermore, even after controlling for tobacco use, epidemiologic studies have reported a twofold to fourteenfold increased risk for oral cancer among heavy drinkers (often defined as individuals who consume more than four alcoholic beverages or 60 g of alcohol per day). The risk generally appears to be dose-dependent and time-dependent, although a few studies have suggested that light or moderate drinking may exhibit a protective effect, especially among females. Nevertheless, the lowest annual oral cancer incidence rate in the United States is found in Utah, where 75% of the population follows Mormon doctrines that forbid tobacco and alcohol use.

Indirect evidence for alcohol’s role in oral cancer development includes the fact that approximately one-third of male patients with oral cancer are heavy alcohol users, whereas less than 10% of the general population can be classified as such. Likewise, cirrhosis of the liver is found in at least 20% of male patients with oral cancer.

The exact role of alcohol in oral carcinogenesis is not well understood, although several mechanisms have been proposed. Ethanol in alcoholic beverages is metabolized into acetaldehyde, which is a known carcinogen. In addition, carcinogenic impurities—such as, polycyclic aromatic hydrocarbons and nitrosamines—may be present in some alcoholic beverages. Moreover, alcohol may help solubilize other carcinogenic compounds and may increase the permeability of oral epithelium to these compounds. Nutritional deficiencies associated with heavy alcohol consumption also may be a contributory factor.

There is much debate in the literature regarding the potential for alcohol-containing mouthwashes to increase the risk for oral cancer. High-quality epidemiologic studies are limited, and inconsistent findings across studies have failed to establish a definite link.

**Occupational Exposures and Environmental Pollutants**

Some studies have reported an increased oral cancer risk for workers in the wood products industry chronically exposed to certain chemicals, such as phenoxyacetic acids. Such workers also are at increased risk for nasal and nasopharyngeal carcinoma. In addition, there is limited and inconsistent evidence for elevated oral cancer risk among metal workers, electrical workers, plumbers, machinists, painters,
and other individuals with occupational exposure to solvents or metal dust.

In regions of Taiwan with a particularly high incidence of oral cancer, investigators have reported elevated levels of heavy metal pollutants (e.g., nickel, chromium, and arsenic) in farm soil and increased blood concentrations of some of these metals in affected patients.

Radiation

The effects of UV radiation on the lips are discussed elsewhere (actinic cheilitis, see page 370). Interestingly, a recent large-scale retrospective study has suggested that certain antihypertensive medications (e.g., hydrochlorothiazide, hydrochlorothiazide-triamterene, and nifedipine) may act as photosensitizers and may potentiate the development of UV-induced lip cancer. However, further studies are needed to confirm these findings and to establish direct causality.

In addition, it is well known that x-irradiation decreases immune reactivity and produces chromosomal abnormalities. Indeed, radiotherapy to the head and neck area increases the risk for later development of a new primary oral malignancy, either a carcinoma or sarcoma. This effect is dose-dependent, but even low-dose radiotherapy for benign entities may increase the local risk somewhat. Although there has been controversy regarding whether dental radiography may pose an increased risk for developing various tumors, dental imaging has not been associated with oral carcinoma.

Vitamin/Mineral Deficiencies and Dietary Factors

Iron deficiency, especially the severe, chronic form known as the Plummer-Vinson or Paterson-Kelly syndrome (see page 772), is associated with an elevated risk for squamous cell carcinoma of the esophagus, oropharynx, and posterior mouth. Malignancies develop at an earlier age than in patients without iron deficiency anemia. Iron deficiency may cause impaired cell-mediated immunity. In addition, because the epithelium of the upper digestive tract has a relatively high turnover rate, rapid loss of iron-dependent enzymes may lead to degenerative changes, including mucosal atrophy and esophageal webs (intertwining fibrous bands of scar tissue), with heightened susceptibility to malignant transformation.

Vitamin-A deficiency produces excessive keratinization of the skin and mucous membranes, and researchers have suggested that this vitamin may help to prevent oral precancer and cancer. Some believe that blood levels of retinol and the amount of dietary betacarotene ingested are inversely proportional to the risk of oral squamous cell carcinoma and leukoplakia. Long-term therapy with retinoic acids and betacarotene also has been associated with regression of at least some leukoplakic lesions and a concomitant reduction in the severity of dysplasia within such lesions.

Several epidemiologic studies suggest that high intake of fruits and vegetables decreases the risk for numerous cancer types, including oral cancer. This finding may be related to the protective effects of not only vitamin A but also various other substances (e.g., vitamins C and E, folate, flavonoids, fiber, lycopene, and phytosterols) present within plant foods. However, tobacco and alcohol may represent confounding factors, because heavy tobacco and alcohol users often consume small amounts of fruits and vegetables. Also, some studies suggest that animal fats and processed or salted meat may increase the risk for oral cancer.

A few studies have reported an increased risk for oral cancer in association with drinking hot maté (an herbal tea mainly consumed in parts of South and Central America). Furthermore, there has been interest in the potential protective effects of green tea, coffee, and their associated polyphenols. However, further studies are needed to confirm and explain the carcinogenic or protective properties of such beverages.

Bacteria

The potential for microflora of the oral cavity to contribute to carcinogenesis represents a growing area of scientific investigation. Studies suggest that oral bacteria may interact with tobacco and alcohol. Ethanol is metabolized into the carcinogen acetaldehyde by not only hepatocytes and oral epithelial cells but also bacteria. In particular, high levels of acetaldehyde production have been associated with certain Streptococcus species, Neisseria species, and other bacteria; overgrowth of such bacteria has been described in smokers and heavy drinkers. In addition to bacteria, Candida may contribute to acetaldehyde production.

Furthermore, some investigators hypothesize that periodontal disease-causing bacteria may induce production of proinflammatory cytokines. These cytokines may enhance cell proliferation and inhibit apoptosis, thereby producing a microenvironment favorable for carcinogenesis. However, epidemiological studies of associations between poor oral hygiene, poor dental status, and oral cancer have yielded variable results. Some of this variation may be due to difficulty in controlling for confounding factors, such as tobacco use, alcohol consumption, nutrition, and socioeconomic status.

Although rarely seen today, tertiary syphilis has been associated with a fourfold increased risk for development of dorsal tongue carcinoma. This risk may be due to the carcinogenic properties of the arsenical agents and other heavy metals that were used to treat syphilis before the advent of modern antibiotic therapy.

Candida

Hyperplastic candidiasis (see page 195) frequently is cited as an oral precancerous condition. Because this lesion appears as a white plaque that cannot be rubbed off, it also has been called candidal leukoplakia. Unfortunately, it is difficult both clinically and histopathologically to distinguish between a true hyperplastic candidiasis and a preexisting leukoplakia with superimposed candidiasis. Experimentally, some strains of Candida albicans have produced hyperkeratotic lesions of the dorsal rat tongue without any other contributing factors. Other studies have
demonstrated that certain strains may produce nitrosamines (carcinogens that can activate certain proto-oncogenes) or may convert ethanol into the carcinogen acetaldehyde. However, the evidence for the promotion of oral carcinogenesis by Candida is largely circumstantial.

**Oncogenic Viruses**

Oncogenic (tumor producing) viruses may play a major role in a wide variety of cancers. Viral integration into the host’s genetic material may result in abnormal cell growth and proliferation. The oncogenic viruses may immortalize the host cell, thereby facilitating malignant transformation. In the past, adenoviruses, Epstein-Barr virus (EBV), herpes simplex virus (HSV), human papillomavirus (HPV), and retroviruses (e.g., human immunodeficiency virus [HIV]) all have been suggested to play a role in the development of oral carcinoma. However, HPV and HIV are the only ones still implicated. HPV is discussed here; oral squamous cell carcinoma in the setting of HIV infection is discussed in the following section on immunosuppression and also on page 252.

HPV actually is best known for its role in the development of cancers of the anogenital region (especially the uterine cervix but also the anus, vulva, vagina, and penis). In addition, over the past decade, a strong link between HPV and oropharyngeal carcinoma has been established. In contrast, only a small subset of oral carcinomas has been attributed to HPV infection.

The high-risk HPV types (see page 331) are most closely associated with dysplasia and squamous cell carcinoma. In particular, detection of HPV 16 in exfoliated oral epithelial cells is associated with a nearly fourfold increased risk for oral cancer and a more than fourteenfold increased risk for oropharyngeal cancer. Investigators have proposed that persistent oral infection with HPV 16 and other high-risk HPV types increases the risk for eventual development of oropharyngeal cancer. HPV 16 has been identified in more than 90% of HPV-positive oropharyngeal squamous cell carcinomas. Similarly, in HPV-positive oral squamous cell carcinomas, HPV 16 appears to be the most common type, although some authors have reported a greater diversity of high-risk HPV types in oral carcinomas compared to oropharyngeal carcinomas.

In the United States, based upon data from the SEER Program, investigators have estimated that from 1988 to 2004 the incidence of HPV-positive oropharyngeal cancers increased by 225% (from 0.8 to 2.6 per 100,000 population) and the incidence of HPV-negative oropharyngeal cancers decreased by 50%. If this trend were to continue, by the year 2020, the annual number of HPV-positive oropharyngeal cancers would be expected to surpass the annual number of cervical cancers. This epidemiologic shift has been hypothesized to result from an increase in oral sexual behavior and a decline in tobacco use. Significant increases in HPV-positive oropharyngeal cancer incidence also have been reported in Sweden, Australia, Canada, and other countries. In North America since the year 2000, the proportion of oropharyngeal cancers attributable to HPV infection has been estimated to be approximately 70%.

On the other hand, the proportion of oral carcinomas caused by HPV infection appears to be small. Various reviews of the literature have estimated the prevalence of HPV DNA in oral squamous cell carcinomas as determined by PCR to range from 20% to 40%; nonetheless, the presence of HPV DNA is not indicative of transcriptionally active HPV infection and cannot discriminate between biologically relevant versus bystander infection. Instead, quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) for detection of high-risk HPV E6 and E7 oncogene expression is considered the gold standard for evidence of HPV infection as a likely cause of tumor development. The primary mechanisms by which HPV is believed to contribute to carcinogenesis are linked to the products of these viral oncogenes: 1) E6 protein promotes degradation of the tumor suppressor protein p53 and 2) E7 protein leads to inactivation of the tumor suppressor protein pRb. Using qRT-PCR, one multi-center retrospective study reported that only 6% of oral squamous cell carcinomas analyzed could be attributed to HPV infection.

The characteristic risk profile for patients with HPV-positive head and neck squamous cell carcinoma differs from that for patients with HPV-negative disease. In both patient groups, there is a male predilection, although the average age is approximately 10 years younger among the HPV-positive group. Unlike HPV-negative lesions, HPV-positive lesions tend to affect individuals of higher socioeconomic status. The proportion of HPV-positive cases affecting blacks is much smaller than that affecting whites (4% versus 34%, respectively). Compared to HPV-negative cases, HPV-positive cases are more strongly associated with certain parameters of sexual behavior (e.g., increased number of lifetime sexual or oral sexual partners, early age at sexual debut). In addition, HPV-positive lesions are less likely to occur in patients with an extensive history of tobacco and alcohol history. Nevertheless, patients with HPV-positive tumors often have some history of tobacco and alcohol use, and there are conflicting reports regarding potential interactions between HPV, tobacco, and alcohol in promoting head and neck cancer development. Furthermore, studies assessing a possible association between marijuana use and HPV-positive head and neck carcinomas have yielded variable results.

**Immunosuppression**

Immunosuppression may play a role in the development of at least some malignancies of the upper aerodigestive tract. Without effective immunologic surveillance and attack, it is thought that malignant cells cannot be recognized and destroyed at an early stage. Persons with HIV infection and those who are undergoing immunosuppressive therapy for malignancy or organ transplantation are at increased risk for oral squamous cell carcinoma and other head and neck malignancies, especially when tobacco smoking and alcohol abuse are present.
Oncogenes and Tumor Suppressor Genes

The molecular basis of carcinogenesis involves an accumulation of mutations or epigenetic changes in two broad classes of genes: **proto-oncogenes** and **tumor suppressor genes**. Proto-oncogenes may be transformed into activated oncogenes by environmental agents (e.g., viruses, irradiation, and chemical carcinogens) or inherited changes. Activated oncogenes promote uncontrolled cell division and are involved in the initiation and progression of a wide variety of malignancies. Tumor suppressor genes, on the other hand, inhibit cell division and indirectly allow tumor production when they become inactivated or mutated. Most authorities propose that an accumulation of several genetic aberrations is necessary before the affected cell expresses a malignant phenotype.

Genetic aberrations commonly identified in oral squamous cell carcinomas include abnormalities of the ras, myc, and epidermal growth factor receptor (EGFR; also known as c-erbB1) oncogenes, and the TP53, pRb, p16, and E-cadherin tumor suppressor genes. Head and neck squamous cell carcinomas associated with tobacco and alcohol use often exhibit mutated TP53, pRb overexpression, and decreased p16 expression. In contrast, HPV-associated cases typically express wild-type TP53, low levels of pRb, and increased levels of p16.

Clinical and Radiographic Features

Persons with oral squamous cell carcinoma are most often older men who have been aware of an alteration for 4 to 8 months before seeking professional help (8 to 24 months among lower socioeconomic groups). There is minimal pain during the early growth phase, which may explain the delay in seeking professional care. If the health care professional does not have a high index of suspicion, then additional weeks or months may elapse before a biopsy is performed.

Oral squamous cell carcinoma has a varied clinical presentation, including the following:

- **Exophytic** (mass-forming; fungating, papillary, and verruciform)
- **Endophytic** (invasive, burrowing, and ulcerated)
- **Leukoplakic** (white patch) (Fig. 10-97)
- **Erythroplakic** (red patch)
- **Erythroleukoplakic** (combined red-and-white patch) (Fig. 10-98)

The leukoplakic and erythroplakic examples are probably early cases that have not yet produced a mass or ulceration, and the clinical features are identical to those described for premalignant leukoplakia and erythroplakia (see pages 355 and 363).

An exophytic lesion typically has a surface that is irregular, fungating, papillary, or verruciform, and its color may vary from normal to white or red, depending on the amount of keratin and vascularity (Figs. 10-99 and 10-100). The surface is often ulcerated, and the tumor feels hard (indurated) on palpation (Fig. 10-101).
The endophytic growth pattern has a central, depressed, irregularly shaped ulcer with a surrounding “rolled” border of pink, red, or white mucosa (Fig. 10-102). The rolled border results from invasion of the tumor downward and laterally under adjacent epithelium. Traumatic granulomas, deep fungal infections, tuberculosis, tertiary syphilis, and oral lesions of Wegener granulomatosis or Crohn’s disease may exhibit a similar clinical appearance.

Destruction of underlying bone, when present, may be painful or completely painless; it appears on radiographs as a “moth-eaten” radiolucency with ill-defined or ragged margins (an appearance similar to osteomyelitis) (Fig. 10-103). Perineural invasion may cause paresthesia.

**Lip Vermilion Carcinoma**

Carcinoma of the lip vermilion typically is found in light-skinned persons with chronic exposure to UV radiation from sunlight. Seventy percent of affected individuals have outdoor occupations. It usually is associated with actinic cheilosis (see page 370) and may arise at the site where the patient holds a cigarette, cigar, or pipe. Almost 90% of lesions are located on the lower lip.

The typical vermilion carcinoma is a crusted, oozing, nontender, indurated ulceration that is usually less than 1 cm in greatest diameter when discovered (Figs. 10-104 and 10-105). The tumor usually grows slowly, and most patients are aware of a “problem” in the area for 12 to 16 months before diagnosis. Metastasis is a late event; at diagnosis, fewer than 10% of patients have lymph node metastasis, usually in the submental region. Perineural invasion may result in extension of the tumor into the mandible through the mental foramen. Although this tumor typically is diagnosed and treated at an early stage, patient neglect can result in considerable destruction of normal tissue (Fig. 10-106).

**Intraoral Carcinoma**

In the United States, the most common sites for intraoral carcinoma are the tongue (usually the posterior lateral and ventral surfaces) and floor of mouth. Other sites of
involvement (in descending order of frequency) are the gingiva, buccal mucosa, labial mucosa, and hard palate.

Carcinoma of the tongue accounts for more than 50% of intraoral cancers in the United States (Figs. 10-107). Two-thirds of lingual carcinomas appear as painless, indurated masses or ulcers of the posterior lateral border; 20% occur on anterior lateral or ventral surfaces, and only 4% occur on the dorsum. For unknown reasons, the oral tongue represents an increasingly common site of involvement in young patients.

Of all intraoral carcinomas, floor of mouth lesions are the most likely to arise from a preexisting leukoplakia or erythroplakia (Fig. 10-108). The floor of mouth also represents the oral cancer site most often associated with the development of a second primary malignancy, either elsewhere in the aerodigestive tract or in a distant organ. Floor of mouth carcinomas most often arise in the midline region near the frenum.

Gingival and alveolar carcinomas are usually painless and most frequently arise from keratinized, posterior mandibular mucosa (Fig. 10-109). Interestingly, among intraoral carcinomas, gingival lesions are least associated with tobacco smoking and have the greatest predilection for females.
Epithelial Pathology

382  CHAPTER 10

Gingival and alveolar carcinomas have a special propensity to mimic common, benign inflammatory and reactive lesions, such as the pyogenic granuloma, gingivitis (Fig. 10-110), and periodontal disease. Gingival tumors often destroy the underlying bone and cause tooth mobility. The lesion may go unrecognized until after tooth extraction, when it proliferates out of the socket to mimic the hyperplastic granulation tissue of an epulis granulomatosa (see page 484). Cancers that develop in an edentulous area may “wrap around” a denture flange and superficially resemble inflammatory fibrous hyperplasia (epulis fissuratum) (Fig. 10-111). Tumors of the maxillary alveolar ridge may extend onto the hard palate. Recent studies suggest that carcinomas involving the maxillary mucosa may be more aggressive than previously thought, with nearly 30% of cases harboring occult cervical lymph node metastasis.

Similarly, recent evidence suggests that carcinomas of the buccal mucosa may be more aggressive than previously suspected, with reported locoregional recurrence rates ranging from 30% to 80%. The buccal mucosa is an especially common site for oral carcinoma in regions of the world where betel quid use is prevalent.

Carcinomas of the retromolar trigone may spread to numerous adjacent structures, including the oropharynx, buccal mucosa, alveolar ridge, and pterygomandibular raphe (Fig. 10-112). Invasion of the pterygomandibular raphe may lead to involvement of the skull base, masticator space, and floor of mouth.

Oropharyngeal Carcinoma

Subsites for oropharyngeal carcinoma include the soft palate, base of tongue, tonsillar region (i.e., tonsil, tonsillar fossa, and pillars), and posterior pharyngeal wall. Among these subsites, the tonsillar region accounts for the majority (approximately 70% to 80%) of cases. Indeed, the tonsillar region is a favored site for HPV-associated carcinomas, and the majority of oropharyngeal carcinomas in the United States currently are attributed to HPV infection (Fig. 10-113).

Oropharyngeal carcinomas exhibit the same basic clinical appearance as more anterior carcinomas; however, in this posterior location, lesions often go unrecognized for long periods. By the time of diagnosis, tumor size is typically greater than that of oral carcinomas, and the proportion of cases with cervical and distant metastasis is higher. Common presenting symptoms for oropharyngeal carcinoma include...
and enlarged (Fig. 10-115). If the malignant cells have perforated the capsule of the node and invaded into surrounding tissues, then the node will feel “fixed,” or not easily movable. Extracapsular spread (extension of metastatic deposits outside of the lymph node capsule) is a microscopic feature associated with poor prognosis, including increased risk for locoregional recurrence, distant metastasis, and shortened survival.

Occasionally, contralateral or bilateral metastatic deposits are seen, and at least 2% of patients have distant (“below the clavicles”) metastasis at diagnosis; in some studies this figure is as high as 22%. The most common sites of distant metastasis are the lungs, liver, and bones, but any part of the body may be affected.

Carcinoma of the lower lip and oral floor tends to travel to the submental nodes; tumors from the posterior portions of the mouth typically travel to the superior jugular and

**Metastasis**

Metastasis of oral squamous cell carcinoma occurs largely via the lymphatics to the ipsilateral cervical lymph nodes (Fig. 10-114). A cervical lymph node that contains metastatic carcinoma is usually firm to stony hard, nontender,
CHAPTER 10
Epithelial Pathology

384

Primary Tumor (T)

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor 2 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor more than 2 cm but not more than 4 cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor more than 4 cm in greatest dimension or extension to lingual surface of epiglottis</td>
</tr>
<tr>
<td>T4a</td>
<td>Moderately advanced local disease (Lip) Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face, that is, chin or nose (Oral cavity) Tumor invades adjacent structures only (e.g., through cortical bone [mandible or maxilla] into deep [extrinsic] muscle of tongue [genioglossus, hyoglossus, palatoglossus, and styloglossus], maxillary sinus, skin of face) (Oropharynx) Tumor invades the larynx, extrinsic muscles of tongue, medial pterygoid, hard palate, or mandible (Note: Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of larynx.)</td>
</tr>
<tr>
<td>T4b</td>
<td>Very advanced local disease (Lip) Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base, or encases carotid artery</td>
</tr>
</tbody>
</table>

Regional Lymph Node Involvement (N*)

<table>
<thead>
<tr>
<th>Lymph Node</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in a single ipsilateral node 3 cm or less in greatest dimension</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2a</td>
<td>Metastasis in a single ipsilateral node more than 3 cm but not greater than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2b</td>
<td>Metastasis in multiple ipsilateral nodes, none more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2c</td>
<td>Metastasis in bilateral or contralateral nodes, none more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in a node more than 6 cm in greatest dimension</td>
</tr>
</tbody>
</table>

Distant Metastasis (M)

<table>
<thead>
<tr>
<th>Metastasis</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

*Note: Metastases at level VII are considered regional lymph node metastases.


digastric nodes. Metastatic deposits from oropharyngeal carcinoma usually are found in the jugulodigastric or retropharyngeal nodes.

Metastasis is not an early event for carcinomas of the oral cavity proper. However, because of delay in diagnosis, approximately 21% of patients have cervical metastases at diagnosis (60% in reports from tertiary care medical centers). In contrast, oropharyngeal tumors are prone to early metastasis, with more than 50% of affected persons exhibiting cervical lymph node metastasis and 10% exhibiting distant metastasis at diagnosis.

Staging

Tumor size and the extent of metastatic spread are the best prognostic indicators for oral squamous cell carcinoma. Quantifying these clinical parameters is called staging. Table 10-3 summarizes the tumor-node-metastasis (TNM)
CHAPTER 10  Epithelial Pathology

sheets or islands of cells proliferate within the connective tissue, without attachment to the surface epithelium. The invading tumor destroys normal tissue and may extend deeply into underlying adipose tissue, muscle, or bone. Lesional cells may breach the perineurium that encases nerve bundles (perineural invasion) or may invade the lumina of veins or lymphatics (vascular invasion) (Fig. 10-116). There is often a strong inflammatory or immune cell response to invading epithelium, and necrosis may be present. The tumor may induce dense fibrosis (desmoplasia or scirrhous change) and the formation of new blood vessels (angiogenesis).

Histopathologic Features

Squamous cell carcinoma arises from dysplastic surface epithelium and is characterized histopathologically by invasive islands and cords of malignant squamous epithelial cells. At the earliest moment of invasion, the adjectives superficially invasive or microinvasive often are used. The features of epithelial dysplasia are discussed in more detail in the section on leukoplakia (see page 360).

Invasion is represented by irregular extension of lesional epithelium through the basement membrane and into subepithelial connective tissue. Individual squamous cells and

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM Classification</th>
<th>Oral Cavity*</th>
<th>Lip†</th>
<th>Oropharynx‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis N0 M0</td>
<td>72%</td>
<td>96%</td>
<td>56%‡‡</td>
</tr>
<tr>
<td>Stage I</td>
<td>T1 N0 M0</td>
<td>58%</td>
<td>83%</td>
<td>58%‡‡</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2 N0 M0</td>
<td>45%</td>
<td>57%</td>
<td>55%‡‡</td>
</tr>
<tr>
<td>Stage III</td>
<td>T3 N0 M0</td>
<td>32%</td>
<td>48%</td>
<td>43%‡‡</td>
</tr>
<tr>
<td>T4a N0 M0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4a N1 M0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 N2 M0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2 N2 M0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3 N2 M0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4a N2 M0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T N3 M0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4b Any N M0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any T Any N M1</td>
<td></td>
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</tbody>
</table>

‡‡Due to the increasing incidence in HPV-related oropharyngeal carcinoma, recent studies have shown a significant improvement in survival over that reflected in the SEER data from 1998-2001. Some centers have reported an overall 5-year survival rate of 54%-89% for HPV(+) oropharyngeal carcinoma, whereas the 5-year survival rate for HPV(-) tumors ranges from 33%-65%.

Tumor-node-metastasis (TNM) Clinical Staging Categories for Oral and Oropharyngeal Squamous Cell Carcinoma with Corresponding Survival Rates

system for staging oral and oropharyngeal carcinoma. This staging protocol depends on three basic clinical features: 1. T—Size of the primary tumor, in centimeters 2. N—Regional lymph node involvement 3. M—Distant metastasis

These three parameters are tallied together to determine the stage (Table 10-4). In general, the higher the stage, the worse the prognosis. In other words, a stage IV lesion is associated with a much worse prognosis than a stage I lesion. However, for oropharyngeal carcinoma, survival rates are similar for patients with stage I, II, and III disease (see Table 10-4); instead, HPV status appears to be the most important prognostic factor for patients with oropharyngeal carcinoma (see later).
widespread agreement regarding the use of such methods is lacking. For oropharyngeal squamous cell carcinoma, detection of transcriptionally active HPV infection is especially important in determining prognosis. HPV-positive oropharyngeal squamous cell carcinomas often are poorly differentiated and nonkeratinizing with basoloid cytologic features; in addition, the majority of cases are diagnosed at an
advanced clinical stage. Despite these features, HPV-positive oropharyngeal squamous cell carcinomas typically exhibit better treatment outcomes compared to HPV-negative cases. The gold standard for determining whether a carcinoma likely was caused by HPV is high-risk HPV E6 and E7 oncogene expression analysis by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR). However, this method is best suited for fresh frozen tissue and is technically demanding. In comparison, detection of p16 by immunohistochemistry is more widely available, is readily performed on formalin-fixed paraffin-embedded tissue, and is considered a highly sensitive (albeit not highly specific) surrogate for transcriptionally active, high-risk HPV infection in oropharyngeal carcinomas (see Fig. 10-113, B). (The molecular basis for this finding is that overexpression of p16 results from inactivation of the tumor suppressor pRB [retinoblastoma protein] by the HPV oncoprotein E7.) Also, in the case of a cervical lymph node with metastatic carcinoma of unknown origin, some studies suggest that p16 immunoreactivity may be useful in directing the search for the primary tumor to the oropharynx. Furthermore, investigators have found that in situ hybridization (ISH) for HPV 16 exhibits strong agreement with p16 immunohistochemistry, although it may fail to detect the minority of oropharyngeal tumors caused by other HPV types (see Fig. 10-113, C). In particular, the recent development of RNA ISH probes complementary to E6 and E7 mRNA allows for detection of transcriptionally active HPV in routinely processed tissue. Also, there is currently much interest in evaluating liquid-phase hybridization assays for detection of HPV in cytologic preparations from head and neck squamous cell carcinomas. Importantly, widely accepted testing algorithms, validated commercially available assays, and standardized reporting criteria for determination of HPV status in oropharyngeal and other head and neck tumors still need to be established.

In contrast to oropharyngeal squamous cell carcinomas, p16 immunohistochemistry performed on oral squamous cell carcinomas exhibits low positive predictive value for transcriptionally active HPV infection and is not useful for prognostication. Furthermore, there is only limited data regarding qRT-PCR analysis of high-risk HPV E6 and E7 expression in oral squamous cell carcinoma, with no significant correlation with prognosis demonstrated thus far.

**Treatment and Prognosis**

Clinical staging guides the treatment of squamous cell carcinoma. Most lip vermilion carcinomas are detected at an early stage and treated by surgical excision (typically a wedge resection) with excellent results. In contrast, advanced cases may be treated by definitive radiation therapy or combined chemoradiation therapy. At diagnosis, less than 10% of all lip vermilion carcinomas have metastasized; therefore, neck dissection seldom is indicated. However, a notable exception is squamous cell carcinoma of the upper lip vermilion, which exhibits a high risk for regional lymph node metastasis (apparently related to the extensive lymphatic network in this location). Fortunately, squamous cell carcinoma only rarely occurs in the upper lip.

For intraoral squamous cell carcinoma, early-stage lesions usually are treated with surgery; definitive radiation therapy may be an alternative for patients unable to tolerate surgery. Moderately advanced tumors typically are treated with surgery followed by either radiation therapy or concurrent chemoradiation therapy. Very advanced disease or cases in which surgery would result in unacceptable functional outcomes may be treated with radiation therapy and/or chemotherapy.

In addition to advanced stage, indications for postoperative (adjuvant) radiation or chemoradiation therapy in the treatment of intraoral carcinoma may include close or positive resection margins, high-grade histopathologic features, extracapsular spread, and perineural or angiolymphatic invasion. **Intensity-modulated radiation therapy (IMRT)** often is used to target the treatment area while minimizing damage to neighboring tissue. **Brachytherapy** (placement of tiny, radioactive seeds) may be used for select applications (e.g., definitive treatment of small intraoral tumors or as an adjunct with IMRT to deliver an additional radiation dose).

In patients with intraoral carcinoma, cervical lymph node involvement is evident at presentation in approximately 30% of cases and occult (or subclinical) in about 10% to 40% of cases. However, the risk for regional metastasis varies considerably by subsite. In the past, **radical neck dissection** (en bloc removal of the lymphatics of the lateral triangle of the neck along with associated nonlymphatic structures, including the internal jugular vein, submandibular gland, sternocleidomastoid muscle, and spinal accessory nerve) was standard treatment for clinically evident or suspected cervical lymph node metastasis. However, over the past several decades, **modified radical neck dissection** (similar to radical neck dissection but with preservation of nonlymphatic structures) and **selective neck dissection** (removal of only select cervical lymph node groups) have gained favor; these techniques are associated with decreased
morbidit y and, depending upon the extent of disease, often allow for disease control comparable to that of classical radical neck dissection. Histopathologic findings (e.g., number of positive nodes and presence of extracapsular spread) in a selective neck dissection may aid in determining the need for postoperative radiation or chemoradiation therapy.

The depth of invasion or tumor thickness may help predict occult cervical lymph node metastasis despite early T-stage and may be used to determine the need for elective selective neck dissection. Although some investigators have used these terms interchangeably, depth of invasion represents the distance from the basement membrane to the deepest portion of the tumor, whereas tumor thickness is the distance from the tumor surface to the deepest portion of the tumor. Many studies suggest a significantly increased risk for nodal metastasis with a depth of invasion or tumor thickness greater than about 3 to 5 mm; however, suggested cutoffs vary considerably by tumor subsite and study methodology. In addition, sentinel-node biopsy (biopsy of the first lymph node in the lymphatic basin to receive drainage from the tumor) has shown promise in identifying patients with occult neck metastasis, but this technique remains investigational for patients with oral cancer.

Chemotherapeutic agents commonly used for treating intraoral carcinoma include platinum-containing compounds (e.g., cisplatin and carboplatin), 5-fluorouracil, and taxanes (e.g., paclitaxel and docetaxel). Induction or neoadjuvant chemotherapy may be administered initially to shrink a tumor prior to additional therapy and has been advocated by some investigators to decrease the risk for distant metastasis; however, studies suggest this approach may yield either no or minimal improvement in locoregional disease control and patient survival. In contrast, for patients with locally advanced (stage III, IVa, or IVb) disease, current evidence supports postoperative concurrent chemoradiation therapy (especially incorporating cisplatin) for optimal locoregional control and disease-free survival. For intraoral carcinomas with distant metastasis (stage IVc), single- or multi-agent chemotherapy may be administered.

In addition, there are several promising targeted therapies, including monoclonal antibodies (e.g., cetuximab and panitumumab) or small molecule tyrosine kinase inhibitors (e.g., erlotinib) directed against epidermal growth factor receptor (EGFR); anti-vascular endothelial growth factor (VEGF) antibodies; and mammalian target of rapamycin (mTOR) inhibitors. In particular, cetuximab has been approved by the United States Food and Drug Administration for treatment of head and neck squamous cell carcinoma and typically is combined with radiation and/or chemotherapy. Molecular-based targeted therapies are anticipated to become increasingly important treatment strategies in the future.

For oropharyngeal squamous cell carcinoma, early-stage disease may be treated by either definitive radiation therapy or surgery; however, most cases are diagnosed at an advanced stage and require multimodal therapy involving various combinations of surgery, radiation therapy, or chemotherapy. Oncologists traditionally have preferred radiation or concurrent chemoradiation therapy over surgery in this anatomic location; however, recent advances in surgical techniques have led some to reconsider this view.

Based upon available data for patients recently diagnosed in the United States, the estimated 5-year relative survival rate for oral and pharyngeal cancers combined is approximately 64%. Although some patients die of their disease as many as 10 years after initial treatment, the great majority of deaths occur within the first 5 years. The prognosis varies considerably by tumor stage and subsite (Tables 10-4 and 10-5). Because most lip vermilion carcinomas are diagnosed at an early stage, the overall 5-year relative survival rate is excellent (approximately 95%). In contrast, intraoral and oropharyngeal carcinomas often are diagnosed at later stages, with significantly lower 5-year relative survival rates (e.g., 51% for floor of mouth lesions and 65% for oropharyngeal lesions).

For both intraoral and lip vermilion carcinomas, tumor stage is the best prognostic indicator. However, for oropharyngeal carcinoma, HPV tumor status (i.e., presence or absence of transcriptionally active HPV [see page 378]) is considered the most important prognostic factor, followed by tobacco exposure and tumor stage. Compared to patients with HPV-negative tumors, those with HPV-positive tumors typically exhibit a better response to chemotherapy and/or radiation therapy, with an approximately 60% reduction in risk of death and 30% greater 5-year absolute survival rate. Improved survival may reflect the unique biology of HPV-positive carcinomas as well as the low rate of comorbidity among the relatively young age group typically affected. Possible biologic reasons for favorable prognosis include an intact p53-mediated apoptotic response to radiation and a lack of field cancerization (see next section). Investigations of targeted therapies and less intensive treatment regimens for HPV-positive oropharyngeal tumors are ongoing.

Various molecular markers associated with oral squamous cell carcinoma, such as TP53 mutations, have shown

### Table 10-5 Overall 5-year Relative Survival Estimates for Oral and Pharyngeal Cancers

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Estimated 5-Year Relative Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity and pharynx</td>
<td>65%</td>
</tr>
<tr>
<td>Lip</td>
<td>88%</td>
</tr>
<tr>
<td>Tongue</td>
<td>65%</td>
</tr>
<tr>
<td>Floor of mouth</td>
<td>54%</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>65%†</td>
</tr>
</tbody>
</table>

equivocal results as prognostic indicators. Several investigators have reported that overexpression of survivin (a member of the inhibitor of apoptosis protein family) is associated with poor prognosis, but the clinical utility of this finding requires further study. Moreover, unlike oropharyngeal carcinoma (see later), there is no clear correlation between HPV tumor status and prognosis for oral squamous cell carcinomas.

In the United States, deaths from oral and pharyngeal cancers have been decreasing over the past several decades. The age-adjusted death rate for oral and pharyngeal cancers combined decreased from 4.3 per 100,000 population in 1975 to 2.5 per 100,000 population in 2010. From 2000 to 2010, the mortality rate decreased by approximately 1.3% annually. In particular, for oropharyngeal cancers, 5-year relative survival rates have improved—from approximately 51% to 59% for those diagnosed from 1995 through 2001 to approximately 65% for those diagnosed from 2002 through 2005. (This trend is reflected in the difference between oropharyngeal survival rates shown in Tables 10-4 and 10-5). Areas of investigational interest for continuing declines in oral and pharyngeal cancer mortality include improvements in prevention, early diagnosis, and treatment.

**Multiple Carcinomas**

Patients with one carcinoma of the mouth or throat are at increased risk for additional concurrent (synchronous) or, more commonly, later (metachronous) primary surface epithelial malignancies of the upper aerodigestive tract, stomach, lungs, and other sites. This risk has been estimated to be as low as 6% and as high as 44%; the highest figures are associated with male patients who continue to smoke and abuse alcohol after therapy. Overall, 9% to 25% of patients with oral carcinoma develop additional mouth or throat malignancies.

This tendency for the development of multiple mucosal cancers is hypothesized to result from field cancerization—a process whereby exposure to carcinogens, such as tobacco and alcohol, creates a diffuse field of altered epithelial cells with increased potential for malignant transformation. Molecular analyses of various markers, including loss of heterozygosity (LOH), microsatellite alterations, TP53 tumor suppressor gene mutations, and X-chromosome inactivation, have identified genetic alterations shared between tumor tissue and adjacent clinically normal-appearing tissue in one-third to one-half of cases examined. In addition, investigators have shown that a significant proportion of second primary tumors develop from the same preneoplastic precursor lesion or “field,” with the remaining cases representing tumors that develop independently. Furthermore, researchers have proposed that patches of clonal cells can progress to develop additional mutations and give rise to subclones in a process known as clonal divergence, which would account for the genetic heterogeneity typically seen among these tumors. Interestingly, field cancerization does not appear to be associated with malignancies attributed to HPV infection.

**Verrucous Carcinoma (Snuff Dipper’s Cancer; Ackerman’s Tumor)**

Verrucous carcinoma is a low-grade variant of oral squamous cell carcinoma. In 1948, Ackerman described this lesion in detail, although the term verrucous carcinoma had been used in 1944 in a series of cases reported by Burford, Ackerman, and Robinson. Ackerman postulated that some of these lesions might be associated with smokeless tobacco use, because 11 of his 31 patients were “tobacco chewers.” However, there was no mention of the type of smokeless tobacco used and no mention of whether any of these patients also had smoked tobacco. In addition to the oral mucosa, verrucous carcinoma has been identified at several extraoral sites, including laryngeal, vulvovaginal, penile, anorectal, sinonasal, and esophageal mucosa, as well as the skin of the breast, axilla, ear canal, and soles of the feet. Extraoral cases are unrelated to tobacco use. Several investigators have identified DNA from HPV types 6, 11, 16, and 18 in a minority of oral verrucous carcinomas, although the possibility that these cases represent coincidental HPV infection cannot be excluded.

Verrucous carcinoma represents less than 1% to 16% of all oral squamous cell carcinomas, depending on the local popularity of smokeless tobacco use. The only epidemiologic assessment of this tumor in a Western culture reported an average annual incidence rate of one to three oral lesions per 1 million population each year. Among 411,534 cases of head and neck carcinoma recorded in the National Cancer Database from 1985 to 1996, only 0.6% of cases were diagnosed as verrucous carcinoma.

Some oral verrucous carcinomas arise in people who chronically use chewing tobacco or snuff. Cases also occur in those who combine habits (i.e., smokeless tobacco, smoking, and alcohol), exclusively smoke tobacco, or have no identifiable risk factors. However, exact figures are difficult to assess because patients often deny their habits. Nevertheless, among smokeless tobacco users, conventional squamous cell carcinoma is much more likely to develop than this low-grade variant.

**Clinical Features**

Verrucous carcinoma is found predominantly in men older than 55 years (average age: 65 to 70 years). In areas where women frequently use dry snuff, however, older females may predominate. The most common sites of oral mucosal involvement include the mandibular vestibule, buccal mucosa, gingiva, tongue, and hard palate. The involved area often corresponds to the site of chronic tobacco placement. In cultural groups who keep the tobacco in the maxillary vestibule or under the tongue, these locations are involved most commonly.
tissue (Fig. 10-122). Lesions usually show abundant keratin (usually parakeratin) production and a papillary or verruciform surface. Parakeratin typically fills the depressions (parakeratin clefts) between the surface projections. These projections may be long and pointed or short and blunted. The lesional epithelial cells generally show no significant cytologic atypia. There is frequently an intense inflammatory cell infiltrate in the subjacent connective tissue. The histopathologic diagnosis of verrucous carcinoma requires an adequate incisional biopsy. Because the individual cells are not very dysplastic, the pathologist must evaluate the overall histomorphologic configuration of the lesion to make the diagnosis. Adequate sampling also is important because conventional squamous cell carcinoma develops concurrently within up to 20% of verrucous carcinomas.

**Treatment and Prognosis**

The treatment of choice is surgical excision. The surgery generally need not be as extensive as that required for conventional squamous cell carcinoma of a similar size. If cervical lymph node enlargement is clinically evident, then a selective neck dissection may be performed, although most such cases turn out to represent reactive lymphadenopathy rather than metastasis. Approximately 90% of patients are disease free 5 years after surgery, but some patients will require at least one additional surgical procedure during
that time. The treatment failures usually occur in patients with the most extensive involvement or in those unable to tolerate extensive surgery because of unrelated systemic diseases. An additional cause of treatment failure is the initial inability to identify focal, concurrent conventional squamous cell carcinoma; such cases should be treated as conventional squamous cell carcinomas.

Radiotherapy is an alternative primary treatment modality but provides poorer local control and, thus, is considered less effective than surgery. In addition, radiotherapy has been unpopular because of published reports of poorly differentiated or anaplastic carcinoma developing within the lesion after treatment. However, more recent analysis suggests that this threat is overexaggerated. In a limited number of cases, tumor regression after chemotherapy, radiochemotherapy, or photodynamic therapy has been reported, although these treatment alternatives require further study.

**SPINDLE CELL CARCINOMA**
(SARCOMATOID SQUAMOUS CELL CARCINOMA; POLYPOID SQUAMOUS CELL CARCINOMA; CARCINOSARCOMA; PSEUDOSARCOMA)

Spindle cell carcinoma is a rare variant of squamous cell carcinoma characterized by dysplastic surface epithelium in conjunction with an invasive spindle cell element. With routine light microscopy, it may be indistinguishable from connective tissue sarcomas or other spindle cell malignancies. Spindle cell carcinoma of the upper aerodigestive tract is closely associated with tobacco and alcohol use. Some cases develop after radiotherapy for a more differentiated squamous cell carcinoma, a phenomenon known as dedifferentiation. Transcriptionally active HPV appears to be exceptionally rare in this variant.

In the past, this biphasic lesion was thought to be a “collision” tumor between a carcinoma and sarcoma, but most authorities now consider the spindle cells to represent anaplastic carcinoma cells. Electron microscopy and immunohistochemical analysis support the concept that these lesional cells are of epithelial origin, with the ability to produce mesenchymal intermediate filaments. Based on immunohistochemical studies, some investigators have hypothesized that a dysfunctional cadherin-catenin complex important for intercellular adhesion causes the tumor cells to shift from a squamous to a spindled type, with increased infiltrative behavior.

**Clinical Features**

Spindle cell carcinoma may arise anywhere within the upper aerodigestive tract, with a predilection for the larynx and oral cavity. In the mouth, the alveolar mucosa, tongue, buccal mucosa, and lower lip are common sites, but other areas may be involved. Males are affected more often than females. According to the largest reported series restricted to oral cases, the mean age at diagnosis is 57 years (range: 29 to 93 years).

In contrast to other oral cancers, spindle cell carcinoma typically appears as a pedunculated, polypoid mass, but occasionally it may appear as a sessile, nodular or fungating mass (Fig. 10-123). The surface often is ulcerated. Pain and paresthesia are prominent features. The tumor grows rapidly, tends to metastasize early, and typically is diagnosed at a late stage. Lower lip lesions seem to have a special propensity to travel along nerves through the mental foramen and into the mandibular canal.

**Histopathologic Features**

Spindle cell carcinoma is composed predominantly of fascicles of anaplastic, spindle-shaped cells (Fig. 10-124). Some spindle cells may appear as obvious epithelial elements, but others strongly resemble atypical mesenchymal cells. On rare occasions, bone, cartilage, or muscle differentiation may be seen. Numerous mitotic figures often are present. The overall picture is similar to that of an anaplastic fibrosarcoma (see page 516), except for the often-inconspicuous squamous element.