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Early Diagnosis of Asymptomatic Oral and Oropharyngeal Squamous Cancers

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Introduction

Squamous cell carcinomas of the oral cavity and oropharynx are not difficult to diagnose once they have become symptomatic (Figs. 1 and 2). A patient's complaints of pain, bleeding, ulceration, a mass, otalgia, and/or dysphagia usually will direct the clinician to the primary lesion, which is typically at least stage II and often has associated cervical lymphadenopathy (Fig. 3). Between 1983 and 1990, 53 percent of patients with cancers of the oral cavity and pharynx demonstrated regional or distant metastases.[1] Despite aggressive combinations of surgery, radiotherapy, and chemotherapy, five-year survival rates for all stages combined are poor (55 percent for whites; 34 percent for blacks). Morbidity remains high.

Early, asymptomatic oral and oropharyngeal cancers differ markedly from advanced cancers in their clinical presentation, course, and outcome (Fig. 4). Early diagnosis and treatment are rewarded with optimal survival and minimal dysfunction. Unfortunately, there is a tendency for clinicians, based on past literature, to focus on symptomatology with little effective effort devoted to early detection. Generally, head and neck diagnosis is still predominantly predicated on patient symptoms.

Squamous cell carcinomas of the oral cavity and oropharynx are particularly suited to early diagnosis because sites of involvement are easily accessible for direct examination without special techniques (e.g., endoscopy). In addition, the disease is associated with clearly identifiable risk factors[2-4]; a readily detectable asymptomatic phase that has a distinctive clinical appearance[5-7]; and a safe, efficient adjunctive diagnostic modality.[8-13] Unfortunately, most oral and oropharyngeal cancer screening programs typically result in poor yields.

The diagnosis of nonpalpable, nonulcerated, minimally elevated, asymptomatic cancers in patients with node-negative necks remains elusive for specific reasons. Chief among these are the following: (1) a failure to concentrate efforts on individuals at highest risk; (2) a failure to focus attention on the sites within the oral cavity and oropharynx at highest risk; (3) a lack of appreciation for erythroplasia as the earliest clinically detectable manifestation of oral and oropharyngeal squamous carcinoma; (4) an excessive emphasis on leukoplakia as a precancerous lesion; (5) a tendency to group all dysplasias together without regard to the degree of cellular atypia present; and (6) an underutilization of tolui-

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dine blue as a diagnostic adjunct. Most significant is the commitment and motivation of the examiners, physicians and dentists. In our experience, some clinicians consistently find early asymptomatic cancers while others examining the same patient population do not.

Individuals at Highest Risk

In the United States and western Europe, oral and oropharyngeal squamous carcinoma is predominately a disease of men aged 50 to 70 years and women aged 60 to 80 years and is related primarily to cigarette smoking and alcohol consumption. Numerous studies over the past twenty years have substantiated the relationship between alcohol and cigarette tobacco and cancer of the upper aerodigestive tract (i.e., oral cavity, pharynx, larynx, and esophagus).[14-19] Other risk factors (e.g., syphilis, vitamin deficiency, or chronic irritation from dentures, sharp teeth, hot or spicy foods, or various other physical agents) currently are acknowledged to have little relevance.

Nondrinking smokers were shown to have two to four times the risk of developing carcinoma as abstainers of alcohol and tobacco.[14] Heavy-drinking smokers have a risk six to fifteen times greater than abstainers.

A study of US veterans confirmed the synergistic effects of alcohol and tobacco and also proposed an independent role for alcohol in oral cancer.[15] The cancer risk for alcohol is more dose-related than for cigarettes. The data indicated that for someone who smokes and drinks, doubling the alcohol consumption leads to much greater risk of oral cancer than doubling cigarette consumption (Table 1). This study also suggests that beer may be a more significant risk factor than whiskey.

In France, a retrospective study of 200 male patients with esophageal cancer and 778 controls found that when the adjusted relative risks were calculated for various levels of alcohol and tobacco consumption, the effects of drinking and smoking appear to be independent of one another.[16] When alcohol and tobacco intake were considered together, the risks observed were consistent with a multiplicative model.

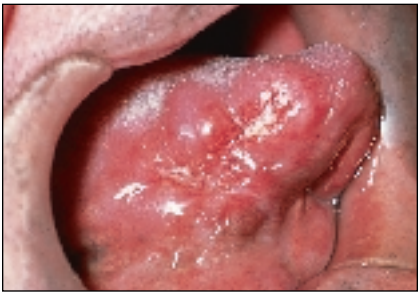

Fig. 1. Advanced symptomatic carcinoma of the tongue: ulcerated, indurated, and primarily endophytic with surface invagination.

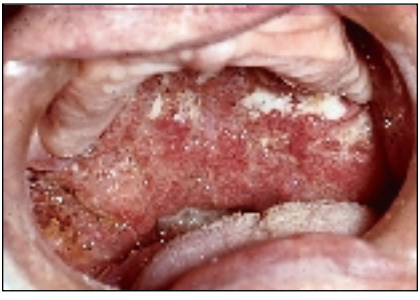

Fig. 2. Massive advanced carcinoma of the soft palate with extension to the hard palate; total replacement of normal mucosa by tumor.

A study in Italy comparing 122 adult consumers of alcohol and tobacco with 606 controls found a four- to six-fold increase in oral and oropharyngeal cancer risk among subjects with medium or high tobacco consumption, as well as an increasing risk associated with greater duration of usage and with earlier age at onset.[17] An effect for alcohol was seen in subjects with an average daily consumption of 120 g (about 12 whiskey equiva-

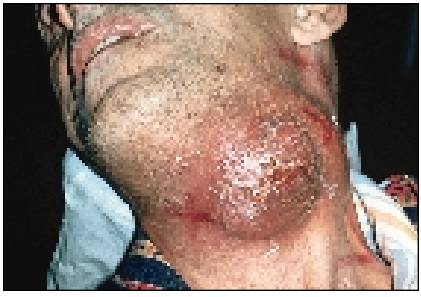

Fig. 3. Cervical lymphadenopathy with central necrosis; metastasis from pharyngeal carcinoma.

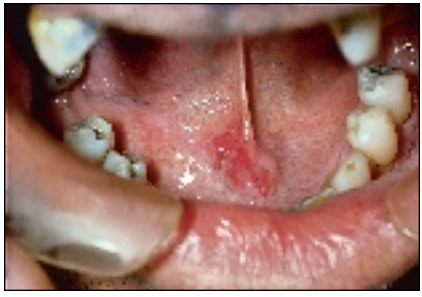

Fig. 4. Asymptomatic erythroplastic invasive carcinoma of the floor of the mouth—red and velvety smooth. Surrounding paler areas are islands of normal mucosa.

lents) or more of alcohol, with a higher risk in beer drinkers.

Male and female patients who developed multiple primaries within five years after an initial cancer were reported to have consumed significantly more alcohol per day than a control group.[18] The relative risk of multiple primary cancers in men and women exposed to the equivalent of forty or more cigarettes and three or more whiskey equivalents per day for at least thirty years was 3.9 times that of patients exposed to the equivalent of fewer than twenty cigarettes and less than three whiskey equivalents per day.

Other forms of tobacco have also been implicated as etiologic agents in oral carcinoma. In the Western world, while not as commonplace as cigarette smoking or alcohol drinking, habitual use of cigars and pipes appears to be a risk factor. In recent years concerns have been expressed about the increased use of smokeless tobacco among the young. The role of this form of unburned tobacco is less well defined. A significant case-control study by Winn et al[20] documents an increased risk in white women older than 60 years, especially at the site of placement. Findings in other studies vary due to methodologic limitations and contrasting data.[21-23] Smoking is frequently a confounding factor,[24] and conclusions vary.[25] Prospective, long-term epidemiologic studies are indicated. Anecdotal data suggest an effect at the site of placement. In Asia, where betel nut quid has been accepted as a risk factor, the question remains as to whether the carcinogen is the tobacco, the nut, or the slaked lime in the quid.

The role of immune competence in the development of upper aerodigestive disease in smokers and drinkers also warrants scrutiny. Despite its local manifestations, squamous cell carcinoma of the upper aerodigestive tract appears to be a regional disease process that becomes clinically evident only after the patient's immunologic capacity is altered. Severe dysplasia, carcinoma in situ, and microinvasive carcinoma may actually arise in many sites within the upper aerodigestive mucosa and remain dormant, becoming established and clinically visible only with a decrease in the patient's immune competence. The significance of immune competency in the development and progression of cancer may be evident when aerodigestive malignancies arise in patients positive for the human immunodeficiency virus (HIV). These cancers generally occur at an earlier age and seem to behave more aggressively than in non-HIV-positive patients.

Oral and oropharyngeal carcinoma is often associated with additional syn-

Table 1
Oral/Oropharyngeal Cancer Risks Associated with Smoking* and Drinking† Habits

	Cases	Controls	Relative Risks	
			Crude	Adjusted
Smoking Habits				
Minimal smoking	14	173	1.0	1.0
Cigar/pipe	14	41	4.2	4.1
10-19 cigarettes/day	16	48	4.1	3.2
20-39 cigarettes/day	82	150	6.8	4.5
>40 cigarettes/day	55	85	8.0	5.0
Total	181	497		
Drinking Habits				
Minimal drinking	10	206	1.0	1.0
<6 WEs/day‡	23	106	4.5	3.3
6-9 WEs/day	47	52	18.6	15.2
>10 WEs/day	101	133	15.6	10.6
Total	181	497		

*Adjusted for drinking habits and age.

†Adjusted for smoking habits and age.

‡WE = Whiskey equivalent. One WE = one ounce 86-proof whiskey, four ounces of dry wine (11 to 12 percent alcohol), or 12 ounces of beer.

Data from Mashberg et al.[15]

chronous or metachronous primary squamous cancers of the lung, larynx, pharynx, and esophagus.[26] The presence of a first cancer in the upper aerodigestive tract signifies an increased risk of having or developing a second cancer anywhere in the upper aerodigestive tract.[27] This phenomenon of "field cancerization," in which significant dysplastic changes occur throughout a wide epithelial field in high-risk patients (heavy smokers and drinkers) was confirmed by a later report.[28] These studies indicate that the initial lesion heralds a general susceptibility to other squamous carcinomas. As a result, it is not uncommon for a patient followed for a treated initial carcinoma without recurrence to be confronted with synchronous or metachronous multiple primaries. When patients with index early oral or oropharyngeal carcinomas succumb to cancer, the lesion directly responsible for the patient's death is almost always an additional primary tumor of the hypopharynx, lung, or esophagus, not the index lesion.

In one series of 732 patients with squamous carcinoma of the oral cavity, 16.3 percent had additional malignancies of the head and neck.[29] In another

Table 2
Other Primary Cancers of the Upper Aerodigestive Tract and Lung in 101 Patients with Asymptomatic Oral/Oropharyngeal Carcinomas

Location	Number	More Than One Year Prior to Oral Primary	Synchronous (Within One Year of Oral Primary)	More Than One Year After Oral Primary
Hypopharynx	10	–	8	2
Oropharynx	4	–	3	1
Larynx	7	2	5	–
Lung	9	1	4	4
Esophagus	3	–	3	–
Total	33	3 (9%)	23 (70%)	7 (21%)

Data from Mashberg and Samit.[33]

study, a 22 percent incidence of second squamous cancer of the upper aerodigestive tract was reported in patients with carcinoma of the mouth, pharynx, or larynx.[30] Additional studies confirm the increased incidence of aerodigestive second primaries.[31,32]

In a prospective pilot study of a group of 101 heavy drinkers and smokers with asymptomatic index oral carcinomas, thirty-three (32.7 percent) of the patients had second primaries.[33] The sites of the second primaries included the hypopharynx (10), lung (9), larynx (7), oropharynx (4), and esophagus (3). Of these cases, twenty-three (70 percent) were synchronous lesions, occurring within one year of diagnosis of the oral primary. Seven (21 percent) of these lesions were diagnosed more than a year later, and three lesions (9 percent) were discovered at least one year prior to the oral primary (Table 2). This small sample suggests an even greater incidence of second primaries of the upper aerodigestive tract and lung in patients with an index oral carcinoma than previously reported in the literature.

Clinicians should recognize that once a first primary cancer has been detected, it is necessary to evaluate the patient for additional primaries via triple endoscopy and chest x-ray. After treatment close and careful surveillance with repeated endoscopy and chest x-ray every twelve months is indicated.

Sites at Highest Risk

Geographic and regional differences in the intraoral distribution of squamous cell carcinoma are commonly acknowledged. Environmental carcinogens and local customs each probably contribute to the site-distribution pattern for any given population. Cancers related to alcohol drinking and cigarette smoking, the predominant risk factors in the United States and Europe, have been shown to be localized to distinct sites within the oral cavity.

Although the hard palate, buccal mucosa, gingiva, and tongue were once

considered common sites for squamous cell carcinoma, studies have demonstrated that three specific intraoral areas are most predisposed to develop squamous cell carcinoma in drinkers and smokers.[7,34] The floor of the mouth, ventrolateral tongue, and soft palate complex (soft palate proper, lingual aspect of the retromolar trigone, and anterior tonsillar pillars) should be regarded as high-risk sites (Fig. 5).

The site and size of 222 asymptomatic squamous cell carcinomas were documented in 161 cigarette smokers who were also drinkers. Of 207 intraoral lesions (excluding 15 of the lip), 201 lesions (97 percent) were found in three locations: 101 (50 percent) in the floor of the mouth, 64 (32 percent) in the soft palate complex, and 36 (18 percent) in the ventral or lateral tongue.[7] These lesions were predominantly T1 (2 cm or less) making localization more certain. Of the 101 lesions in the floor of the mouth, 73 (72.3 percent) occurred in the anterior portion, with 33 (32.7 percent) involving the papilla at the orifice of Wharton's duct (Fig. 6). Significantly, excluding the 15 lesions located on the lip, only six lesions (less than three percent) were found in other sites: one in the hard palate, three in the alveolar gingiva, and two in the buccal mucosa. The paucity of early, asymptomatic lesions of the hard palate, buccal mucosa, and alveolar lesions suggests that the traditional sites described in the past literature may be points of termination or extension rather than sites of origin. For example, a symptomatic T2 or T3 lesion in the floor of the mouth extending to or invading the alveolus may be documented erroneously as an alveolar or gingival lesion. Similarly, a large soft palate lesion that extends anteriorly may be mistakenly described as a hard palate malignancy. A similar distribution pattern was reported in an Italian study.[17]

In a paper published in 1964, most carcinomas of the upper aerodigestive

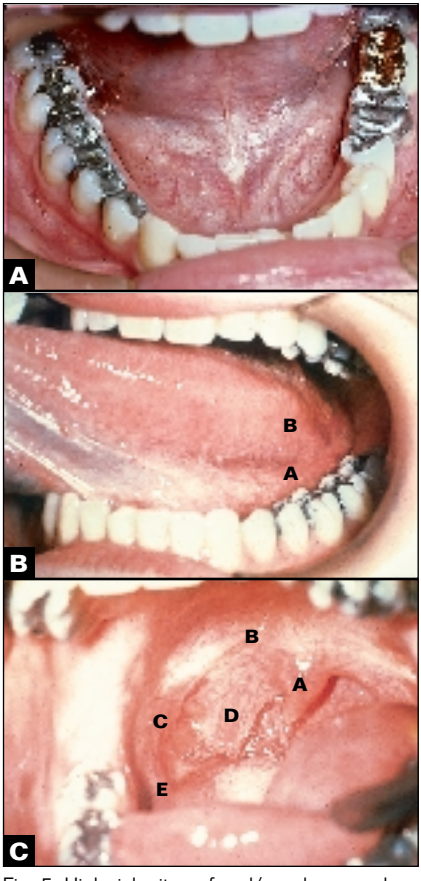

Fig. 5. High-risk sites of oral/oropharyngeal cancer. (A) The anterior floor of the mouth, the most common site for development of oral squamous carcinoma in cigarette smokers who are also drinkers. (B) Ventrolateral tongue and posterior floor of the mouth—sites A and B are of particular concern. Unless there is adequate tongue retraction to the contralateral side, visualization is poor. (C) Soft palate complex—A, the uvula; B, the posterior soft palate; C, anterior tonsillar pillar; D, posterior tonsillar pillar; and E, lingual aspect of the retromolar trigone and junction of the tongue and anterior pillar.

tract were found in specific locations.[35] These sites comprised a portion of the lateral food channels and the sphincters controlling the volume of food passing through those channels. In addition, involvement of "reservoir systems," which act to pool food and prevent the bolus from inundating the air passage, was described. A preponderance of lesions in these same areas was confirmed by another report.[32] Such reservoirs may collect dissolved or concentrated carcinogens, permitting more prolonged contact with the mucosa.

A study of 359 male US military veterans with 424 cancers of the oral cavity and oropharynx found tobacco smoking was more strongly associated with soft palate lesions than with lesions in more anterior sites.[36] Although the soft palate is not a dependent reservoir, it is possible that inhaled tobacco smoke is concentrated in this area and exerts a direct carcinogenic effect. Individuals with cancer of the floor of the mouth and oral tongue had higher risk ratios for alcohol drinking than subjects with cancers of other sites. Because the anterior floor of the mouth is the most dependent part of the oral cavity, alcohol may remain in prolonged contact with the mucosa there and act as a carcinogen.

Toluidine blue clinically stains malignant lesions, but not normal mucosa.

The histologic similarity of tissues in high-risk areas also may be significant. Tissues at high-risk sites have a thin epithelium relatively devoid of keratin and a submucosa that contains fat and glands. In contrast, tissues in the low-risk areas (e.g., the dorsum of the tongue, the hard palate, or the buccal mucosa) are more richly keratinized or highly specialized. Unprotected by ker-

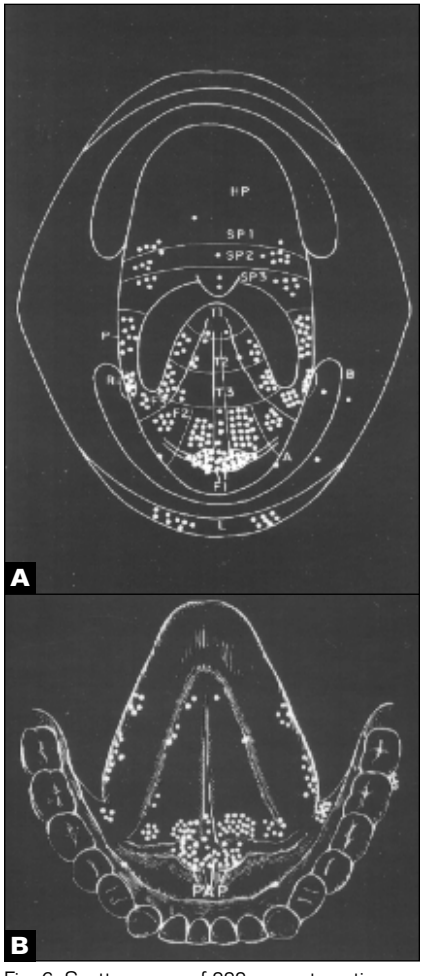

Fig. 6. Scattergrams of 222 asymptomatic squamous cell carcinomas (reprinted with permission from Mashberg and Meyers[7]). (A) Subdivided sites as follows: T = ventrolateral tongue (1, 2, and 3 refer to anterior, middle, and posterior thirds); F = floor of the mouth; SP = soft palate proper; P = anterior pillar; R = lingual aspect of retromolar trigone; L = lip; A = alveolus; B = buccal mucosa; and HP = hard palate. (B) Detailed scattergram of the floor of the mouth and ventrolateral tongue. Note the concentration of lesions in the anterior floor of the mouth, especially at the papilla (PAP) at the exit of Wharton's duct (submaxillary gland orifice).

Table 3
Color Components of Asymptomatic Oral/Oropharyngeal Squamous Carcinomas

	Invasive Carcinoma			Carcinoma in Situ		
Color	**Number**	**Percent**		**Number**	**Percent**	
Red only	76	32	64%	24	27	54%
Red > white	76	32		25	27	
Red = white	56	23		27	30	
White > red	13	6	12%	9	10	16%
White only	13	6		5	6	
Other	2	1		0	0	
Total	236	100		90	100	

Data from Mashberg and Feldman.[39]

atin or specialized structures, high-risk areas may be more subject to the local effects of carcinogens.

Intraoral Examination of the Asymptomatic Patient

The high-risk sites require careful visual scrutiny in an oncologic examination of the oral cavity. These areas are difficult to evaluate without adequate lighting. Standard dental lights and some fiberoptic light systems appear to be best for detection of early lesions. Head mirrors, lamps, and pen lights do not have sufficient intensity or color balance to allow an appreciation of minute mucosal alterations.

A dental or laryngeal mirror facilitates adequate visualization of areas that cannot be seen directly. Use of a wooden tongue depressor as a retractor does not permit visualization of all pertinent intraoral mucosal surfaces because light cannot be directed or reflected with the instrument. In addition, the mirror is more rigid and better tolerated by patients, further facilitating the examination.

For inspection of the anterior and middle thirds of the floor of the mouth and the anteroventral two thirds of the tongue, the mandible should be horizontal when the mouth is open. The tip of the tongue should be extended upward, making contact with the hard palate posteriorly. Examination of the posterior floor of the mouth, retromolar trigone, and posterior ventrolateral aspect of the tongue (including the area of the foliate papillae) necessitates grasping the anterior one third of the tongue with a 2 x 2-inch gauze sponge, distracting it to the contralateral labial commissure and withdrawing it from the oral cavity as far as possible. Applying external pressure in the area of the submandibular gland on the ipsilateral side permits the posterior floor of the mouth to be elevated and its contiguous structures to be visualized. At the same time, the mirror should be used to view indirectly the lingual aspect of the retromolar trigone. With the tongue still hyperextended, the anterior

Table 4
Sizes of Asymptomatic Oral/Oropharyngeal Squamous Carcinomas*

Size (Cm)		Invasive Carcinoma Number	Invasive Carcinoma Percent	Carcinoma in Situ Number	Carcinoma in Situ Percent
0.1-1.0	T1	85	36	39	44
1.1-2.0	T1	100	42	37	41
2.1-3.0	T2	33	14	11	12
3.1-4.0	T2	17	7	3	3
> 4.1	T3T4	1	1	0	–
Total		236	100	90	100

*Greatest diameter.

Data from Mashberg and Feldman.[39]

pillar (glossopalatine fold) may also be examined. The soft palate, uvula, and posterior pillars may be visualized directly by depressing the middle one third of the tongue and asking the patient to take a deep breath.

Although palpation is an important part of the head and neck examination, direct visualization of the mucosal surfaces is most significant in detecting early lesions, which usually have little mass and minimal depth. However, palpation should supplement mirror examination in an evaluation of the base of the tongue and vallecula—areas not accessible to direct visualization. The neck should always be evaluated for cervical adenopathy.

Erythroplasia—The Earliest Clinical Manifestation

The earliest and most consistent clinical presentation of squamous carcinoma is the persistent erythroplastic lesion, an asymptomatic, innocuous-appearing, red, inflammatory, atrophic, mucosal alteration, with or without a keratinized component. Studies repeatedly confirm this to be the earliest manifestation of oral and oropharyngeal squamous carcinoma in the industrialized Western world (i.e., the United States and Europe), particularly in smokers and drinkers.[6,7,37,38]

In a study of 236 patients with asymptomatic, intraoral carcinomas, 64 percent were red or predominantly red, while 12 percent were white or predominantly white; 23 percent were equally red and white (Table 3).[39] The color distribution pattern for 90 carcinomas in situ was similar. Most asymptomatic erythroplastic lesions (80.1 percent) were found to be less than 2 cm in diameter, and 38.2 percent were 1 cm or less (Table 4).[39]

There are two distinct types of erythroplastic lesions that suggest carcinoma.[37] The first is a granular, velvety-red lesion with stippled or patchy areas of

normal mucosa or keratin within or peripheral to the lesion (Figs. 7 and 8). These white-appearing areas lie on a red, inflamed mucosal surface. Usually, the mucosa is not ulcerated, but may be "heaped up."

The second type is a smooth, nongranular lesion, primarily red with little or no keratosis (Figs. 4, 9, and 10). The mucosal surface, however, is unlike that of a nonspecific inflammatory lesion in that it seems atrophic and worn. These smooth, nongranular lesions may wax and wane, their appearance changing from one day to the next probably as the degree of inflammation varies.

Ulceration, bleeding, induration (palpability), and exophytic growth beyond 1 mm are uncommon in both types of early lesion (Table 5). Frequently, these significant areas of mucosal abnormality are not well defined. Many are irregular with a blending of inflamed and normal mucosa. Some contain islands of normal mucosa or keratin entrapped by the growth and coalescence of separate erythroplastic areas. This pattern imparts a speckled or patchy appearance to the lesion.

Because the appearance of these lesions is altered by saliva, the mucosal surface should be dried gently prior to examination. When dry, the lesions often appear more granular or slightly abraded. There are no reliable clinical signs that differentiate in situ from invasive carcinoma, although textural changes such as roughness or granularity greatly increase the probability that a lesion is invasive. Cervical metastases are rare at this stage.[37,39] Typically, an area of reddened mucosa is significant if it is present in one of the acknowledged high-risk sites and if it persists for more than fourteen days after eliminating all suspected chemical, physical, thermal, and biologic etiologies. Despite their very early nature, these lesions should not be regarded as precancers; histologic documentation reveals early invasion or microinvasion (72 percent) or carcinoma in situ (28 percent).

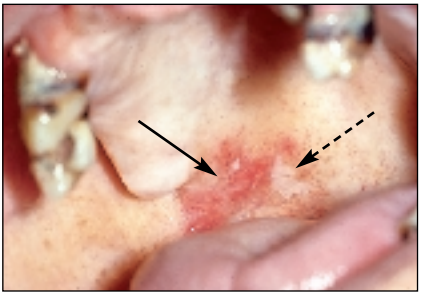

Fig. 7. Asymptomatic invasive carcinoma of the soft palate. The solid arrow points to diffuse inflammation—erythroplasia (red) with associated areas of keratin; the broken arrow indicates a keratin patch. Biopsy of a keratinized area is frequently unrevealing, whereas biopsy of an erythroplastic site is usually diagnostic.

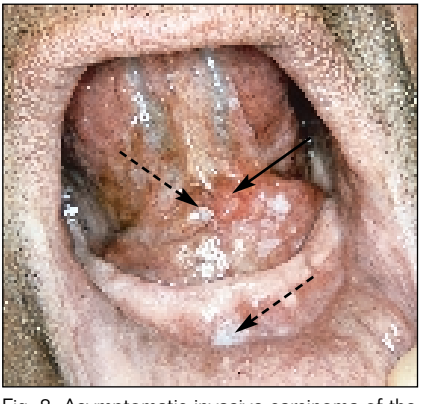

Fig. 8. Asymptomatic invasive carcinoma of the floor of the mouth. The broken arrow indicates keratin at the salivary papilla. The solid arrow on the contralateral papilla identifies an erythroplastic area. This site is indicated for biopsy (see Figure 11 for microscopic findings). The broken arrow on the labial aspect of the alveolus indicates a benign keratinized area.

The erythroplastic character of these lesions appears to be related to a reactive inflammatory barrier (i.e., a submucosal vascular proliferation and a

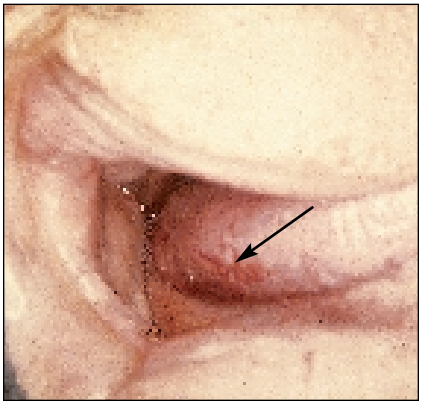

Fig. 9. Irregular erythroplastic asymptomatic carcinoma on the lateral aspect of the mid-tongue; the mucosal surface appears atrophic.

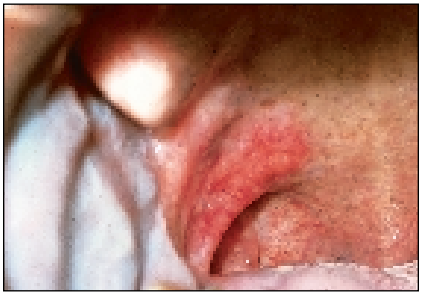

Fig. 10. Asymptomatic carcinoma of the anterior tonsillar pillar. The only change noted is diffuse redness of the entire pillar.

round cell infiltrate) associated with the overlying malignant squamous cells. Microscopic specimens of early cancer almost invariably demonstrate such an inflammatory reaction below the basement membrane, probably reflecting angiogenesis or an immune response to the developing cancer (Fig. 11). Histologically, these lesions have been shown to have minimal depth.[40]

Although the mucosal changes in early cancer may resemble the tissue responses associated with candidiasis, lichen planus, or local tissue injury of a physical, chemical, or thermal nature, diagnostic distinctions can be made. Malignant lesions are usually discrete entities located in the high-risk areas of the mouth, are not associated with a specific etiology, and persist despite removal of local factors. Occasionally, there may be more than one primary neoplasm due to field cancerization. Nonneoplastic inflammatory lesions, diffuse or localized, can usually be attributed to a specific etiology or event and typically subside within fourteen days following elimination of local factors. If a lesion persists beyond the observation period, biopsy is mandatory.

An Unjustified Emphasis on Leukoplakia

The evidence suggests that early diagnosis of oral and oropharyngeal cancer may be impeded because of a persistent reliance on paradigms relating leukoplakia to precancer to cancer. The premise that clinical leukoplakia may be a forerunner of malignancy or a significant indicator of early carcinoma has been shown to be questionable. Keratin is a response to irritation, carcinogenic or otherwise, and the overwhelming number of irritants do not imply carcinogenic potential (Figs. 12 and 13). Only about six percent of early invasive carcinomas or carcinomas in situ have been shown to be purely white lesions,[39] and only 0.13 to 6.0 percent of leukoplakias followed for a prolonged period are eventually diagnosed as cancer.[41-48] However, the submucosal inflammatory barrier, which is an early response to the developing malignancy, appearing as a red or erythroplastic area, is invariably present.

The tendency to describe all mucosal aberrations with a keratotic component as leukoplakias and to disregard other components occurs when clinicians respond reflexively to whiteness in documenting the appearance of these lesions (Figs. 7 and 8). This frequently results in a

Table 5
Surface Characteristics of Asymptomatic Oral/Oropharyngeal Squamous Carcinomas

	Invasive Carcinoma		Carcinoma in Situ	
Size (cm)	**Number**	**Percent**	**Number**	**Percent**
Texture				
Smooth	91	39	56	62
Granular	141	60	34	38
Fissured	3	1	0	–
Total	235	100	90	100
Integrity				
Not ulcerated	206	88	87	97
Ulcerated	29	12	3	3
Crusting	0	–	0	–
Total	235	100	90	100
Elevation				
Not elevated	124	53	62	69
< 1 mm elevation	79	33	26	29
≥ 1 mm elevation	33	14	2	2
Total	236	100	90	100
Induration				
Not indurated	204	88	85	94
Indurated	27	12	5	6
Total	231	100	90	100
Bleeding				
No bleeding	231	98	89	99
Bleeding	5	2	1	1
Total	236	100	90	100

*The totals for certain characteristics are less than 236 because these parameters were not documented for some lesions.

Data from Mashberg and Feldman.[39]

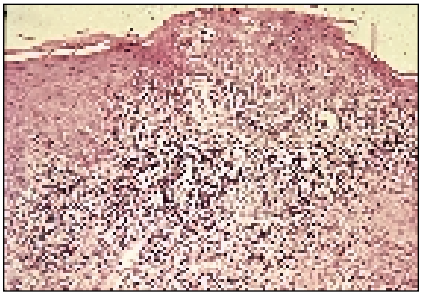

Fig. 11. Microscopic section of erythroplastic area shown in Figure 8. Note dysplasia, nests of squamous carcinoma and the inflammatory barrier below the basement membrane.

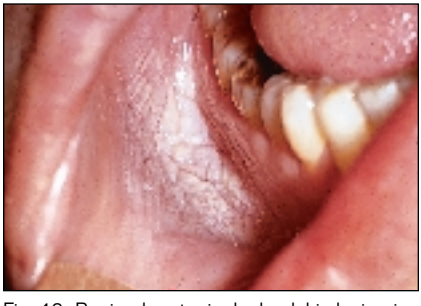

Fig. 12. Benign keratosis: leukoplakic lesion in the buccal sulcus; frequently related to use of smokeless tobacco.

disregard for mucosal alterations that signify an asymptomatic carcinoma in favor of those that do not.

Although leukoplakia has been defined by the World Health Organization as a clinical white mucosal lesion that does not rub off and is not associated with any identified disease process, the archaic histologic definition implying the presence of dysplastic cells with malignant potential still persists, especially when the term is associated with premalignancy. This ambiguity has generated much confusion. Patient management would probably be improved by deleting the term altogether in any discussion of malignancy. The term premalignancy is also misleading, because it implies a potential toward malignant change in benign lesions where none may exist. The concept that benign keratotic mucosal lesions, without evidence of dysplasia, progress to malignancy more often than normal tissue has not been corroborated by controlled studies.

Dogmatic adherence to the proposition that leukoplakia is highly significant clinically has even resulted in the coining of special terms to distinguish those lesions that are significant (nodular leukoplakias or leukoplakias interspersed with erythroplasia) from those that are not (homogeneous leukoplakias or purely white leukoplakias).[49] The erythroplastic component of mixed lesions is significant, not the leukoplakia.

Despite evidence to the contrary, the concept of a malignant potential for leukoplakia is so pervasive that clinicians, responding reflexively to the paradigm of the progression of white lesion to precancer to cancer, often disregard an adjacent innocuous-appearing red lesion. This is evident in cases in which the clinical description that accompanies a biopsy specimen from a mixed lesion conscientiously describes the white component but omits mention of the red component.

This is not to imply that clinical leukoplakia is to be discarded. All mucosal aberrations should be investigated. Doubts as to etiology or significance should result in biopsy.

Clinical interests might be best served by eliminating the use of the terms erythroplasia or leukoplakia as clinical descriptions. Clinicians should be encouraged to use descriptive adjectives instead (e.g., red, white, yellow, speckled, mixed, granular, etc.).

There are reports in the current literature concerning chemoprevention.[50-52] These studies generally presume that significant numbers of leukoplakias demonstrate cellular dysplasia and that these dysplasias are progressive and have a

propensity to transform to malignancy. This rationale, which equates leukoplakia with precancer, has led to a search for biologic modifiers (e.g., 13 cis-retinoic acid, beta carotene, etc.) that will affect areas of leukoplakia.

It seems difficult to validate the direction these clinical and research efforts have taken because the evidence does not support the concept of leukoplakia as a premalignant lesion of oral epithelium. While studies of the effects of retinoids or carotenes on histologically proven severe dysplasia, carcinoma in situ, or early invasive carcinoma might be significant, the ability of these agents to effect changes in what is usually a self-limiting, clinically insignificant, mucosal lesion seems of little importance.

While most pure white lesions exhibit little or no cellular dysplasia and probably never progress, for any clinical group of leukoplakias that includes mixed red and white lesions, progression and malignant transformation will be inadvertently and artificially created whenever the white components are biopsied before the red. The issue is further clouded because of the multiplicity of different histologic entities that is also included under the general term leukoplakia (e.g., inflammatory changes; mild, moderate, or severe dysplasia; etc.). To group such clinically and histologically disparate lesions together to determine an average transformation rate for leukoplakia is not reasonable, because the resultant rates do not accurately reflect the risks associated with a particular lesion.

Lastly, agents that can influence cellular differentiation may be capable of causing undesirable or paradoxical outcomes when administered in synthetic forms or for short periods. In one of the previously cited studies, two in situ and five invasive cancers developed in seven study patients within 28 months after maintenance therapy.[51] In a study on the incidence of lung cancer among male smokers after dietary supplementation with α-tocopherol or β-carotene, there was no reduction in lung cancers in either group, and, unexpectedly, the men who received β-carotene were found to have lung cancers more frequently than those who did not receive β-carotene.[53]

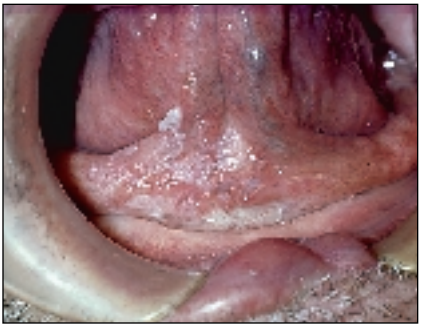

Fig. 13. Carcinoma in situ in the floor of the mouth. Pebbly, heaped-up keratin with associated red, inflamed areas of mucosa should increase the index of suspicion in such "leukoplakic" lesions.

Dysplasia, Carcinoma in Situ, and Invasive Carcinoma

Cellular atypia or dysplasia describes alterations in the relationships of cells and in the size, shape, and staining characteristics of their nuclei. Predominant microscopic features that indicate dysplastic cellular activity include the following: (1) increased or abnormal mitoses, (2) changes in the nuclear/cytoplasmic ratio, (3) hyperchromatic nuclei, (4) loss of cell polarity, (5) nuclear pleomorphism, (6) the loss of cellular adhesion with increased intracellular spacing, and (7) disturbances in the normal maturation sequence. Although individual dysplastic cells on occasion may be found at random throughout the thickness of the epithelium, the presence of a group of these cells arising from the basal layer is considered a lesion.

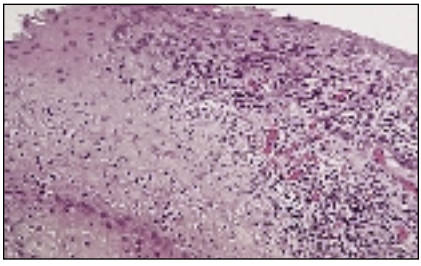

Fig. 14. Severe dysplasia: cellular atypia involving about two thirds of the epithelium in one field. Note the inflammatory barrier below the area of concern.

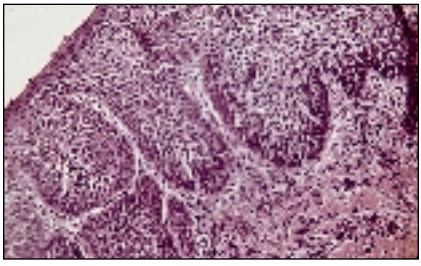

Fig. 15. Carcinoma in situ: cellular atypia or dysplasia occupying the full thickness of the epithelium; questionable disruption of the basement membrane is shown in the upper right.

There is a tendency among clinicians to group all dysplasias together without regard to the degree of cellular atypia present.[54] However, it is critical to distinguish among the various degrees of dysplasia. Dysplastic changes that involve increasing proportions of the epithelium may be reported as mild, moderate, or severe dysplasia or are expressed as percentages (e.g., 30 percent, 60 percent, or 90 percent atypia).

Mild dysplasia usually represents a simple inflammatory lesion or healing mucosa. It is not highly indicative of an early malignant process and typically resolves without treatment. Lesions with minimal dysplasia should be observed periodically to rule out further clinical change. Little clinical concern is necessary except to assure appropriate follow-up and re-evaluation. Moderate dysplasias are best excised conservatively.

Severe dysplasias, on the other hand, warrant far greater emphasis and concern (Fig. 14). Whether these lesions progress to carcinoma in situ or invasive carcinoma is probably moot, because they frequently coexist with carcinoma in situ or invasive carcinoma. At the very least, a diagnosis of severe dysplasia warrants examination of multiple sections from the original specimen. Because an initial biopsy may be limited and carcinoma may be present in the adjacent mucosa, rebiopsy or examination of multiple sections may demonstrate areas of early malignancy adjacent to the severe dysplasia. Significantly, the diagnosis of severe dysplasia is somewhat subjective and is dependent upon pathologic interpretation. What one pathologist considers severe dysplasia, another may call in situ or even microinvasive carcinoma.

For these reasons, it is suggested that severe dysplasias be regarded as malignant lesions, not as precancers that may develop into a malignancy. A diagnosis of severe dysplasia in the oral or oropharyngeal mucosa should merit the same aggressive treatment traditionally reserved for carcinoma in situ or early invasive carcinoma. The severely dysplastic lesion should alert the clinician that the entire mucosa is at risk and that comprehensive examination, including endoscopy, is indicated. Studies suggest similar findings in the esophagus.[55,56]

When the epithelial lining in a particular microscopic field is replaced with atypical cells throughout its entire thickness from the basement membrane to the surface, the diagnosis is carcinoma in situ (Fig. 15). Carcinoma in situ should be regarded as a significant lesion and aggressively managed, because it is likely that

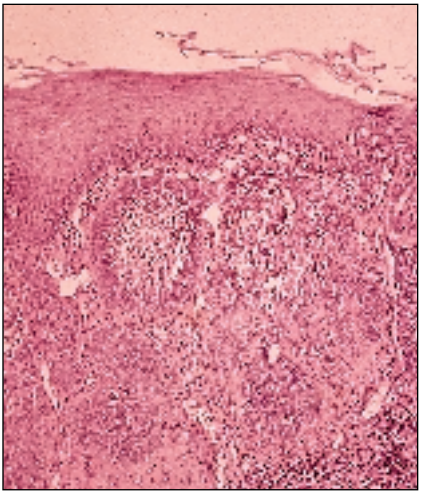

Fig. 16. Invasive carcinoma with inflammatory barrier and increased vascularity.

untreated lesions may progress to invasive carcinoma. In addition, because areas of carcinoma in situ are frequently present within invasive tumors, it is possible that a biopsy diagnosis of carcinoma in situ does not accurately reflect the nature of the entire lesion.

When nests or sheets of abnormal cells disrupt the basement membrane and extend into the underlying connective tissue, the diagnosis of invasive squamous cell carcinoma is established (Fig. 16). More than 90 percent of all upper aerodigestive cancers are squamous cell carcinomas.

The degree of microscopic differentiation demonstrated by an individual lesion may correlate with the tumor's aggressiveness or relative radioresponsivity. Well-differentiated carcinomas, which closely resemble normal squamous epithelium, are generally considered to be less aggressive than poorly differentiated tumors, which are seen microscopically as amorphous masses of highly dysplastic cells with little order or uniformity. The clinical behavior of an individual tumor is unpredictable. For example, a well-differentiated tumor may be aggressive due to the host's inadequate immune response. The degree of differentiation cannot be determined clinically. Invariably, a submucosal vascular reaction and round cell infiltrate, which appear to be an immune response to the developing lesion, are found beneath areas of carcinoma in situ and early invasive carcinoma on microscopy. This inflammatory barrier is extremely significant in the clinical appearance and detection of asymptomatic lesions.

Tumor Staging

Head and neck cancers are staged clinically to correlate treatment outcomes and survival with the extent of disease initially present. Results from one patient to another or one institution to another may then be compared to determine, on a percentage basis, which modalities of treatment are most effective for a particular site or extent of tumor involvement.

Staging for all primary sites within the oral cavity and oropharynx varies only as far as the tumor (T) classification (tumor size and the presence of deep muscle or bone invasion). Node (N) and metastasis (M) classifications are identical throughout.[57] It is important to recognize that wide variation can exist among identically staged cancers at the same primary site. For example, although an asymptomatic, nonpalpable, 0.5-cm area of erythroplasia with or without keratin and a 1.9-cm, indurated, palpable ulcer in the floor of the mouth may both be T1 cancers (2 cm or less), their prognoses would be quite different. Palpability and symptomatology are significant when assessing prognosis. It is suggested that these factors be incorporated into the staging classification.

Cervical node involvement in head and neck cancer is relatively orderly and usually follows a predictable course de-

Table 6
Induration of Asymptomatic Oral/Oropharyngeal Squamous Carcinomas with Associated Cervical Adenopathy

Size of Primary Lesion	Total Number	Positive Nodes	
		Indurated	Nonindurated
T1	185	3	1
T2	50	0	3
T3, T4	1	0	0
Total	236 (100%)	3 (1.3%)	4 (1.7%)

Data from Mashberg and Feldman.[39]

pending on the primary tumor site, size, and time. Early, asymptomatic lesions rarely demonstrate metastases at the time of diagnosis.[39] In more advanced lesions, dissemination to ipsilateral submandibular and jugulodigastric nodes is common, with subsequent spread to additional neck node groups. Contralateral or bilateral nodal metastases may be present, especially late in the clinical course or when midline oral structures (e.g., base of tongue) are involved. Occasionally, expected node groups are skipped and noncontiguous adenopathy is appreciated. In some cases, cervical adenopathy is present but identification of the primary site is elusive (i.e., occult primary).

When lymph node or remote bone and organ metastases are associated with an early oral primary cancer, it is frequently found that a second, more-advanced primary upper aerodigestive or lung cancer is responsible for the metastases. Documentation of widely disseminated disease arising from a tumor in the head and neck region is most typically a postmortem finding. In most head and neck cancer cases, death is the result of residual or recurrent disease at the primary site or the cervical region and frequently occurs before distant metastases become clinically significant.

Recent studies indicate that the thickness of the primary tumor correlates with survival and nodal metastases, suggesting that tumor thickness may be a useful staging parameter. Spiro et al[58] found the prognosis was excellent in patients with histologically thin oral tumors (2 mm or less), even when the lesions exceeded 2 cm in greatest surface diameter. Clinical studies regarding palpability support this concept.[39] Ninety-seven percent (230/236) of early, asymptomatic, nonindurated, invasive carcinomas had no related cervical adenopathy at the time of diagnosis. Three of four T1 lesions that had related adenopathy were indurated (Table 6).

Evaluating a subset of these patients (stage I and II floor of the mouth cancers), a further study correlated histologic tumor thickness with the incidence of subsequent nodal metastases.[40] Only one patient (1.75 percent) developed positive cervical nodes out of the fifty-seven patients whose lesions were less than 1.5 mm thick. Four of twelve patients (33.3

percent) who had lesions 1.6 to 3.5 mm in thickness and nine of fifteen (60 percent) with lesions 3.6 mm in thickness or more developed lymph node metastases. No correlation was found between histologic grading and the development of neck nodes. Lesions with the least inflammatory response had the highest incidence of subsequent metastases, suggesting a relationship between immune competence and cancer progression. Elective node dissection was recommended for any patient with an N0 lesion measuring more than 1.5 mm in thickness.

Vital Staining

Awareness of the patients and sites at highest risk and the erythroplastic appearance of early lesions should result in a high degree of success in detecting asymptomatic oral and oropharyngeal squamous carcinomas. However, many of these mucosal alterations are initially dismissed because of their innocuous appearance or they are missed because of their subtle nature. The use of a diagnostic adjunct to prevent such occurrences is desirable.

Toluidine blue clinically stains malignant lesions, but not normal mucosa. In vivo, the dye may be taken up by the nuclei of malignant cells manifesting increased DNA synthesis. Alternatively, it has been suggested that diffusion through three to four layers of haphazardly arranged tumor cells allows for deeper penetration of the dye into the intracellular spaces.[8]

Topical application of toluidine blue to clinically detected lesions serves as a diagnostic control over subjective clinical impressions. Innocuous-appearing lesions should not be dismissed if they stain positively. A rinse modality that includes all of the high-risk sites may detect very early multiple primaries or recurrences in patients at high-risk for squamous carcinoma. Lesions not detected during a visual examination may be revealed by the rinse.

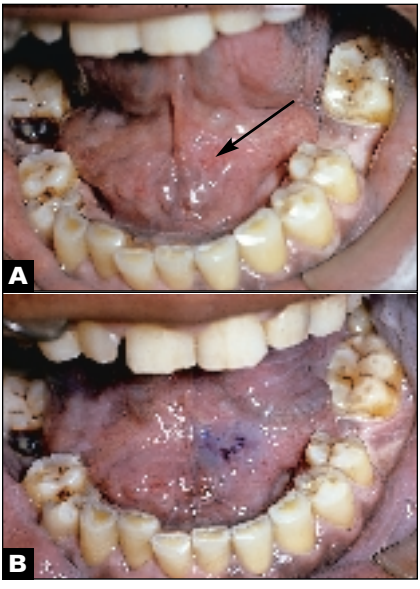

Fig. 17. (A) Barely discernible minute area of erythroplasia in the floor of the mouth. Although the area appears innocuous, it persisted. (B) Same area after toluidine blue stain application; biopsy of stained area revealed squamous carcinoma.

Many authorities[8-13] advocate use of toluidine blue to detect malignancies. These studies indicate that all or parts of all malignant lesions (carcinoma or carcinoma in situ) stain dark blue with topical application of toluidine blue (Figs. 17, 18, and 19). Dysplastic lesions will stain variably, most likely dependent upon the degree of dysplasia present. An occasional equivocal circumscribed light-blue stain should be considered positive. Various modifications and staining techniques have been advocated. A rinse modality that is all encompassing for the oral cavity has been employed with success (Fig. 20).

Normal intact mucosa does not absorb stain, but small areas of mechanically retained dye occasionally may be ob-

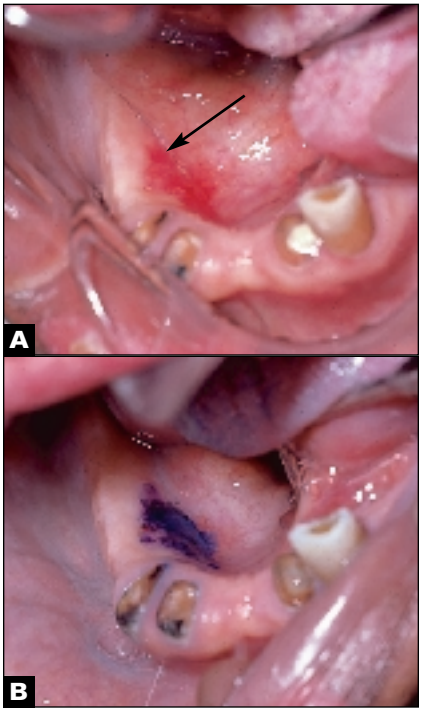

Fig. 18. (A) Granular erythroplastic area at junction of alveolus and floor of the mouth in a patient with lupus. (B) Site stained by toluidine blue application; biopsy revealed carcinoma.

served. These may be removed by gently swabbing the area with acetic acid. Larger regions of extraneous stain also may occur (e.g., the dorsum of the tongue, areas coated with surface debris or exfoliated keratin, and the gingival crevices). Retention in these areas is usually of no concern because oral cancers almost never occur in the mucosa of these sites. Occasionally, a film of stain from the dorsum of the tongue may be transferred to portions of the posterior soft palate during swallowing. Here, the uptake of dye is not well defined, but appears diffuse, filmy, and amorphous. A light-blue film occasionally may also be observed over other large areas of mucosa as a result of dye-tinged saliva. These variants should not be misconstrued as positive or equivocal stains.

Lesions with limited dysplasia do not appear to stain consistently. Correlation between the staining impression and the pathologic diagnosis is tenuous at best in these cases. However, the typical early carcinoma, an area of erythroplasia with or without a white component associated with alcohol consumption and cigarette smoking, usually stains dark blue. These lesions often appear stippled or patchy because neoplasia below the mucosal surface and areas of interspersed keratin or normal mucosa do not pick up stain.

Areas of inflammation occasionally may yield false-positive results (positive stain in the absence of cancer). However, if proper protocol is followed, inflammatory lesions (e.g., denture irritation, minor trauma, etc.) will have resolved by the time the patient is restained fourteen days later. If a lesion stains dark blue after the fourteen-day waiting period, the probability of malignancy is greatly increased. The false-positive rate was about eight percent when the fourteen-day waiting period was observed.[11] Topical application alone resulted in a false-negative rate of 6.7 percent (negative stain in the presence of cancer). When erythroplastic criteria also were used as a prime factor in suspicion, topical application of toluidine blue resulted in false-negative results of less than two percent.

Toluidine blue also serves as a guide to biopsy by localizing tumor cells within the area of erythroplasia. Early cancers often consist of islands of normal mucosa interspersed with tumor and/or areas of keratin. Obtaining multiple random samples from the entire area of involvement is not always a reliable diagnostic procedure, because small foci of malignant cells can be missed. Selection of the most representative biopsy sites should not be left to chance. After the fourteen-day observation interval, biopsies of areas of dye

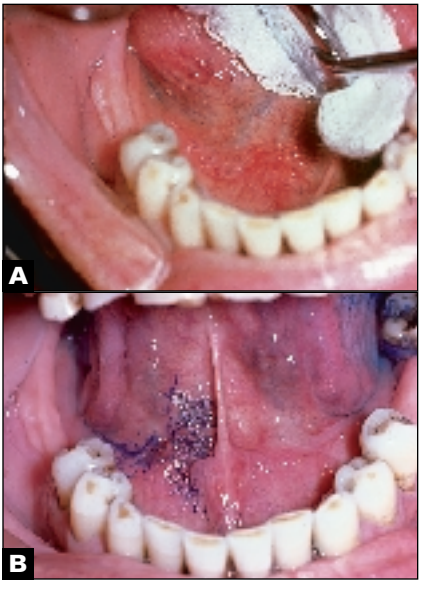

Fig. 19. (A) Diffuse erythroplastic invasive carcinoma right anterior floor of the mouth with areas of interspersed keratin. (B) Erythroplastic atrophic portions of the lesion stain positive in a speckled or striated manner, giving a "denim-like" appearance.

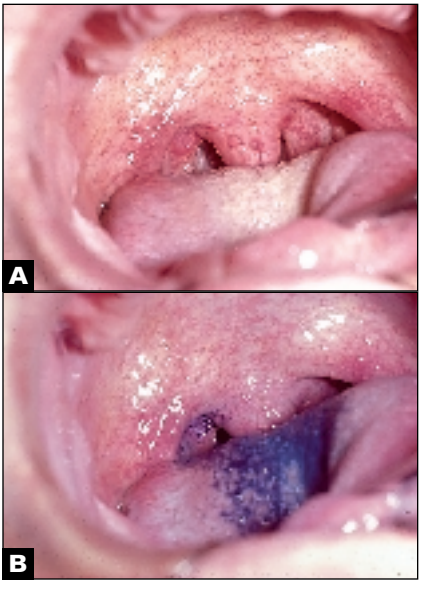

Fig. 20. (A) Vague area on right posterior tonsillar pillar; this was not observed during a clinical examination of the patient. (B) Unsuspected carcinoma stained in a stippled manner by toluidine blue rinse.

retention are most likely to demonstrate severe dysplasia, carcinoma in situ, or invasive cancer on microscopy.

Occasionally, minute carcinomas that stain may not be confirmed microscopically. The area of significant pathology may be so small that it is missed on histologic sectioning. Biopsy specimens taken of very small areas of stain should be correspondingly small to increase the probability that histologic sectioning will involve the pathologic entity. Alternatively, the pathologist should be advised that multiple sections may be required because the area of suspected tumor is very small.

Whether employed as a rinse in the absence of positive clinical findings[12,13] or as a direct application to clinically detected areas of mucosal abnormality,[11] toluidine blue will stain malignant lesions. Although nonmalignant areas of inflammation may also stain, false-positive results may be reduced by restaining after fourteen days, at which time inflammatory changes should have resolved.

Staining is a very simple and expeditious office procedure that does not require an intermediary to interpret the results. The great value of toluidine blue staining lies in its control over false-negative clinical findings (i.e., it detects lesions too subtle to be clinically appreciated, and it discloses which innocuous-appearing lesions are most deserving of additional work-up). It must be stressed, however, that clinical suspicion mandates biopsy regardless of staining outcome.

Although a lesion meets the visual criteria for early cancer, persists beyond the observation period, and stains with toluidine blue, the final diagnosis of carcinoma can be established only by biopsy.

Oral cytology has been advocated as a screening modality for evaluation of intraoral lesions. Although cytology has validity in other anatomic locations, its routine use in oral cancer detection is questionable. The need to have the smears evaluated by an intermediary (a pathologist or cytologist) and the subjective nature of cytologic interpretation reduce the validity of cytologic diagnoses. In vivo staining is superior to cytologic study because the information obtained is immediate and specific. The development of well-defined visual criteria, the accessibility of oral surfaces, and the absence of significant morbidity make toluidine blue staining the procedure of choice. Regardless of suspicion, lesions should be stained in preference to smearing, especially in high-risk patients (drinkers, smokers, and those with a history of previous upper aerodigestive malignancy).

Work-up of Suspicious Lesions

When an asymptomatic lesion is detected, the work-up should include a standardized protocol. Probable sources of acute or chronic irritation should be removed if possible and attempts should be made to curtail the use of alcohol and tobacco. The patient should return for follow-up observation in 10 to 14 days. Inflammatory lesions resulting from trauma or chronic irritation will usually be markedly improved or resolved. Until proven otherwise by biopsy, any lesion that persists with no apparent etiology should be considered suspicious. Clinical bias should be replaced by confirmatory evidence as to the true nature of a mucosal alteration, especially if persistent with no apparent etiology.

A complete head and neck examination and history to rule out other mucosal entities are indicated. Evaluate the oral cavity, hypopharynx, pharynx, and supraglottic larynx by visual examination, palpation, and indirect mirror visualization. The neck should be carefully palpated for cervical adenopathy prior to biopsy, because lymphoid hyperplasia related to the biopsy cannot be clinically differentiated from tumor involvement with certainty.

Unless the status of neck nodes is established definitively before biopsy, the patient may be subjected to unnecessary surgery or radiotherapy. Special attention should be directed to the size, location, texture, and mobility of any nodes and to the presence or absence of tenderness. Soft, freely mobile, tender nodes suggest an inflammatory reaction. Nodes that are firm or hard, not freely mobile, or nontender are more suggestive of tumor involvement. The presence of clinically positive cervical nodes associated with an early lesion suggests the existence of a second primary lesion in the upper aerodigestive tract or lung.

Biopsy

Biopsy diagnosis of lesions is an absolute requirement before therapy can be initiated. Although visual criteria and techniques for the clinical detection of asymptomatic cancers have been refined, severe dysplasia, carcinoma in situ, and invasive carcinoma can be demonstrated only on microscopy, the only valid method for diagnosis.

The biopsy specimen must be representative of the lesion under investigation. Adequate depth, through the epithelium into connective tissue, is necessary to determine the integrity of the basement membrane and to search for invasive tumor cells. Inclusion of a zone of adjacent, clinically normal tissue is not absolutely required for the pathologist to recognize malignant changes. However, when necrosis or ulceration is present, the inclusion of some clinically uninvolved tissue from the periphery of

the lesion in the specimen usually assures a representative sample of active tumor, rather than nondiagnostic necrosis.

Incisional biopsy is the procedure of choice for microscopic diagnosis of suspected malignant intraoral lesions. Intentional excisional biopsy is generally not indicated in the diagnosis of oral cancer. Total removal of all abnormal tissue for diagnostic purposes is justifiable only when the lesion is almost certainly benign on clinical grounds or when the suspect lesion is so small that total removal (at least 1-cm margins in all dimensions) ensures a cure without compromise of function.

If a lesion is considered suspicious for malignancy, a negative biopsy should not be accepted as the final word. Microscopic diagnoses of early lesions are subjective and re-evaluation of the original sections is sometimes indicated. In some cases, the original specimen may have been nonrepresentative or inadequate for diagnosis. Well-founded clinical suspicion or positive toluidine blue uptake, even in the face of negative microscopic findings, mandate direct consultation with the pathologist and repeat biopsy if necessary.

Summary

An examination of the oral cavity and oropharynx in asymptomatic patients at high risk requires an orderly visual inspection of the entire oral and oropharyngeal mucosa with particular attention to the tongue, floor of mouth, soft palate, uvula, tonsillar pillars, and the lingual aspects of the retromolar trigones. Completion and clear documentation of the entire examination should be recorded. Detected lesions that do not resolve in a reasonable length of time—two to three weeks—require intense and assiduous investigation. The following specifics should be considered.

1. Alcohol drinkers and cigarette smokers, especially those 40 years of age and older, are at very high risk for the development of upper aerodigestive tract and lung squamous carcinomas.

2. The floor of the mouth, the ventrolateral tongue, and the soft palate complex are the high-risk sites within the oral cavity and oropharynx.

3. Persistent mucosal erythroplasia rather than leukoplakia is the earliest visual sign of oral and oropharyngeal carcinoma. These lesions should not be regarded merely as precancerous changes. The evidence indicates that these lesions in high-risk sites should be considered to be invasive carcinoma or carcinoma in situ unless proven otherwise by biopsy.

4. Toluidine blue staining is a useful diagnostic adjunct, particularly as a method of ruling out false-negative clinical impressions. It may also be used as a rinse in high-risk patients to encompass the entire oral mucosa after a negative clinical examination and as a guide to improve biopsy yields.

5. If oral or oropharyngeal cancer is identified, evaluations of the larynx, hypopharynx, esophagus, and lungs should be performed to rule out multiple primary cancers. Yearly aerodigestive surveillance should be continued after satisfactory treatment of the index cancer. CA

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