Preface - Oral Cancer Background Papers

The intent of these background papers is to provide an overview of the science related to the prevention and control of oral and pharyngeal cancer. They address current knowledge and practice, emerging trends, and opportunities and barriers to further progress. The papers were developed to set the stage for the development of recommendations for public health policy in the areas research, professional and public education, public health policy, and collaboration during a national strategic planning conference that was held on August 7-9, 1996.

Each paper was prepared by a different set of authors representing different specialities, backed by current literature reviews, personal experience, and in-depth critiques. Although the papers are presented in consistent tone and format, they are designed to raise the critical issues for improving future prevention efforts, and to offer constructive recommendations and strategies for action.

Finally, it is hoped that these papers will facilitate a concerted effort to increase visibility for a too frequently forgotten killer; strengthen education for the public and public health professionals; generate additional resources for screening, diagnosis, and treatment; encourage multidisciplinary cooperations and management of these cancers, and enhance future efforts in research.

On behalf of the Division of Oral Health, National Center for Chronic Disease Prevention and Health Promotion, we are grateful to the individuals listed on the pages that follow for their assistance in preparing this manuscript. Without their constructive and dedicated input, this project would not have been possible.

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ORAL CANCER BACKGROUND PAPERS

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Working Draft

Introduction

Working Draft

For over five decades cancer has been the second leading killer of Americans. Each year, both newly diagnosed cases and the number of deaths due to cancer increase. In 1996, the American Cancer Society estimates that more than 1,200,000 new cases will be diagnosed and that more than a half million people will die. Many of these cancers can be prevented through lifestyle choices that reduce one's risk for the disease. Oral cancer, the focus of this document, is an example of a largely preventable disease that in most instances can be linked to behaviors that include long-term tobacco use, heavy use of alcohol, and a poor diet.

More than 30,000 Americans will be diagnosed with oral cancer this year. For some time, the 5-year survival rate for this group of cancers has been about 50%, despite advances in surgery, radiation, and chemotherapy. In addition to premature death, the morbidity associated with the disease, the mental anguish of patients, family and friends, and the financial costs make oral cancer a major public health concern. Therefore, it is a high priority to lower the number of new cases of oral cancer as well as to reduce its morbidity and mortality. It is a challenge that will take us to the year 2000, and beyond.

Prevention of oral cancer is critically important and can be accomplished in four ways, by: (1) understanding cause-and-effect and modifying associated risks; (2) recognizing and controlling precancerous lesions; (3) establishing the earliest possible diagnosis and administering timely and appropriate therapy; and (4) effectively managing the complications of treatment.

A consortium of health agencies, led by the Centers for Disease Control and Prevention and the National Institute for Dental Research/National Institutes of Health, have established objectives, goals, and programs to carry out the mission of reducing morbidity and mortality from oral cancer by the Year 2000. As a first step, the CDC held a workshop in 1992, leading to this position paper. The second step will be a national conference in August 1996, to set forth recommendations for public action. These recommendations and strategies will be compiled and disseminated by CDC and its partners. Follow through on the commitments made by the individuals and groups assembled at the conference will be the next step in making the prevention and early detection of oral cancer more of a priority in this country.

These background papers on oral cancer complete the first stage in this effort. They have been prepared to cover all aspects of this disease by experts, representing a comprehensive array of specialties and expertise. The intent was to produce a realistic, brief, and factual status report that proceeds logically from epidemiology to rehabilitation.

As the incidence of oral cancer remains stable, the demographics are changing, with a progressive increase in women. Several decades ago the male-to-female ratio approximated 10 to 1; the ratio is now about 2 to 1. This shift is due in part to increasing tobacco and alcohol consumption among women, in part to increasing longevity. Senior citizens now account for about 13% of the U.S. population, and most are women. Among known risk factors, aging appears to have the greatest

association with carcinogenesis. The aging process influences proto-oncogene products causing cellular dysregulation through alterations in cell growth and suppressor proteins. Hence, geriatrics and carcinogenesis go hand in hand.

Review of histologic types shows that the great majority of oral malignancies are squamous cell carcinomas; they arise from the mucosa of the oral cavity and are epithelial in origin. Since these are surface tumors, (with the exception of salivary glands and the infrequent occurrence of sarcomas), the location enhances early detection. However, by the time many oral cancers are diagnosed, they are already in advanced stages. Therefore, efforts to reduce oral cancer incidence, morbidity, and mortality must be multi-pronged and multi-disciplinary.

Understanding causative factors is a necessity as prevention strategies are developed. Aging is a risk factor without a solution, but effective control of two other risk factors, tobacco and alcohol consumption, is attainable and worthwhile. Research that produces a better understanding of precancerous subcellular markers will aid both prevention and early detection, thereby reducing morbidity and mortality. Studies of nutritional factors, chemoprevention, viral influences, and oncogene products also will be important.

Precancerous oral lesions, primarily leukoplakias and erythroplakias, occur frequently in adults. Developing useful approaches to their prevention, increasing the accuracy of diagnosis, discovering more biologic markers for these lesions, and improving their management will all further the goal of oral cancer control.

However, in spite of all attempts to prevent them, oral cancers will continue to occur. Therefore, early diagnosis combined with adequate treatment will continue to be critical for reducing the morbidity and mortality associated this disease. At the same time, clinical research continues in the use of surgery, radiation, and chemotherapy to improve survival rates. Unfortunately, new, more aggressive approaches often produce more complications.

The quality of life—for both those who achieve a remission and those who may live for a period of time with persistent tumor—is a major concern. Alterations in saliva or taste, significant pain, oral and dental infections, mucosal and bone necrosis, and difficulties with mastication, swallowing, and speech may severely depress patients and often reduce their quality of life to an unacceptable level. Rehabilitation is critically important and should be considered at the time of treatment planning.

In summary, these background papers set the stage for an extremely important campaign to prevent and control a major factor affecting American wellness. The scientific foundation provided by these papers in the areas of oral cancer prevention, risk reduction, early detection, and treatment is the framework for developing a national action plan. This plan, which will be created during a strategic planning conference in August 1996, will focus on five key issue areas; (1) data collection, evaluation, and research; (2) professional education and practice; (3) public education; (4) public health policy;

and (5) advocacy, collaboration, and coalition building. This plan, which will be published and disseminated as conference proceedings, will serve as a springboard for moving this effort forward. Reducing risk, by eliminating tobacco and heavy alcohol use, will be a critical component of the overall strategy, as will health promotion and health education efforts targeted to a variety of audiences. The reality of increasingly scarce resources will challenge our efforts in the areas of research; however, increased awareness may stimulate the development of public health policy and the formation of creative new alliances between the public and private sectors. Although we have a tremendous challenge ahead of us, we owe it to ourselves and the public we serve to face it head on and to count our successes one at a time.

ORAL CANCER BACKGROUND PAPERS

Chapter I: Descriptive Epidemiology

Working Draft

A. State of the Science

Definition of Oral/Pharyngeal Cancer

Cancers of the oral cavity and pharynx account for 3% of all cancers in the United States. Oral cancer usually includes cancer of the lip, tongue, salivary glands, and other sites in the mouth; while pharyngeal cancer includes cancers of the nasopharynx, oropharynx, and hypopharynx. More than 90% of oral or pharyngeal cancers are squamous cell in origin.

For classification purposes, oral and pharyngeal cancers sometimes are grouped with laryngeal and esophageal cancers, with which they share etiologic features. However, in these background papers, they will not be. Furthermore, oral cancer will be defined to include cancers of the lip, tongue, other mouth sites, and the oropharynx. Cancers of the salivary gland, nasopharynx, and hypopharynx will not be included, as they account for less than 10% of all oral cancers and are etiologically and biologically distinct. Sarcomas will also not be discussed for similar reasons.

Epidemiologic Measures and Data Sources

Incidence, mortality, and survival are the primary measures for assessing the impact of cancer in population groups. *Incidence* is the frequency of new cancer cases during a defined period of time, generally expressed as the rate per 100,000 persons per year; the *mortality rate* is the frequency of cancer deaths per 100,000 persons per year. The *observed survival rate* is the proportion of persons with cancer who survive for a specified period of time after diagnosis, usually 5 years. This statistic is often presented as a relative survival rate, in which survival from cancer is corrected for the likelihood of dying from other causes.

Data for describing the patterns of oral cancer come from two main sources, mortality data derived from death certificates and cancer registries. The National Center for Health Statistics (NCHS), within the Centers for Disease Control and Prevention (CDC), collects and analyzes death certificate data from all 50 states and is the main source of U.S. mortality statistics. These data permit assessment of the incidence, survival, and mortality rates for different segments of the population (defined by age, sex, race/ethnicity, or other characteristics).

Cancer registries attempt to include all cancer cases among residents of a defined geographical area. Data collection involves checking all possible sources of cases—hospitals, pathology laboratories, physicians' offices, and death records. A number of registries exist in the United States and Puerto Rico. In fiscal year 1994, 37 states received support from CDC for cancer registries: 25 to enhance established registries and 9 to develop registries where none existed. These state-based programs of cancer surveillance, authorized by Congress in 1992, will provide the basis for appropriate policy decisions and allocation of scarce program resources.

The National Cancer Institute (NCI) collects data from nine cancer registries (5 states and 4 metropolitan areas) as part of its Surveillance, Epidemiology, and End Results (SEER) program. Although they are not nationally representative in the statistical sense, the SEER sites were selected for their epidemiologically significant population subgroups and account for about 14% of the U.S. population. For the past 20 years, SEER data have represented the primary source for statistics on national incidence and survival.

Incidence and Mortality Data

Based on 1991 SEER data, the overall incidence and mortality rates for oral and pharyngeal cancer combined are 10.4 per 100,000 population and 2.9 per 100,000 population, respectively. The annual incidence of 15.7 per 100,000 for males far exceeds the rate of 6.0 per 100,000 for females.[1]

Mortality rates show similar differentials: 4.5 per 100,000 per year for males, 1.7 per 100,000 per year for females. This gender difference is also evident in the lifetime risks of developing oral cancer: 1.5% for males and 0.7% for females (based on 1989-91 incidence rates).

Black males in the United States have an incidence rate of oral cancers about one-third higher than their white counterparts (20.7 versus 15.3 per 100,000 annually) but more than twice the mortality rate (8.9 deaths versus 4.1 deaths per 100,000). In contrast, black women have an incidence rate (6.2 per 100,000) that is similar to that of white women (5.9 per 100,000), although the difference in mortality rates between these groups is more substantial (2.4 versus 1.6 per 100,000).

Geographic variations in mortality have been noted. For the period 1987-1991, states with the highest mortality rates were: Alaska (4.1 per 100,000), Delaware (4.1 per 100,000), South Carolina (4.0 per 100,000), and Louisiana (3.7 per 100,000). The District of Columbia had a mortality rate more than twice the total national rate (6.8 versus 3.0 per 100,000). Arkansas, Idaho, Wyoming, South Dakota, and Utah had the lowest rates (2.2, 2.1, 1.8, 1.7, and 1.3 per 100,000, respectively). From the 1950s through the 1970s, the Southeast had high mortality rates, but these have since decreased.

Trends over time in oral cancer incidence are very different for different subgroups of the population. From 1973 to 1991, the oral cancer incidence rate climbed from 16.8 to 20.7 per 100,000 persons per year among black men, but declined slightly for white men from 17.5 to 15.3 per 100,000. Among women, incidence rates remained relatively constant at about 6.2 per 100,000.

Persons with oral cancer often have multiple primary lesions, and have up to a 20-fold increased risk of having a second oral cancer. Persons with primary tumors of the oral cavity and pharynx also are more likely to develop cancers of the esophagus, larynx, lung, and stomach.[2-5]

Differences exist by anatomical site as well. Within the oral cavity and pharynx, 29% of cancers involve the tongue and another 17% the lip. Among pharyngeal sites, the oropharynx is the most common site for tumors (39%), followed by the hypopharynx (32%).[6]

Survival

Five-Year Relative Survival Rates

Based on data from 1983-1990, the overall 5-year survival rate for oral cancer was 52.5%. Females fared somewhat better than males (58% versus 50%). Blacks did far worse than whites; only 34% of blacks survived 5 years after the initial diagnosis, compared with 55% of whites. There was a great difference within the black subgroup, however, as the survival rate for black males was only 28%, versus 47% for black females. Overall, the percentage of persons surviving 5 years after the initial diagnosis of oral cancer had not changed appreciably since the 1974-1976 time period.

For cases diagnosed in 1981-1986, the 5-year survival rate for pharyngeal cancers (33%) was slightly more than half that for cancers of the oral cavity (60%). Survival by specific anatomic site ranged from a low of 23% for unspecified or ill-defined sites in the pharynx to a high of 91% for lip cancer. There were significant racial differences for most of the specific anatomic sites, with blacks having poorer survival in each instance.[6]

Five-Year Relative Survival by Historical Stage at Diagnosis

Stage at diagnosis refers to the extent of disease at diagnosis. There are three stages: localized, regional, and distant metastasis. Five-year relative survival rates vary with the stage at diagnosis; localized cancers have the highest survival rates and cancers with distant metastasis the lowest. At diagnosis of oral cancer, most individuals have localized or regional disease: 37%, localized; 43%, regional; 10%, distant; and 10%, unstaged. Five-year survival rates for all oral cancer cases are 79% for those with localized disease, 42% for regional disease, and 19% for disease with distant metastases.[1]

There appear to be no major differences by sex for the distribution of stages at time of diagnosis; however, women with regional and more advanced disease have greater survival rates than do men.[1]

B. Emerging Trends

Incidence Trends

In a review of SEER data from 1973 to 1985, Silverman and Gorsky[7] found that more than 95% of oral cancers occurred in persons older than 40, with a median age at diagnosis of 63 years. As the over-65 population in the U.S. now exceeds 30 million people (about 13% of the population) and has

been the fastest-growing segment of the population in the past decade, further increases in the incidence of oral cancer can be expected.

Significant changes in the racial and ethnic composition of the U.S. population also are anticipated in coming decades. The proportion of blacks in the population (now about 13%) is expected to increase; blacks have historically borne disproportionately high burdens of oral cancer. Hispanic and Asian populations are expected to increase proportionately at even higher rates. Unfortunately, SEER data do not adequately document cancer incidence in these two groups, but the recent addition of two new SEER sites in California and CDC support for state-based cancer surveillance should provide improved data for future analysis.

Changes in risk behaviors, including tobacco and alcohol use, are also likely to have considerable impact on cancer incidence. The Surgeon General's 1964 report on smoking noted that 42% of Americans smoked; today, the figure is about 27%.[8] Alcohol use has also declined, though not as dramatically as smoking.[9] Yet, there has been no commensurate decline in oral cancer incidence during the past 30 years, other than a relatively small decrease in white males. The lengthy lag time between exposure and disease occurrence no doubt explains some of this discrepancy, as does the reality that many factors other than tobacco and alcohol use contribute to development of cancers of the oral cavity and pharynx.

Prediction of incidence trends must also consider the use of tobacco products by the young. As smoking has declined, smokeless tobacco use by young males has increased,[10] particularly in some regions of the country. The 1986-1987 National Institute for Dental Research (NIDR) Survey of Oral Health in Schoolchildren found that 16% of males in grades 6-12 reported current or past use of smokeless tobacco products[11] and almost 39% of current users of snuff products had detectable oral lesions.[12] A preliminary analysis of SEER data for white males under age 30 found that, between 1950 and 1982, the mortality rate doubled.[13] SEER data show substantial increases in incidence and mortality rates for tongue cancer in young males since 1973.

Changes in the intake of protective nutrients (e.g., in fresh fruits and vegetables and dietary supplements) could potentially affect cancer incidence rates in the future.[14,15] (See Chapter III for additional discussion.)

Mortality and Survival Trends

All the factors affecting incidence presumably would affect mortality rates as well; however, some factors influence mortality and survival but not incidence. Among these factors are stage at diagnosis, access to treatment, and the success of treatment.

Unfortunately, the SEER data show no evidence of a significant improvement since 1973 in the

proportion of oral cancer cases diagnosed at earlier (more localized) stages. This disappointing information suggests that efforts at early detection have either not been widely applied or have been inappropriately targeted.

Somewhat more encouraging is that mortality rates have been observed to decline modestly since 1973, even though there was no significant change in incidence or survival rates over the same period.[16] Although potential explanations for this apparent discrepancy have been offered (e.g., improved access to care through Medicare, improved treatment methods, a real decline in incidence masked by improved detection), the data do not permit such conclusions. Surprisingly, the improvement in mortality was not accompanied by a similar improvement in 5-year survival rates, which would have been expected if improved treatment had been responsible for the reduced mortality rates. This apparent inconsistency might be partly explained by the fact that much of the decline in overall mortality comes from a substantial decrease in incidence of lip cancer, which has the highest 5-year survival rate (90%) among oral sites—leaving a residual base of cancer sites with poorer survival times.

C. Opportunities and Barriers to Progress

The National Health Interview Survey (NHIS) has traditionally been a valuable source of data on cancer risk behaviors; the 1990 Health Promotion and Disease Prevention Supplement included questions on public knowledge of oral cancer symptoms and risk factors.[17] The NHIS presents as an opportunity to develop a broader science base on the knowledge, attitudes, and behaviors of the public regarding cancers of the oral cavity. A long-term strategy for expanding use of the NHIS to include selected research objectives in this area might aid initiatives in oral cancer considerably.

The lack of national prevalence data on premalignant lesions has been a significant barrier to understanding fully the occurrence and development of oral cancers. The third NCHS National Health and Nutrition Examination Survey (NHANES III) has attempted to address this concern by including evaluations of oral soft tissues in the oral examination process. These evaluations are based on visual criteria alone and do not entail routine histologic confirmation of findings, but they will still be important as they will be used to develop the first national estimates of the prevalence of such conditions in U.S. adults. Understanding of the significance of premalignant lesions would be further advanced by studies that include longitudinal follow-up to observe malignant transformation. Combined with sociodemographic and behavioral data, such information could help to identify factors associated with malignant outcomes.

Despite the generally high quality of existing epidemiologic data from the sources previously described, there are significant gaps in the science base, including limitations in the coverage of minority populations. However, SEER has attempted to select geographic sites at least partly on the

basis of minority coverage. For example, 10 predominantly black rural counties in Georgia were added in 1978 and American Indians in Arizona were added in 1980 (the Commonwealth of Puerto Rico was a participating site until 1989). In 1992, coverage of Hispanic populations was expanded by adding two new sites in California.

There is substantial evidence that there are racial or ethnic differences in oral cancer beyond the black/white differences noted in publications using the SEER data. An elevated incidence of cancers of the nasopharynx has been reported in persons of Chinese ancestry in the United States and elsewhere;[15] decreased incidence of oral cancers has been observed in American Native populations compared with American whites;[18] and the incidence and mortality rates of oral cancers in Puerto Rico in 1983-1987 were substantially greater than those in the combined U.S. SEER sites for the same time period.[17] A 1981 SEER monograph reported incidence rates for Hawaiian ethnic groups, Hispanics, and American Indians from selected registries,[19] but this material is now dated. It seems likely that CDC's National Program of Cancer Registries will make available more complete, timely, and standardized data on oral cancer by age, race, ethnicity, and geographic region since this program permits participating states to enhance existing data collection or establish new registries.
In addition to more extensive information about demographic risk factors, more information is needed about the reasons for demographic differences in cancer incidence and mortality. Devesa et al. analyzed mortality trends for oral, esophageal, and laryngeal cancers in the United States from 1950 to 1984 and explored trends in tobacco use, alcohol consumption, and nutritional factors as possible explanations for some of the marked race and sex differences.[20] Their finding that only in non-white males did mortality trends tend to parallel the trends for smoking suggests that demographic differences may be important. Goldberg et al. examined mortality trends from 1973-1987 and concluded that the disparity in mortality between males and females was due mainly to differences in incidence, whereas the disparity between races was more likely attributable to differences in survival.[16] Other investigations of this type should be encouraged, as should studies of the reasons for differences in cancer rates between geographic regions.

Incidence of oral cancer among women rose nearly 50% from the late 1940s to 1983-1984 but has remained relatively stable since then. The increase has been attributed to changes in the patterns of smoking and alcohol use among women in recent decades, but nutritional and other factors may have also played a major role.[21]

One of the populations potentially at high risk for several forms of cancer, some of which may present in the oral cavity, is the group of immunocompromised persons infected with HIV. Although the SEER program does not collect data on HIV seropositivity, Kleinman et al.[6] reported a significant increase in the national SEER incidence of oral Kaposi's sarcoma and non-Hodgkin's lymphoma from 1981 to 1987—a period of time coinciding with the developing HIV epidemic in the United States. In addition, Swango et al.[22] reported that the incidence of oral cancer in 1989 was 12-14 times greater among 20-54-year-old males in the San Francisco/Oakland area, among whom HIV is relatively common, than in the other SEER sites combined (see Chapter III).

A variety of behavioral factors are also associated with increased risk for oral cancers. The best known are alcohol and tobacco use[22,23] and environmental risk factors such as exposure to sunlight (for lip cancer).[11,12] However, only alcohol and tobacco use are periodically monitored on a national level. The CDC's Office on Smoking and Health is the primary federal agency charged with routine surveillance of tobacco use. This office uses the NHIS as a key component of its efforts; that survey also collects information on alcohol use periodically. In addition, each year the CDC collects state-specific data on tobacco and alcohol use through the Behavioral Risk Factor Surveillance System (BRFSS). However, although NHIS and BRFSS data help to document current use patterns and trends, they are not particularly valuable in establishing associations between use patterns and cancer incidence.

There are also behavioral factors associated with decreased risk of oral cancer, most notably the consumption of certain nutrients. Accurately tying trends in cancer incidence to changes in risk or protective behaviors would require national databases that target specific age groups, account for the multiple interactions between behavioral and demographic risk factors, and factor in the considerable lag time between exposure to risk or protective factors and the eventual occurrence of disease.

Glossary

age-adjusted rate – a weighted average of age-specific cancer incidence or mortality rates, in which the weights are the proportions of persons in the corresponding age groups of a standard population. Using this rate permits comparisons across populations with dissimilar age distributions.

age-specific rate – the unadjusted rate for a specific age group.

incidence rate – the number of new cancers of a specific type or anatomic site occurring in a specified population during a year, expressed as the number of cancers per 100,000 people.

mortality rate – the number of deaths occurring in a specified population during a year, expressed as the number of cancers deaths per 100,000 people. For this report, only deaths for which oral or pharyngeal cancer was the underlying cause of death are included in the definition.

observed survival rate – the proportion of cancer patients surviving for a specified period of time after diagnosis.

relative survival rate – the likelihood that persons will not die from causes *directly associated with their cancer* at some specified time after diagnosis. It is calculated by adjusting the observed survival rate to remove the effect of death from non-cancer causes. The 5-year relative survival rate is commonly used as an indicator of cancer survival.

stage at diagnosis – the extent of disease at the time it is diagnosed. There are three stages: localized, regional, and distant metastases. Localized cancers have the highest survival rates, and cancers with distant metastases the lowest.

[Terms and definitions adapted from *Cancers of the Oral Cavity and Pharynx: A Statistics Review Monograph, 1973-1987.*[6]]

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ORAL CANCER BACKGROUND PAPERS

Chapter II: Histopathology, Biology and Markers

Working Draft

A. State of the Science

The development of oral cancer seems to begin in many cases with exposure of the mucosal surfaces of the upper aerodigestive tract to topical carcinogens, predominantly alcohol and tobacco.[1-4] In some persons exposed to these carcinogens or co-carcinogens, premalignant and malignant lesions develop in a multi-step process within the mucosa.[5,6] However, oral cancers occur in some patients with no history of tobacco or alcohol usage and no other apparent risk factors. Additionally, it is not clear that all of the tumors have an apparent "precancerous" state.

There is an emerging body of evidence that persons who develop head or neck cancer may have undergone alterations in p53 or other tumor suppressor genes; however, this has not been proven.[7-13] In addition, there is evidence that altered p53 genes may cooperate with other oncogenes, such as ras, to generate cells with a growth advantage for tumor progression, a multifunctional process associated with cutaneous carcinogenesis as well.[14] Increasing immunosuppression from HIV infection also appears to be a factor in predisposing oral mucosa to malignant changes (see Chapter III).

Neoplasms of diverse cellular origin arise in the oral regions, including nasopharyngeal carcinoma, lymphoma, mucosal melanoma, sarcomas, and salivary gland tumors. This chapter will focus on squamous cell carcinomas and their variants, as these cancers constitute over 90% of oral malignancies.

The earliest detectable morphologic changes are the appearance of the "premalignant" lesions of leukoplakia and erythroplakia. Genetic alterations in these premalignant lesions have also been demonstrated (see Chapter IV).[17-19] *Leukoplakia* is a white plaque that cannot be removed by gentle scraping and for which no other etiology can be identified. Microscopically, leukoplakias exhibit hyperplasia of keratinocytes, as represented by hyperorthokeratosis, hyperparakeratosis, and/or acanthosis.

The term *dysplasia* is reserved for lesions showing combinations and degrees of cytologic atypia (e.g., hyperchromatism, increased nuclear size, pleomorphism, dyskeratosis, and increased or abnormal mitotic figures).[1,18] Atypia confined to basilar and parabasilar keratinocytes constitutes *mild dysplasia*, whereas atypia extending into the midspinous layer is termed *moderate dysplasia*. When cellular atypia extends to the surface layer, the terms *severe dysplasia* and *carcinoma in situ* (complete top-to-bottom cytologic atypia) are applied. Architectural changes are also a feature of dysplasia, the most significant being a bulbous or teardrop shape of rete ridges. For oral mucosa in general, up to 20% of clinically defined leukoplakias that are biopsied may exhibit dysplasia; lesions located in the floor of the mouth approach a 40% prevalence of dysplastic change.[19] Dysplastic leukoplakias have a high propensity to progress to invasive squamous cell carcinoma. However, leukoplakias without present evidence of dysplastic changes may progress to dysplasia and subsequently to carcinoma; still, many leukoplakias fail to undergo malignant transformation.[20,21]

Erythroplakia is a velvety red patch of oral mucosa that does not conform to other defined oral disease processes that appear red clinically. There is a high prevalence of dysplastic change among these lesions, approaching 80-90%, and progression to invasive carcinoma is high.[1,2,22] Although dysplastic, the epithelium is usually atrophic, and submucosal vasodilation with inflammatory cell infiltration is a consistent finding. When erythroplakias coexist with white foci, they are termed speckled leukoplakias or erythroleukoplakias; such lesions will exhibit hyperkeratosis in the white areas.

Malignancies arising from the mucosa of the oral cavity are epithelial in origin and are, therefore, classified as squamous cell carcinomas more than 90% of the time.[23,24] According to the degree of differentiation, three subtypes are defined: (1) well-differentiated squamous cell carcinoma showing more than 75% keratinization; (2) moderately differentiated squamous cell carcinoma with 25-75% keratinization; and (3) poorly differentiated squamous cell carcinoma with less than 25% keratinization.[1,2] The majority of cases are of moderate differentiation. A clear relationship between histologic differentiation and clinical prognosis has not been established, although a lack of differentiation has been associated with more rapid growth and spread. The morphologic classification of squamous cell carcinoma by degree of differentiation is used in the description of the histopathologic specimen.

There are histopathologic variants of squamous cell carcinoma, all of which are rare, that affect prognosis and the selection of therapeutic modalities. Spindle cell or sarcomatoid squamous cancers, occasionally found in the oral cavity, are most frequently encountered on the lip and in the larynx. Radiation therapy to a pre-existing conventional squamous cell carcinoma is a common antecedent event; however, spindle cell carcinomas may arise de novo.[25] Other rare variants of oral, head, and neck carcinoma include pseudoglandular, basaloid, and small cell neuroendocrine carcinomas, the latter two being radiosensitive. Because these tumors share histopathologic features with other neoplasms (i.e., melanomas, neuroblastomas, lymphomas), the use of specific immunohisto-chemical markers is warranted.

Verrucous histopathologic patterns characterize a subset of oral epithelial tumors. Because there is evidence that these carcinomas evolve from leukoplakias that also exhibit a verrucoid architecture, they are termed proliferative verrucous leukoplakia (PVL).[17] Two specific forms of squamous cancers may arise from PVL lesions. The first, verrucous carcinoma, is characterized by marked hyperparakeratosis, acanthosis, parakeratin crypts, and large “pushing” bulbous rete ridges, said to resemble “elephant’s feet.”[26] It should be noted that verrucous carcinomas do not have dysplastic cytologic features; they also do not metastasize.

The second variant, also often preceded by PVL, is the papillary form of squamous cell carcinoma. Histologically, these lesions exhibit either an exophytic papillary pattern of growth or a verrucous inverting architecture.[27,28] Both patterns harbor dysplastic cytologic changes; a small number (less than 10%) have been shown to metastasize to regional nodes.

Oncogenes and proto-oncogenes are DNA sequences that encode factors that drive the cell cycle and include growth factors, their ligands, internal signaling pathway protein kinases, cyclins, cyclin-associated kinases, and DNA transcription factors, many of which can be demonstrated in tumor tissues. Conversely, anti-oncogene or tumor suppressor gene protein products retard or inhibit the cell cycle or activate pathways that lead to programmed cell death (apoptosis). Loss of suppressor gene product or inactivation by mutation of both alleles will favor cell proliferation and malignancy. These proteins can also be detected in tissues by immunohistochemical and molecular analytic methods.

Oncogenes and tumor suppressor genes are currently being studied in both defining the multistep carcinogenetic process and as prognostic factors for disease-free and overall survival.[1,6] For example, amplification of the epidermal growth factor receptor (EGFR) gene has been demonstrated in human specimens.[29,30] In one study, EGFR levels were shown to be higher in poorly differentiated tumors than in well-differentiated or moderately differentiated tumors.[31] In addition, increased EGFR levels have been shown to correlate with larger primary tumor lesions.[32] On the other hand, studies of the erb-B-2 oncoprotein have indicated that the expression of erb-B-2 is common in human head and neck cancer but does not seem to be of prognostic significance.[33]

Normal p53 protein serves as a suppressor of cell growth; a possible correlation between p53 mutation and prognosis is being investigated. Generally, mutations of p53 are demonstrated in about 50% of head and neck cancers and have also been seen in premalignant lesions.[34] The incidence and specific type of p53 mutation may depend on the risk factor exposure pattern.[35-38] A retrospective study by Brachman et al.[7] suggested that tumors with p53 mutation had a shorter time to treatment failure than tumors lacking a p53 mutation. Shin et al. reported on tumor samples from 118 patients[8] (tumor sites were the oral cavity, oropharynx, larynx, and hypopharynx); median survival was significantly shorter in patients with a p53 mutation in their primary tumor specimen than in those with no such mutation. However, there was no difference in recurrence rates of the primary tumor according to p53 status, although patients with p53 mutation had a higher likelihood of developing a second primary malignancy.

Studies of the chromosome 9p21-22 indicated mutations in this region in over 70% of examined head and neck tumors;[9,10] a similar incidence of allelic loss was found in preinvasive lesions. These findings suggest that loss of genetic information on chromosome 9p is an early event in head and neck squamous cell carcinogenesis. It also appears that information on the myc oncogene may be useful for prognosis, but this remains controversial.[6] Decreased expression of the nuclear retinoid receptor (RAR-beta) has also been associated with head and neck carcinogenesis.[39]

B. Emerging Trends

The most interesting emerging trend in this area is using molecular biology to define more carefully

a tumor's biological behavior ("biological staging"). Another interesting trend currently being investigated is the use of the polymerase chain reaction (PCR) to determine if surgical margins obtained at the time of surgery that are histopathologically free of tumor contain a small amount of histologically undetectable tumor cells. Specifically, the use of PCR to detect specific p53 mutations identified in the primary tumor in the histopathologically negative surgical margin could be very useful, as these mutations would indicate the presence of residual (histopathologically undetected) tumor cells. It will be very important to establish whether the presence of submicroscopic tumor cells contributes to prognosis and clinical outcome.

The recent development of in situ PCR will allow amplification of both DNA and RNA directly in tissue section; this technique should be extremely helpful in the future to localize tumor cells containing altered oncogenes or tumor suppressor genes. An improved understanding of the molecular biology of head and neck cancer may also contribute to future therapeutic improvements. Finally, molecular probes may be used to facilitate the early detection of second malignancies.

Head and neck cancer increasingly appears to be a complex disease entity that requires highly specialized input from pathologists, surgeons, radiologists, and medical and oral oncologists. The need for laboratory scientists; specialists in social services, speech, and swallowing disorders; restorative dentists; and maxillofacial prosthodontists clearly identifies this malignancy as one that should be studied and treated at large academic centers with ongoing clinical and laboratory research programs. Such an environment will promote the use of increasingly refined laboratory techniques for improved diagnosis and therapy.

A good deal of current laboratory and clinical research is focusing on identifying the relative contributions of certain oncogenes and tumor suppressor genes on carcinogenesis, tumor stage, and clinical outcome. Although abnormalities of some oncogenes and tumor suppressor genes have been identified, their relative contribution and optimal use in diagnosis, prognosis, or treatment remain unknown. The same might be said for the role of Epstein-Barr, hepatitis, and herpes simplex viruses; further clinicolaboratory studies will be needed to define which are clinically relevant and when they should be investigated. Figure 1 shows biomarkers that may prove useful in assessing cycling cells in precancerous lesions and at surgical tumor margins, and in predicting aggressive behavior, invasion front, and metastatic potential.[40] Genetic analysis at a molecular/chromosomal level is emerging as a science that may aid in identifying risk and possibly prevention as well.

Finally, a reliable and predictable histopathology grading system should be developed to include, in addition to differentiation of tumor cells, such factors as basement membrane protein expression and invasion patterns, perineural invasion, and immunologic responses.[41]

Figure 1: Biomarker Predictors in Oral Precancerous & Cancerous Lesions

Marker	Detection Method	Target
Proliferation		
PCNA, Ki67, BrU	IHC	Cycling cells
Histone	mRNA ISH	
AgNORs	Silver stain	
Genetic		
Ploidy	FC	Aneuploid cells
Oncogenes		
C-myc	IHC	Cycling cells
Tumor Suppressor		
p53 mutations	IHC, PCR	Cycling cells
Cytokeratin 8/19	IHC	Anaplasia
Blood Group Antigens	IHC	Anaplasia
Integrins/ECM Ligands	IHC	Invasion and metastatic potential

Abbreviations:

IHC	immunohistochemistry
FC	flow cytometry
PCR	polymerase chain reaction
ISH	in-situ hybridization

C. Opportunities and Barriers to Progress

The emergence of molecular biology with its new prognostic and, ultimately, therapeutic tools represents an enormous opportunity. The use of biologic markers to screen patients who are at increased risk may help to predict the probability of disease progression, aid in the diagnosis made by routine histopathologic studies, assess the prognosis of the individual cancer patient, develop treatment protocols, and evaluate the response to therapeutic agents. A major barrier to progress is a health care climate in which a large proportion of patients receive either uncoordinated "multispecialty" or traditional surgical care without proper usage of laboratory, clinical, and therapeutic investigational tools. Thus, research is slowed at single institutional and national levels (e.g., Cooperative Groups). Proper recognition that survival rates are too often poor with "standard therapy" in patients with advanced disease should lead to a greater appreciation for research.

Another barrier to progress is the cost of biologic markers combined with the failure of third parties

to cover them. Laboratory standardization of biologic marker techniques and variability in interpretation of tissue results compromise the diagnostic significance of these markers.

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ORAL CANCER BACKGROUND PAPERS

Chapter III: Risk Factors

Working Draft

Introduction

Although oral cancer undoubtedly has a multifaceted etiology, tobacco use and alcohol consumption are widely considered to be its major risk factors.[1] Over the past 30 years, a series of authoritative reports issued by the U.S. government and various international health agencies have conclusively established that tobacco use, especially cigarette smoking, is causally related to at least 8 major cancer sites and increases the mortality rate for several others.[2-13] Although other lifestyle and environmental factors also have been identified as risk factors for oral cancer,[14] tobacco use remains the single most important and preventable cause of this disease.

A. State of the Science

Cigarettes

Reports by the U.S. Public Health Service have clearly established a direct causal relationship between cigarette smoking and cancer of the oral cavity.[4,5,15,16] A number of major prospective cohort mortality studies have been critical in both elucidating the causal nature of the association and estimating the magnitude of the disease burden. Two such studies, Cancer Prevention Study (CPS) I and II, sponsored by the American Cancer Society (ACS), are the largest epidemiological studies ever undertaken, each following more than 1 million men and women.[5] Evidence from these and other epidemiological studies has provided key documentation of the association between cigarette smoking and oral cancer.

The mortality risk for oral cancer in cigarette smokers is substantially greater than that observed among life long "never smokers."[4,5] Although estimates vary, most studies have reported mortality ratios for smokers versus never smokers of about 5-6:1, with several reporting ratios in excess of 10:1. Furthermore, the risk for death from oral cancer is consumption related; the more cigarettes consumed daily and the more years one has smoked, the greater the risk.[4,16]

In CPS II, which followed over 1.2 million individuals for 6 years beginning in 1982, male cigarette smokers had a relative risk for oral cancer 27.7 times greater than that of a male never smoker; the rates among women who smoked were nearly 6 times greater.[5] Estimates of the percentage of oral cancers attributable to cigarette smoking have been quite consistent, generally ranging from 75% to 90%.[4,5, 17-19]

A recent analysis conducted for the President's Cancer Panel on Avoidable Causes of Cancer estimated that 80% of all oral cancer deaths (International Classification of Disease Codes 140-149) expected to occur in 1995 would be directly attributable to cigarette smoking, 91% among men and almost 60% among women.[20] These estimates do not consider the possible interaction between smoking and other risk factors and, therefore, may overestimate the impact of smoking. Conversely,

however, these estimates do not include those oral cancers that result from non-cigarette tobacco use such as pipe and cigar smoking and the use of snuff and chewing tobacco.

Numerous studies examining the relative risk for oral cancer among former smokers have found that the risk for oral cancer was lower among former smokers after the first few years of abstinence than for those who continued to smoke. These studies have found that after 3 to 5 years of smoking abstinence, oral cancer risk decreased by about 50%.[5]

Cigars and Pipes

Although cigarette smoking is the form of tobacco use most often linked with increased incidence of oral cancer, regular use of pipes or cigars also increases the risk of disease.[3,4,11,21] Both prospective and retrospective studies have consistently documented that pipe and cigar smokers experience mortality rates for oral cancer either similar or higher than those risks observed among cigarette smokers.[4,5] A 1982 Surgeon General's Report, *The Health Consequences of Smoking: Cancer*, concluded:[16]

> **"Cigarette smoking is a major cause of cancers of the oral cavity in the United States. Individuals who smoke pipes or cigars experience a risk for oral cancer similar to that of the cigarette smoker."**

Smokeless Tobacco (Snuff and Chewing Tobacco)

Only recently has the scientific and public health community turned its attention to the possible health implications of smokeless tobacco use.[10,22,23] In 1981, Winn and colleagues[24] published a seminal study involving 255 women living in rural North Carolina; they found a four fold increased risk of oral cancer among nonsmokers who dipped snuff. This association could not be explained by smoking or alcohol consumption, dentures, poor dentition, diet, or use of mouthwash. For long- term users there was a 50-fold increased risk for cancer of the gum and buccal mucosa. Even women who had used smokeless tobacco less than 25 years had a 14-fold greater risk for these cancers (Table 1). In 1982, the following statement was published in the *Report of the Surgeon General, the Health Consequences of Smoking: Cancer:*[16]

> **"Long term use of snuff appears to be a factor in the development of cancers of the oral cavity, particularly cancers of the cheek and gum."**

Table 1: Estimated Relative Risk of Oropharyngeal Cancer According to Duration of Snuff Use and Site[24]

Anatomic Site	Duration of Snuff Use (yrs)	Relative Risk
Gum and Buccal Mucosa	0	1.0
	1-24	13.8
	25-49	12.6
	≥50	48.0
Other Mouth and Pharynx	0	1.0
	1-24	1.7
	25-49	3.8
	≥50	1.3

The Winn study was one of the first to provide strong evidence for a causal relationship between smokeless tobacco use and oral cancer. As results from other studies began to emerge, the National Cancer Advisory Board (NCAB) of the National Cancer Institute issued a resolution on smokeless tobacco in 1985, which stated that the NCAB "considers the use of smokeless tobacco to pose a serious and increasing health risk." In September 1985, the International Agency for Research on Cancer (IARC) issued its own report on smokeless tobacco, which concluded:[10]

> **"In aggregate, there is sufficient evidence that oral use of smokeless tobacco is carcinogenic to humans."**

In April of the following year, the Surgeon General released a report during Congressional testimony on new legislation for labeling smokeless tobacco.[22] The overall conclusion of this comprehensive review clearly established the use of smokeless tobacco as a health risk:

> **"After a careful examination of the relevant epidemiologic, experimental, and clinical data, the committee concludes that the oral use of smokeless tobacco represents a significant health risk. It is not a safe substitute for smoking cigarettes. It can cause cancer and a number of noncancerous oral conditions and can lead to nicotine addiction and dependence.**"

The report also reached a number of conclusions regarding smokeless tobacco use and oral cancer that parallel those reached by the IARC review.

> **"The scientific evidence is strong that the use of snuff can cause cancer in humans. The evidence for causality is strongest for cancer of the oral cavity, wherein cancer may occur several times more frequently in snuff dippers**

compared to nontobacco users."

Since the publication of both the IARC's and the Surgeon General's reports, additional studies have appeared in the scientific literature that strongly support the conclusion that smokeless tobacco use, particularly use of snuff, is causally related to oral cancer.[23]

Chemistry, Pharmacology, and Toxicology of Tobacco and Tobacco Smoke

Because the majority of carcinogens in tobacco smoke are the byproduct of pyrolysis, they are also found in pipe and cigar smoke, often in much higher concentrations.[3] The International Agency for Research on Cancer has generated a significant body of research demonstrating the biological activity of these agents in both laboratory animals and humans.[10,11] Chemical analysis reveals that smoke from a single cigarette is composed of over 4,000 different constituents, including some that are pharmacologically active, toxic, mutagenic, or carcinogenic.[3,25]

Smokeless tobacco also contains carcinogens, some at extremely high levels.[10,22,23,26] It is especially significant that the preparation of smokeless tobacco products, which entails curing, fermentation, and aging, occurs under conditions favoring the formation of tobacco-specific N-nitrosamines (TSNAs) from nicotine and other tobacco alkaloids such as nornicotine, anatabine, and anabasine. During tobacco chewing and snuff dipping, it is likely that additional amounts of carcinogenic TSNAs are also formed endogenously in the oral cavity.[27]

Two of the six TSNAs identified in smokeless tobacco, N'-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1 3-pyridyl-1-butanone (NNK), are strong carcinogens in mice, rats, and hamsters, capable of inducing both benign and malignant tumors of the oral and nasal cavity as well as of the lung, esophagus, and pancreas.[27-29] Polynuclear aromatic hydrocarbons (PAHs) in tobacco smoke have been implicated extensively in oral carcinogenesis, and NNK and NNN, which are found in both tobacco and tobacco smoke, likely play a major etiological role in cancers of the oral cavity as well.

In summary, in light of the vast number of toxic and carcinogenic compounds that exist in tobacco and tobacco smoke and the level of exposure to these agents among tobacco users, it is not surprising that tobacco use is so profoundly implicated in the causation of human cancer. A number of these compounds have been directly implicated in the production of oral carcinomas and exist in both cigarette smoke and in smokeless tobacco in concentrations that have induced oral malignancies in laboratory animals.

Alcohol

Most patients with oropharyngeal cancer drink alcohol. One study found rates as high as 94% in men and 82% in women.[1] However, one problem with identifying alcohol as an independent risk factor for oral cancer is that heavy drinkers are usually heavy users of tobacco products. Another problem is that consumption of alcohol and a poor diet might affect the risk for oral cancer. Furthermore,

assessment of alcohol intake is inherently imprecise because of a bias toward underreporting and the often episodic nature of usage. Thus, it is hard for a patient to estimate "average" use.

All three forms of alcohol (beer, hard liquor, and wine) have been associated with oral cancer, although hard liquor and beer have a higher associated risk.[29-34] Studies that have found alcohol use to be a factor for oral carcinogenesis have usually concluded that the level of consumption was important; one study found elevated risk only if 56 or more glasses of wine per week were consumed.[34] Another study showed a significant increase only if the average *daily* consumption of alcohol exceeded 120 grams.[30] That evidence is contradictory about the role of alcohol in oral cancer may relate to the difficulty in measuring intake or to alcohol's effect on other variables (or both), but it is reasonable to assume that any form of alcohol taken in excess may promote oral cancer.

Cigarettes and Alcohol

A combination of "heavy" smoking and "heavy" drinking results in odds ratios (ORs) for oral cancer of up to 38 for men and 100 for women.[1] (An *odds ratio* is a measure of association that quantifies the relationship between an exposure and health outcome.) An OR of 38 in men indicates a multiplicative effect, because the OR for "heavy" smoking alone among men is 5.8; for "heavy" drinking alone it is 7.4. Another study of smoking and drinking showed these factors to have a greater than additive but less than multiplicative effect.[35] In this study, the risk of oral cancer attributed to smoking (76%) was higher than the risk attributed to alcohol consumption (55%).[35] Similarly, Brunneman et al. found the oral cancer risk attributable to tobacco to be higher (72%) than for alcohol (23%).[29] It is apparent that, used in combination, alcohol and tobacco exert a synergistic effect that substantially increases the risk for oral cancer. Blot et al. estimated that tobacco smoking and alcohol drinking combine to account for approximately three-fourths of all oral and pharyngeal cancers in the United States.[1] Research on pigs has shown that applying 5% or 15% ethanol enhances the permeability of tobacco carcinogens in porcine mucosa, especially in the floor of the mouth.[36,37]

Mouthwash

There is some concern that mouthwashes might cause oral cancer because they have high alcohol content (as great as 26%) and are used frequently. However, Elmore and Horwitz, who combined the data from seven case control studies that evaluated mouthwash use and oral cancer, found that ORs ranged from 0.82, which suggested a protective effect, to 2.5 at the highest mouthwash exposures. They concluded that there is insufficient evidence to establish a causal relationship between the use of mouthwash and oral cancer.[38]

Diet

Although dietary factors have been identified as having a possible association with oral cancer, accumulated scientific evidence that use of tobacco and alcohol increases oral cancer risk far outweighs any evidence linking a deficient diet to increased risk.

Low beta-carotene intake has been associated with an increased risk of lung, laryngeal, gastric, ovarian, breast, cervical, and oral cancers.[39-44] Several studies have shown that a low intake of fruits and vegetables, which are the primary sources of beta-carotene, is also related to a generalized increased cancer risk and mortality.[45-51] Conversely, an increased consumption of fruits and/or vegetables has been associated with a decreased risk of oral or oropharyngeal cancer when compared with low intake levels.[46,52-54] Garewal[55] summarized the findings of 54 studies that evaluated fruit and vegetable intake in the development of cancers in the upper aerodigestive tract; he found that 52 of the studies demonstrated a protective effect.

A low intake of vitamin C has been associated with an increased risk of cancers of the stomach, esophagus, oral cavity, larynx, and cervix.[56,57] Patients who ingest high levels of vitamin C and fiber have half the risk of oral cancer as those with the lowest level of consumption.[55]

One study found that patients with low serum levels of vitamin E had more than double the general risk of gastrointestinal cancers.[57] In another study, which evaluated more than 2,000 cases, the use of vitamin E supplements correlated with a diminished risk for oral and pharyngeal cancer.[59] The most consistent dietary findings across multiple cultural settings are that high fruit consumption has a protective effect and that high alcohol consumption has a carcinogenic effect.[43]

Actinic Radiation

Sunlight, through actinic radiation, helps to produce cancer along the vermilion border of the lip. Because these "sunlight" induced cancers are much more common in fair-skinned individuals exposed to the outdoor life than in individuals with darker pigmentation, it appears that darker pigment protects against actinic radiation damage.[60, 61] (The wavelengths of the light thought to be responsible for the actinic damage are in the 2900-3200 Å range.)

Dental Factors

There is little evidence to suggest that poor oral hygiene, improperly fitting dental prostheses, defective dental restorations, or misaligned or sharp teeth promotes oral cancer.[62] Gorsky and Silverman[63] evaluated 400 patients with oral cancer to determine whether dentures were a risk factor and found no correlation between the wearing of dentures and the patient's cancer.

Viruses and Their Interactions with Oncogenes

Alterations of cellular oncogenes, which lead to altered expression of their products, have been implicated in human cancers.[64] Cellular oncogenes, also known as proto-oncogenes, acquire their transforming properties or become activated by gene amplification, point mutations, and gene rearrangements. Oncogenes can encode growth factors and growth factor receptors, act on internal signaling molecules, and regulate DNA transcription factors.[65-68] Other genes encode proteins that inhibit the cell cycle or promote programmed cell death (apoptosis). Tumor suppressor genes may become inactivated or mutated with consequential loss of control over cell division.[68,69] The

retinoblast and p53 gene products are examples.

Consideration of risk factors should recognize that many molecular events governing control of cell cycles are influenced by viruses. Those most commonly implicated in oral cancer transformation have been the human papillomavirus (HPV),[70,71] herpes group viruses,[72] and the adenoviruses.[73] Of these, HPV and herpes have been the most thoroughly studied and are now considered to be the most likely "synergistic viruses" involved in human oral cancer. The herpes viruses most often linked to oral cancer are the Epstein-Barr virus (EBV) and cytomegalovirus (CMV); both EBV DNA and CMV DNA have been demonstrated in oral carcinomas.[72] The hamster cheek pouch model has been used to evaluate the role of herpes simplex virus (HSV),[74] and reports indicate that HSV can act synergistically with chemical carcinogens to initiate oncogenic transformation in this animal model.[75] However, there is still debate as to whether the presence of HSV in such tissues shows a cause-and-effect association between virus and cancer.

More than 100 different HPV types have been isolated from benign and malignant neoplasms. HPV antigens and gene products have been detected in biopsies of oral cancer and precancer;[76-79] HPV has also been identified in nodal metastases from oral, head, and neck cancers. The genotypes most often found in oral carcinoma are HPV 16 and 18, but HPV can also be found in normal oral mucosa. Whether or not HPV plays an active role in the initiation of oral malignancy, whether it is simply a passenger virus, and whether the virus acts in synergy with exogenous agents such as tobacco or alcohol to promote neoplasia are all questions that still await answers.

Some viruses, particularly HPV and herpes, interact with oncogenes and tumor suppressors. Recent evidence suggests that the HPV 16/E5 gene can induce malignant transformation in epithelial cells, possibly acting by enhancing growth-factor-mediated intercellular signal transduction.[79] The E6 and E7 HPV 16 and 18 gene products act as oncoproteins by interacting with host cell p53 apoptotic protein, promoting its elimination.[80] Loss of p53, in turn, removes inhibition of cell-cycling influences. Still, there are substantial gaps in our knowledge about how oncogenes, tumor suppressor genes, and viruses promote oral cancer.

Immunocompetence

Studies suggest that HPV 16 transfectants play a significant role in oral cancer development by altering intercellular immune surveillance mechanisms.[74] The most common interpretation of surveillance mechanism data is that specific cellular defense mechanisms acting against cancer development, such as anti-oncogenes, can be mutated by viruses. This theory is supported by the fact that HPV 16 E6 and E7 gene products may be able to bind various human gene products, particularly the p53 gene, thereby deregulating control of cell proliferation and differentiation. There are also studies demonstrating that HPV-related lesions can mediate protection against certain tumor cells.[76]

Oral cancer does not appear to be a common consequence of systemic immunosuppression even

though, among HIV-positive immunocompromised individuals, HIV-associated oral malignancies have been reported.[81] The most common are Kaposi's sarcoma (KS) and non-Hodgkin's lymphomas. KS is a malignant reactive lesion that stems from factors (cytokines) that induce the formation of tumors in a number of tissues and organs. The most prominent feature of Kaposi's is produced by an angiogenesis factor, which leads to the characteristic appearance of a vascular lesion. Skin is the most common site for KS, but about half of all patients will have oral manifestations. In many of these individuals, the disease will manifest itself first in the oral cavity; sometimes, other sites will not be affected. KS can afflict any oral mucosal site, the palate being the most frequent and the gingiva second.

The occurrence of non-Hodgkin's lymphoma (NHL) continues to increase as the number of HIV-infected individuals grows and their longevity extends. Inappropriate B-lymphocyte stimulation and the presence of Epstein-Barr virus play a role in this disease, but the co-factors are poorly understood.[82] Frequently, these lymphomas are extranodal and can involve the mouth. In some cases, oral NHL has been either the first or only evidence of NHL tumor.

B. Emerging Trends

Tobacco

Estimates from the most recent data available (1993) indicate that 46 million adults in the United States are current smokers, or 25% of persons aged 18 years or older (27.7% of men and 22.5% of women).[83] The annual prevalence of cigarette smoking among adults in the United States declined 40% during 1965-1990 (from 42.4% to 25.5%) but was virtually unchanged from 1990 to 1992.[84]

Newspaper and other media sources have suggested a renewed interest in cigar smoking; recent consumption figures from the US Department of Agriculture lend some support to this trend.[85] Last year, 2.29 billion large cigars (including cigarillos) were consumed in the U.S., an increase of almost 7% from the previous year, and the first reported increase in several decades. However, regular cigar smoking remains almost exclusively an older male behavior. In 1991, only 3.5% of all adult males reported they had used cigars, whereas in 1970 16% had reported themselves to be regular users of cigars.[84]

Pipe tobacco consumption dropped below 10 million pounds for the first time in U.S. history in 1994.[85] Consistent with this drop in consumption, prevalence has also declined. Two percent of all adult males report they currently smoke pipes, the lowest figure ever recorded on national surveys.[84]

Although these smoking trends among adults are encouraging, the trends among our children are not. It is estimated that 3,000 young people become *regular* smokers every day.[86] Data for 1995 from the University of Michigan's 1995 Monitoring the Future Study indicate that 32.5% of the nation's

high school seniors are current smokers and 21.6% smoke daily.[87]

The consumption of smokeless tobacco, especially snuff, continues to increase, having tripled between 1972 and 1991. In 1991, the prevalence of smokeless tobacco use among adults was 2.9%, 5.6% among men and 0.6% among women. Among 18- to 24-year old men, the rate was 8.2%.[88] More recent data on the prevalence of use in 1995 among secondary school students is particularly disturbing. In 1995, the 30-day prevalence of use among eighth, tenth, and twelfth grade males was 11.8%, 17.2%, and 23.6%, respectively.[87]

Unless these current trends are reversed, the nation will fall short of meeting two key Year 2000 Health Objectives—a reduction to a 15% prevalence of regular smoking among adults, and a reduction of smokeless tobacco use by males ages 12-24 to a prevalence of no more than 4%.[89]

Viruses and Oncogenes

Increased knowledge and techniques have developed a data base to better understand the cause, progression, and treatment of viral infections, which will allow better understanding of risks and their control.

Immunocompetence

The utility of cell markers as predictors of malignant transformation or disease progression is discussed in Chapter II. As more scientific data emerge on the molecular events that take place in oral cancer and the interaction of viral products with oncogenes, interventions may be engineered. Vaccines, antivirals, and gene transfer techniques may prove beneficial in targeted high-risk patients.

C. Opportunities and Barriers to Progress

Significant progress in prevention depends upon research breakthroughs in the biologic factors related to cancer development and in innovative techniques to reduce their negative consequences. In the absence of scientific breakthroughs, however, some risks of cancer are best controlled currently through behavior modification (also discussed in Chapter IX).

Tobacco

Efforts to prevent tobacco use, particularly efforts targeted to youth, hold the most promise for preventing tobacco-related diseases, including oral cancer. Additionally, advice on tobacco use cessation provided by physicians, dentists, and other primary care clinicians can significantly affect individual decisions to discontinue a type of tobacco use. The National Cancer Institute has published two manuals, one for physicians and one for the oral health team, to facilitate the delivery of one-on-one smoking cessation advice in medical and dental offices.[90,91]

Community- or office-based programs in smoking or smokeless tobacco cessation take a variety of forms. Many individuals receive office-based assistance from their family physician or dentist. A monograph published by the National Cancer Institute (NCI) of the National Institutes of Health, entitled *Tobacco and the Clinician: Interventions for Medical and Dental Practice*, summarizes the lessons learned from a number of physician- or dentist-administered office-based smoking cessation programs.[92] The monograph also evaluates the effectiveness of various worksite, school, and community-based smoking control efforts. Because 70% of smokers see a physician each year and 52.6% visit a dentist, the potential for the health care community to affect smoking prevalence in the United States is very large; unfortunately, it is substantially underutilized.[93]

Local hospital-based or worksite programs that offer tobacco cessation are frequently developed through research projects funded by organizations such as the American Cancer Society, the American Lung Association, the National Cancer Institute, and the Centers for Disease Control and Prevention (CDC). One such project is supported by CDC as part of their National Tobacco Prevention and Control Program's Initiatives to Mobilize for the Prevention and Control of Tobacco Use (IMPACT). Through cooperative agreements to state health departments, comprehensive tobacco prevention and control programs are being developed with participation by diverse community groups, coalitions, and leaders.

It is evident from our experiences thus far that a multi-pronged initiative that involves office-based clinician assistance and community-based interventions, such as restricting advertising and limiting the access of youth to tobacco products, is the best approach to prevent tobacco initiation and encourage cessation among current users. Strategies for discouraging initiation among young people should include using the popular media to promote abstinence from tobacco, offering school-based educational programs, enforcing state and local restrictions on the sale and advertising of tobacco products,[94] and encouraging in-office counseling by primary care clinicians.

Intervention programs to help individuals stop using smokeless tobacco are less widely available and have been less successful than smoking cessation programs. Additional research to identify effective interventions for smokeless tobacco is needed, particularly in light of recent increased use among young adult males.

Alcohol

Minimal use of alcohol does not appear to be associated with a significantly elevated oral cancer risk. However, all patients diagnosed with either a premalignant or malignant oral lesion should refrain from any use of alcohol. There should be more health education about how using both tobacco and alcohol increases the risk of oral cancer; health promotion efforts should emphasize the danger of combining the two substances.

Mouthwash

Although there is no certain link between oral cancer and mouthwash, its excessive use should be

discouraged.

Diet

Although there is evidence that certain dietary deficiencies may be linked to oral cancer, at present it is not possible to recommend useful guidelines for prevention, other than the current general recommendation to consume five servings of fruits or vegetables per day.[95] A recent comprehensive review of epidemiological investigations in this area identified high fruit consumption as a protective factor in preventing oral and pharyngeal cancers across a variety of cultural settings.[43] Additional research is necessary.

Actinic Radiation

Sunscreens and sunblocks are effective in protecting the lip from the damaging effects of ultraviolet light. These products can and should be promoted to the public as part of an overall skin cancer prevention message.

Dental Factors

Reassuring patients that dental appliances, restorative materials, and routine trauma do not appear to increase the probability of oral cancer is an important health message. Additionally, patients should be encouraged to consult their dentist or physician if they observe any unusual growths or lumps in their mouths.

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ORAL CANCER BACKGROUND PAPERS

Chapter IV: Premalignant Lesions

Working Draft

Introduction

Classification schemes for lesions of the oral cavity typically have used the clinical appearance of lesions to determine which are premalignant.[1] Leukoplakia and erythroplakia are two clinical lesions widely considered to be premalignant. However, using clinical features to classify lesions is difficult because they vary in appearance and are likely to be interpreted subjectively by the clinician. A histopathologic diagnosis is generally more indicative of premalignant change than clinically apparent alterations.

A. State of the Science

Clinical Lesions Associated with Premalignancy

Leukoplakia

The term *leukoplakia* is sometimes used inappropriately to indicate a premalignant condition. In fact, the term describes a white plaque that does not rub off and cannot be clinically identified as another entity. Most cases of leukoplakia are a hyperkeratotic response to an irritant and are asymptomatic, but about 20% of leukoplakic lesions show evidence of dysplasia or carcinoma at first clinical recognition.[1] However, some anatomic sites (floor of mouth and ventral tongue) have rates of dysplasia or carcinoma as high as 45%. There is no reliable correlation between clinical appearance and the histopathologic presence of dysplastic changes except that the possibility of epithelial dysplasia increases in leukoplakic lesions with interspersed red areas. In one large study,[2] lesions with an erythroplakic component had a 23.4% malignant transformation rate, compared with a 6.5% rate for lesions that were homogeneous. The term *erythroleukoplakia* has been used to describe leukoplakias with a red component.

Erythroplakia

An *erythroplakia* is a red lesion that cannot be classified as another entity. Far less common than leukoplakia, erythroplakia has a much greater probability (91%) of showing signs of dysplasia or malignancy at the time of diagnosis.[3] Such lesions have a flat, macular, velvety appearance and may be speckled with white spots representing foci of keratosis.

Lichen planus

The premalignant or malignant potential of *lichen planus* is in dispute. Some believe that the occasional epithelial dysplasia or carcinoma found in patients with this relatively common lesion may be either coincidental or evidence that the initial diagnosis of lichen planus was erroneous.[4] It is frequently difficult to differentiate lichen planus from epithelial dysplasia; one study found that 24% of oral lichen planus cases had 5 of the 12 World Health Organization (WHO) diagnostic criteria for epithelial dysplasia, and only 6% had no histologic features suggestive of that disorder.[5] However,

as many reports on lichen planus patients followed over time indicate a higher than expected rate of malignant transformation,[6] it is prudent practice to biopsy the lesion at the initial visit to confirm the diagnosis and to monitor it thereafter for clinical changes suggesting a premalignant or malignant change.

Other Lesions

Premalignant changes arising in other oral lesions are uncommon. White lesions such as linea alba, leukoedema, and frictional keratosis are common in the oral cavity but have no propensity for malignant transformation. The health professional can usually identify them by patient history and clinical examination.

Clinical Features of Oral Premalignancy

A diagnostic biopsy should be considered for any mucosal lesion that persists for more than 14 days after obvious irritants are removed; simply noting the clinical appearance or presentation of a lesion is not enough to determine premalignant changes. The following overview describes clinical features generally but is insufficient to identify premalignancy in a specific patient.

Anatomic Location

Studies relating premalignant tissue changes to anatomic sites have produced varying results. One study found that 21.8% of oral epithelial dysplasias occurred on the buccal mucosa, 13.7% on the palate, and 12.3% on the floor of the mouth.[7] A study of leukoplakia by Shafer and Waldron[8] found that the mandibular mucosa and sulcus were involved in 25.2% of their cases and on the buccal mucosa in 21.9%. Because many oral premalignancies present as leukoplakias, the similar findings are not unexpected. Interestingly, the distribution of locations is much different from that of squamous cell carcinomas of the oral cavity, for which the tongue, oropharynx, lip, and floor of mouth are the most common sites.[9] Perhaps there is a subset of epithelial dysplasias, such as those that occur on the buccal mucosa, that have a lower rate of malignant transformation than those found at other sites.

Age

The mean age at diagnosis of oral premalignancy is 50-69; less than 5% of diagnoses are in patients under 30 years of age.[7,10,11] Thus, the aging process itself is the greatest risk factor for premalignant and malignant changes.

Sex

Studies have shown that epithelial dysplasia has a predilection for males, but the decrease in the male:female ratio for oral squamous cell carcinoma suggests the picture may be changing.[7,10,11] This may be due to increased use of tobacco and alcohol among women (see Chapter I).

Clinical Appearance

Although most premalignant lesions are white (leukoplakia), they vary considerably in their initial presentation. These lesions are usually asymptomatic; the development of pain or soreness may be associated with a malignant change.

Probability of Malignant Change

About 5-18% of epithelial dysplasias become malignant.[7,11,12] Although expecting a greater probability of malignant change for dysplasias with a greater histologic degree of epithelial dysplasia seems intuitive, that relationship is hard to prove because only a few cases of epithelial dysplasia have been diagnosed but not excised, then monitored to see whether malignant change occurred. A greater risk of malignant change in an epithelial dysplasia has been associated with the following factors: (1) erythroplakia within a leukoplakia, (2) a proliferative verrucous appearance, (3) location at a high-risk anatomic site such as the tongue or floor of mouth, (4) the presence of multiple lesions, and, paradoxically, (5) a history of <u>not</u> smoking cigarettes.[2]

Transition Time from Epithelial Dysplasia to Malignancy

Although most oral carcinomas have adjacent areas of epithelial dysplasia, some carcinomas may not evolve from epithelium with top-to-bottom dysplastic changes but rather arise from basilar keratinocytes. Silverman and colleagues[2] monitored 257 patients with oral leukoplakia; 22 had a diagnosis of epithelial dysplasia, the remaining 235, hyperkeratosis. Eight of the 22 (36.4%) with epithelial dysplasia developed carcinoma. Of the 107 patients with a homogeneous leukoplakic lesion and a diagnosis of hyperkeratosis, 7 (6.5%) developed carcinoma. However, 30 (23.4%) of the 128 patients with erythroplakic lesions and a diagnosis of hyperkeratosis were eventually diagnosed with carcinoma. The time from initial diagnosis of either epithelial dysplasia or hyperkeratosis to carcinoma ranged from 6 months to 39 years. In another study, reported by Lumerman and colleagues,[11] 7 (15.9%) of 44 patients with oral epithelial dysplasia identified in a biopsy service developed carcinoma; mean time from biopsy to cancer diagnosis was 33.6 months.

Epithelial dysplasia has been more extensively studied in association with the uterine cervix than with the oral cavity. Based on clinical reviews, approximately 12% of cervical epithelial dysplasias progress to carcinoma in situ.[13] The estimated median time for this progression depends on the histologic severity of the epithelial dysplasia: 58 months for mild, 38 months for moderate, and 12 months for severe.[14] Approximately 73% of carcinoma in situ cases evolve into full-blown carcinoma.[15] How important this information is for understanding progression to oral cancer is unclear, but it is consistent with observations that not all oral epithelial dysplasias evolve into carcinoma in situ or full-blown carcinoma and that this transition—when it does occur—takes months or years.

Diagnosis

Verifying the premalignant status of an oral lesion requires a biopsy. However, there is a noninvasive clinical test—the topical application of toluidine blue to a suspicious area—that helps identify the

presence of dysplastic or carcinomatous lesions.[16] Mashberg and Samit reported that proper use of toluidine blue yielded false-positive and false-negative rates less than 10%;[17] the agent is believed to bind selectively to the DNA and RNA in cells. Clinicians can use toluidine blue to help identify lesions more likely to have premalignant or malignant changes, select an appropriate biopsy site within a large lesion, or monitor high-risk patients who have been previously diagnosed with a premalignant or malignant lesion. They must still exercise clinical judgment, however, when evaluating the results of the toluidine blue stain. In almost all cases in which they encounter an unexplained leukoplakic or erythroplakic lesion, they should perform a biopsy to diagnose the patient. Toluidine blue is an adjunct to biopsy, not a replacement for it.

Histopathologic Diagnosis

Defining "epithelial dysplasia" as an entity with histologic abnormalities suggests that the lesion has a greater probability of undergoing malignant change than does normal tissue. However, histopathologic diagnosis reflects cellular changes that are visibly apparent but does not necessarily predict biologic behavior. The histomorphologic changes of epithelial dysplasia consist of the following:[18]

- Loss of basal cell polarity
- Parabasilar hyperplasia
- Increased nuclear:cytoplasmic ratio
- Drop-shaped rete ridges
- Abnormal epithelial maturation
- Increased mitotic activity
- Mitoses in the superficial half of the surface epithelium
- Cellular pleomorphism
- Nuclear hyperchromaticity
- Enlarged nucleoli
- Loss of cellular cohesiveness
- Individual cell keratinization in the spinous cell layer.

Usually, the diagnosis of epithelial dysplasia indicates that most of these factors are present; but rarely does one lesion have all of them. The histologic grade reflects the degree of involvement: mild cases of epithelial dysplasia are those in which changes are seen within the lower third of the epithelium; moderate cases, those in which at least half the epithelium is involved; and severe cases, those in which most of the epithelium is affected. Carcinoma in situ is similar in appearance to severe epithelial dysplasia, and some authorities do not attempt to distinguish between the two. Perhaps fewer than 20% of oral epithelial dysplasias are severe.[7,10,19]

Hyperkeratosis is an increased thickness of the parakeratin or orthokeratin layer of the epithelium. Interestingly, most epithelial dysplasias show parakeratinization, which might reflect cellular

immaturity. Although most solid tumors and hematologic malignancies are monoclonal in origin, in the oral mucosa it is not uncommon to histologically identify multiple foci of dysplastic change separated by normal cell fields.

Treatment

Surgical excision, which can be accomplished with a scalpel or a CO_2 laser,[20,21] is the treatment of choice for epithelial dysplasia of the oral cavity. The laser provides a relatively bloodless surgical field and in one report actually reduced recurrences.[20,21] However, to date neither technique has been shown to be better than the other in preventing recurrence. Once an incisional biopsy has established the diagnosis of epithelial dysplasia, the remainder of the lesion should be removed completely, as the probability of malignant change, although unknown, must be considered substantial.

Reported recurrence rates for premalignant lesions are as high as 34.4%.[2] One study found an 18% recurrence rate in cases of severe epithelial dysplasia or carcinoma in situ in which the lesion had been excised with a 3-5 mm margin of normal tissue.[22] Whether recurrence relates to continued exposure to risk factors or to an underlying mechanism that initiated the original lesion is unclear, but patients should be closely monitored for recurrence regardless.

The hyperkeratotic lesion is difficult to manage because it has potential for malignant change but is not yet considered dysplastic; Silverman and colleagues found that 37 out of 235 hyperkeratotic lesions (15.7%) underwent malignant change.[2] As a first step, the clinician should remove any local irritants. If after 2 weeks the hyperkeratosis is still present, excision should be considered, especially if the lesion is in a high-risk site (e.g., floor of mouth and ventral tongue) or if the patient has been exposed to established risk factors for oral cancer.

Chemoprevention

If the size of the lesion, its location, or the medical status of the patient would make surgical removal difficult, use of antioxidant supplements should be considered as “chemoprevention” to try to prevent progression to carcinoma.[23,24] Beta-carotene and the retinoids are the most commonly used antioxidant supplements for chemoprevention of oral cancer.[25] However, although antioxidant supplements have shown promise, they have an uncertain success rate and no long-term results. Still, antioxidant supplementation may be appropriate if there is recurrence after surgical excision but concern that a second excision would not prevent another recurrence. Patients with leukoplakia involving a large area of the oral mucosa might also be candidates for antioxidants, as might patients with extensive medical problems that increase their surgical risk.

Beta-carotene is a carotenoid found primarily in dark green, orange, or yellow vegetables. Several clinical trials have found that treating oral leukoplakia solely with beta-carotene supplements is associated with clinical improvement; rates have ranged from 14.8% to 71%.[26-30] No side effects have

been reported in patients given beta-carotene supplements; but there is little information about recurrence following discontinuation of this substance.

Retinoids are compounds consisting of natural forms or synthetic analogues of retinol.[31] Of the more than 1,500 synthetic analogues of vitamin A, 13-*cis*-retinoic acid (13-cRA), also known as isotretinoin or Accutane®, has generated the most interest. 13-cRA has been shown to cause temporary remission of oral leukoplakia, but it also causes side effects in a high percentage of patients. A study at M.D. Anderson Hospital in Houston followed 44 patients with oral leukoplakias who were treated with 1-2 mg/kg/day of 13-cRA for 3 months;[32] nearly 67% of the patients had more than a 50% reduction in lesion size, but 79% experienced a variety of side effects. Other studies have noted that lowering the 13-cRA dose reduced the incidence and severity of side effects, but there have been numerous reports of recurrence after discontinuation. A rise in serum triglycerides has also been reported with use of 13-cRA.

To date, no combination of antioxidants has demonstrated its clear superiority. Beta-carotene with ascorbic acid and/or alpha tocopherol is attractive because of a lack of side effects, but clinical improvement typically takes several months. 13-cRA requires a shorter time to produce a clinical response, but use of this substance necessitates baseline and periodic serologies and close monitoring for side effects; women using it must also avoid becoming pregnant.

B. Emerging Trends

Many human papillomaviruses (HPVs) are associated with papillary and verrucous lesions of skin and mucous membranes. HPV types 16 and 18 present in 90% of cervical carcinomas, and the E6 and E7 early gene products of these viruses are considered to be oncogenes, as they can transform heratinocytes in cultures.[33,34] The E6 and E7 oncoproteins are able to bind the p53 tumor suppressor protein, facilitate its degradation, and inhibit normal apoptotic pathways in these cells; the last feature may favor overproliferation.[35,36] Mutations in p53 are also found in many tumors.

Oncogenic HPVs have been identified in many oral precancerous dysplastic and squamous carcinoma tissues; HPV 16 has been localized in normal oral mucosa as well.[37-44] In an investigation of head and neck squamous cancers using polymerase chain reaction (PCR) methods, over 80% were found to harbor HPV 16.[45] Mutations in p53 are also prevalent in both precancerous and overtly malignant oral tumors.[46-48] However, both determining the role these gene products and other oncogenes play in oral cancer causation and understanding their interplay with other carcinogens such as tobacco products require further investigation.

Finally, identifying an accurate biomarker for the premalignant state would aid in diagnosis and also allow premalignancy rather than carcinoma to be an endpoint in clinical trials.[49] Discovery of a

biomarker to identify those lesions likely to progress to cancer would represent a considerable advancement in patient care.

C. Opportunities and Barriers to Progress

Research opportunities include the following:

- Validating histopathologic criteria or biomarkers that would accurately identify premalignant lesions and those with an enhanced propensity for malignant change.
- Identifying the clinical factors of premalignancy that predict a higher probability of malignant change.
- Clarifying the premalignant risk of lichen planus.
- Comparing the efficacy of conventional scalpel excision with laser excision for control of oral leukoplakias.
- Determining the value for prevention of malignant transformation of completely removing hyperkeratotic lesions.
- Establishing the role of chemoprevention in the primary and/or adjunctive treatment of oral premalignancy.
- Clarifying the role of HPV in the development of oral premalignancy and determining whether presence of the virus has prognostic significance.
- Identifying specific biomarkers such as oncogenes, tumor suppressor gene mutations, cell cycle proteins, or DNA transcription factors that could provide both useful prognostic information on oral carcinogenesis, as well as guidance on where to set margins for surgical excision.

To achieve further progress, a substantial number of suitable patients must be brought together under a unified protocol so that histopathologic, clinical, and treatment factors can be properly evaluated. At present, the small number of suitable patients are divided among numerous centers.

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ORAL CANCER BACKGROUND PAPERS

Chapter V: Early Detection, Diagnosis and Staging

Working Draft

A. State of the Science

Screening and Early Detection

Screening for oral cancer should include a thorough history and physical examination.[1,2] The clinician should visually inspect and palpate the head, neck, oral, and pharyngeal regions. This procedure involves digital palpation of neck node regions, bimanual palpation of the floor of mouth and tongue, and inspection with palpation and observation of the oral and pharyngeal mucosa with an adequate light source; mouth mirrors are essential to the examination. Forceful protraction of the tongue with gauze is necessary to visualize fully the posterior lateral tongue and tongue base.

The clinician should review the social, familial, and medical history and should document risk behaviors (tobacco and alcohol usage), a history of head and neck radiotherapy, familial history of head and neck cancer, and a personal history of cancer. Patients over 40 years of age should be considered at a higher risk for oral cancer.[3]

Diagnosis can be delayed by several months or more if the clinician treats the patient's complaints empirically with drugs instead of providing a thorough physical examination and workup. Patients with complaints lasting longer than 2-4 weeks should be referred promptly to an appropriate specialist to obtain a definitive diagnosis. If the specialist detects a persistent oral lesion, a biopsy should be performed without delay.

The many signs and symptoms of oral cancer are usually divided into early and late presentation. They can be so diverse that the differential diagnosis may not lead to oral malignancy. Table 1 summarizes the signs and symptoms.

Table 1:
Frequent Signs and Symptoms of Oral Cancer

Early	Late
Persistent red and/or white patch	Indurated area
Nonhealing ulcer	Paresthesia, dysesthesia of the tongue or lips
Progressive swelling or enlargement	Airway obstruction
Unusual surface changes	Chronic earache (chronic serous otitis media)/otalgia
Sudden tooth mobility without apparent cause	Trismus
Unusual oral bleeding or epistaxis	Dysphagia
Prolonged hoarseness	Cervical lymphadenopathy
	Persistent pain or referred pain
	Altered vision

Because patients may be at risk for developing multiple primary tumors simultaneously or in

sequence, the entire visible mucosa of the upper aerodigestive tract must be examined. In addition, lymph nodes in the head and neck area—particularly along the jugular chain—must be palpated. Approximately 90% of patients with squamous cell carcinoma in a lymph node in the neck area will have an identifiable primary tumor elsewhere, and about 10% will have cancer in the neck lymph node as an isolated finding ("unknown primary").[4] Thus, most cancers in the neck node represent a metastasis from a primary tumor located in the head and neck region; this primary site must be identified.

Toluidine blue (vital staining) also is a useful adjunct to clinical examination and biopsy.[5,6] The mechanism is based on selective binding of the dye to dysplastic or malignant cells in the oral epithelium. It may be that toluidine blue selectively stains for acidic tissue components and thus binds more readily to DNA, which is increased in neoplastic cells.

Toluidine blue has been recommended for use as a mouthwash or for direct application on suspicious lesions; its value comes from its simplicity, low cost, noninvasiveness, and accuracy (Table 2).[9] In addition, it can help to determine the most appropriate biopsy sites and to surgically delineate margins. Meta-analysis of toluidine blue staining in oral cancer screening found that its sensitivity ranged from 93.5% to 97.8%, and specificity from 73.3% to 92.9%.[7]

The disadvantages of toluidine blue include the risk of obtaining a false negative reaction in a case where the patient is not followed up adequately. In contrast, the infrequent false-positive only subjects the patient to a biopsy. No in vivo observations or reports have suggested a mutagenic effect from this stain.[8]

Table 2: Comparison of Toluidine Blue Uptake with Microscopic Diagnosis[9]

Biopsy Diagnosis	No. Lesions	Positive	Negative	Correct
Carcinoma	62	58	4	94%
Dysplasia	13	11	2	85%
Benign	94	6	88	94%
Total	169			93%

Diagnosis

Currently, the most effective way to control oral cancer is to combine early diagnosis and timely and appropriate treatment. Because more than 90% of all oral cancers are squamous cell carcinomas, the vast majority of oral cancers will be diagnosed from lesions on the mucosal surfaces.

The clinician's challenge is to differentiate cancerous lesions from a multitude of other red, white, or ulcerated lesions that also occur in the oral cavity. Most oral lesions are benign, but many have an appearance that may be confused with a malignant lesion, and some previously considered benign are now classified premalignant because they have been statistically correlated with subsequent cancerous changes.[10] Conversely, some malignant lesions seen in an early stage may be mistaken for a benign change.[11] Any oral lesion that does not regress spontaneously or respond to the usual therapeutic measures should be considered potentially malignant until histologically shown to be benign. A period of 2-3 weeks is considered an appropriate period of time to evaluate the response of a lesion to therapy before obtaining a definitive diagnosis.

A definitive diagnosis requires a biopsy of the tissue. Biopsies may be obtained using surgical scalpels or biopsy punches and typically can be performed under local anesthesia. Incisional biopsy is the removal of a representative sample of the lesion; excisional biopsy is the complete removal of the lesion, with a border of normal tissue. The clinician can obtain multiple biopsy specimens of suspicious lesions to define the extent of the primary disease and to evaluate the patient for the presence of possible synchronous second malignancies. Useful adjuncts include vital staining, exfoliative cytology, fine needle aspiration biopsy, routine dental radiographs and other plain films, and imaging with magnetic resonance imaging (MRI) or computed tomography (CT). Table 3 presents a suggested protocol for patient evaluation.

Most carcinomas of the oral cavity do not need a "panendoscopy" for definitive diagnosis. Such a procedure, which consists of direct laryngoscopy, esophagoscopy, and bronchoscopy, is usually performed as a diagnostic and staging procedure in patients with carcinoma of the oropharynx.

Imaging the Oral Cavity

A diagnostic imaging evaluation consisting of either computer tomography (CT) scanning or magnetic resonance imaging (MRI) is also used to assess the extent of local and regional tumor spread, the depth of invasion, and the extent of lymphadenopathy.[12,13] CT is superior in detecting early bone invasion and lymph node metastasis, but MRI is preferred for assessing the extent of soft tissue involvement and for providing a three-dimensional display of the tumor. MRI is also the preferred technique for imaging carcinoma of the nasopharynx or lesions involving paranasal sinuses or the skull base.

Table 3: Patient Work Up

1 - History and physical examination, including risk factor analysis and exposure to carcinogens.

2 - Head and neck examination:
- direct visualization
- mirror examination
- manual palpation
- toluidine blue staining

3 - Laboratory tests:
- CBC
- liver function

4 - Radiology:
- CT or MRI of head and neck
- chest x-ray
- dental films
- bone scan when indicated

5 - Pathology
- incisional biopsy
- excisional biopsy
- fine needle aspiration biopsy
- molecular markers
- flow cytometry

6 - "Panendoscopy:"
- define T-stage
- draw schematic tumor map
- evaluate for second malignancies

7 - Pre-therapy consultation with:
- radiation oncology
- medical oncology
- head and neck surgery
- reconstructive surgery
- dental oncology
- speech pathology
- psychosocial service

8 - Multidisciplinary Tumor Board:
- finalize staging
- formulate treatment plan

Diagnostic imaging often detects subsurface masses and intraosseous lesions. Although imaging of pathologic lesions does not produce a definite diagnosis, it frequently helps to define the extent of the

tumor. For example, patients who have an unexplained neck node and a negative head, neck, and oral examination may undergo CT scanning followed by a biopsy of the nasopharynx or base of tongue that reveals a suspicious area or tissue change.

Both CT and MRI have limitations as well as advantages, a fact that frequently makes them complementary rather than competitive studies. The advantages of CT include its rapid acquisition time (2-3 seconds per section), patient tolerance, relatively low cost, and superior osseous detail compared with MRI. However, the soft-tissue contrast resolution of CT is relatively poor, which makes it difficult to distinguish between tumor and normal muscle. CT also may require the administration of intravenous contrast material to differentiate vessels from lymph nodes, thereby increasing the risk of an allergic reaction. In addition, CT is frequently degraded by scattered artifacts because of metallic dental appliances.[14]

MRI's several advantages over CT have helped it evolve into a reliable alternative for imaging normal and pathologic head and neck anatomy. The superior soft-tissue resolution of MRI allows high-contrast differentiation between neoplasms and adjacent muscle. In addition, MRI can be obtained in multiple planes (sagittal, axial, coronal, and oblique), which is often helpful in assessing tumor volumes during and after therapy. Finally, the need for intravascular contrast administration is avoided because patent vessels have absent signal, or "signal void," within their lumen, which easily distinguishes them from surrounding soft tissue structures.

However, MRI is not without its drawbacks. Because all the images within a given MRI sequence are obtained simultaneously rather than sequentially, patient movement during an MRI is less well tolerated than with CT. In addition, although the soft-tissue contrast is superb with MRI, fine-bone detail is inferior to that obtained with CT.

Cytology

Under certain conditions, exfoliative cytology (cell scrapings) serves as an adjunct to clinical diagnosis, as it enables more extensive screening and provides microscopic material if there is a delay in or contraindication to biopsy. However, cytologic smears are used infrequently, and patients are not treated on the basis of cytologic findings alone. Smears are most helpful in differentiating inflammatory conditions, especially candidiasis, from dysplastic or neoplastic surface lesions. In addition, cytology may be helpful in detecting field change in oral cancer, especially if this method is used in conjunction with vital staining. Cytology may also be helpful when ulcerations following radiation are suspicious and biopsy is delayed.

Fine needle aspiration biopsy of subsurface masses is also an accepted diagnostic test, one that has increased in popularity over the past few years. This technique is extremely useful in evaluating clinically suspicious changes involving salivary glands and lymph nodes. It expedites diagnosis and

staging and avoids incisional or excisional biopsies that may interfere or complicate definitive treatment. When used by a skilled clinician, fine needle aspiration can often be the best way to establish a definitive diagnosis of unexplained masses of the neck or salivary glands. It is also valuable in following up cancer patients with suspicious enlargements.[15]

Staging of the Disease

The stage of the disease depends on several factors, including the size of the primary lesion, local extension, lymph node involvement, and evidence of distant metastasis. Tumor size, the organ or tissue affected, and the extent of spread are considered to be the best indicators of the patient's prognosis. Table 4 summarizes the most widely accepted staging protocol, the tumor-node-metastasis (TNM) classification of oral cancer. This system has 3 basic clinical features: the size (in centimeters) of the primary tumor; the presence, number, size, and spread (unilateral or bilateral) to the local lymph nodes; and the presence or absence of distant metastasis.

Table 4: Tumor-Node-Metastasis (TNM) Staging System for Oral Carcinoma[16]

	Primary Tumor (T)
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension
T4	(lip) Tumor invades adjacent structures (e.g., through cortical bone, tongue, skin of neck)
T4	(oral cavity) Tumor invades adjacent structures (e.g., through cortical bone, into deep [extrinsic] muscle of tongue, maxillary sinus, skin)
	Regional Lymph Nodes (N)
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greater dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in greater dimension
	Distant Metastasis (M)
MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

The individual clinical parameters in the TNM classification system are grouped to determine the appropriate disease stage (Table 5); stages are ranked numerically from 0 (which has the best prognosis) to IV (the worst prognosis). In general, oral staging classifications do not use histopathologic findings except to determine the definitive diagnosis.

Table 5: TNM Clinical Stage Grouping[16]

Stage	Tumor Size	Nodal Involvement	Distant Metastasis
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N1	M0
	T1	N1	M0
	T2	N1	M0
	Te	N0	M0
Stage IV	T4	N1	M0
	Any T	N2	M0
	Any T	N3	M0
	Any T	Any N	M1

Schematic drawings of the tumor (tumor maps) are frequently prepared to document the site and size of the tumor at the initial time of diagnosis. This initial documentation is later complemented by histopathologic findings and imaging preformed during the treatment phase.

Although the risk of distant metastasis is generally low in patients with oral cancer, there is a correlation between the incidence of distant metastasis and tumor (T) and neck (N) stage.[17] When they do occur, the most frequently involved organs are the lungs, bone, and liver. Patients with advanced T or N stages may be at risk for developing metastases outside the head and neck region; a limited workup (chest x-ray, CBC and liver function tests, bone scan) to exclude such a metastasis may be indicated.

After completion of the initial workup, the final T, N, M (metastasis), and overall stage assignment should be formally determined and documented prior to treatment. Because rehabilitation planning starts with staging and treatment, a multidisciplinary approach is essential (see Chapters VII and VIII).

Disease Progression

Oral squamous cell carcinoma spreads primarily by local extension and somewhat less often by the lymphatics. The extent of tumor invasion depends upon the anatomic site, the tumor's biologic aggressiveness, and host response factors.

The lymphatic system is the most important and frequent route of metastasis. Usually the ipsilateral cervical lymph nodes are the primary site for metastatic deposits, but occasionally contralateral or bilateral metastatic deposits are detected. The risk for lymphatic spread is greater for posterior lesions of the oral cavity, possibly because of delayed diagnosis or increased lymphatic drainage at those sites, or both. Cervical lymph nodes with metastatic deposits are firm-to-hard, nontender enlargements. Once the tumor cells perforate the nodal capsule and invade the surrounding tissue, these lymph nodes become fixed and non mobile.

Metastatic spread of tumor deposits from oral carcinoma usually occurs in an orderly pattern, beginning with the uppermost lymph nodes and spreading down the cervical chain. Because of this pattern of spread, the jugulo-digastric nodes are most prone to early metastasis. Carcinomas involving the lower lip and floor of the mouth are an exception, as they tend to spread to the submental nodes. Although lymph node metastasis is not an early event, as many as 21% of individuals with oral cancer present at diagnosis with nodal metastasis. (This proportion exceeded 50% in a study of patients evaluated at admission to cancer centers.[18])

Hematogenous spread of tumor cells is infrequent in the oral cavity but may occur because of direct vascular invasion or seeding from surgical manipulation. Perhaps 10-34% of patients present with distant metastasis; this risk increases with advanced disease.[3] Among the most common sites for distant metastasis are the lungs, liver, and bones. These patients cannot be cured and are treated with palliative intent, usually involving chemotherapy, radiotherapy, or both.[3]

Approximately 30% of patients will present initially with highly confined localized disease stages (T_1 or T_2). These patients are treated with curative intent, usually involving surgery, radiation therapy, or both. Only about 20-40% of patients will develop a local or regional tumor recurrence. However, over subsequent years, these "cured" patients appear to be at higher risk for developing a second malignancy than for developing a recurrence of their initial tumor. Tumor recurrences most often occur during the first 2 years after therapy; later recurrences are rare. Second malignancies, on the other hand, will be observed at a steady rate—perhaps 3-5% per year. Thus, with sufficient follow-up time, second malignancies or other medical diseases become greater problems than recurrence of the primary disease. The use of drug therapy to decrease the rate of second malignancies is being actively investigated.

Patients with locoregionally advanced disease (T_3, T_4, N_1, N_2, and N_3) are also treated with curative

intent. Given the advanced stage of their disease, surgery and radiation are utilized unless patients are considered inoperable or have unresectable disease. Despite this aggressive bimodality therapy, the majority of these cancers will recur within the first 2 years of follow-up, most commonly either locally or regionally. Some of these patients may have metastases outside the head and neck area, events that might be predicted by their initial T and N stages. Investigational therapy in this group of patients, therefore, must focus primarily on delivering more effective locoregional care. However, should locoregional control be improved, chemopreventive strategies will need to be pursued in this group of patients as well since, in principle, oral cancer patients are at risk for developing second primary malignancies in the oral cavity, pharynx, and respiratory and digestive tracts.

Multiple Carcinomas

Individuals with one carcinoma of the head and neck region have an increased risk of developing a second malignancy; the frequency of that event varies from 16% to 36%.[19] When a second malignancy occurs at the same time as the initial lesion, it is called a synchronous carcinoma. Metachronous neoplasms, on the other hand, are additional primary surface epithelial malignancies that develop in a later time period than the original tumor. About 40% of second malignancies of the upper aerodigestive tract arise simultaneously and represent a synchronous tumor. The remaining multiple cancers in this population represent metachronous disease and usually develop within 3 years of the initial tumor.[19] Second primary tumors are the chief cause of death in patients with an early-stage diagnosis.[20]

The tendency to develop multiple carcinomas in the upper aerodigestive region is known as "field cancerization."[21] Prolonged and diffuse exposure to local carcinogens, particularly tobacco combined with alcohol, appears to increase the malignant transformation potential of exposed epithelial cells in the upper aerodigestive tract and lungs.[22] The overall risk for developing a second head and neck malignancy is 10 to 30 times higher in populations that use tobacco and alcohol than in the general population.[23]

B. Emerging Trends

Early Detection

At the present time, the most effective approach to reducing morbidity and mortality from oral cancer is early detection. However, progress in this area requires changes in public and professional knowledge, attitudes, behaviors, and practices (see Chapter IX for a full discussion).

Diagnosis

Immunohistochemical Techniques

The use of immunohistochemical techniques to establish a definitive diagnosis has expanded during the past decade and continues to be refined. These diagnostic tests help to establish a definitive diagnosis when, by routine histopathology techniques, a lesion appears morphologically benign or its classification is in doubt. Research on the biochemical, genetic, and cellular levels should yield information that will identify high-risk groups for many types of cancer including oral cancer.

Imaging Techniques

Imaging techniques continue to improve at a rapid rate. Newer imaging techniques hold promise for clinical staging of T_2, T_3 and T_4 lesions, but T_1 lesions are typically too small to be visualized.[24] Improvements that increase definition will promote earlier detection of nasopharyngeal, submucosal, and bone lesions. One such technique appropriate for lymph nodes is positron emission tomography, which may help to define tumor activity in clinically negative areas.[25]

Biochemical and Genetic Factors

No matter which diagnostic technique is used, there is the possibility of a false-negative diagnosis. However, studies are under way to identify key markers that should improve accuracy. The development of monoclonal antibodies that have high sensitivity and specificity for epithelial dysplastic and malignant cells would enhance accuracy of diagnosis in some cases where the usual or typical cellular characteristics of precancer or cancer are not apparent. Such antibodies might also minimize errors about "tumor free" margins of surgical resections, thereby reducing a potential source for recurrence. In addition, assuming that an antibody was specific for a particular cellular tumor antigen, binding of cytotoxic chemotherapeutic agents for killing tumors and sparing normal cells would be a logical and possibly feasible follow-up to surgery and radiation therapy to improve cancer control.

Additional knowledge about various cell markers that reflect growth and suppressor protein presence or activity may also prove to be of great value in predicting cell behavior. Genetic/chromosome evaluations may serve a similar purpose in the identification and treatment of tumors.

Current research is exploring the genetics of biochemical processes that may affect the development of oral cancer. Included are gene mutations such as p53 tumor suppressor gene amplification and overexpression of proto-oncogenes c-myc, EGFR and cyclin D1, as well as loss of heterozygosity of specific chromosome loci. Cellular alteration of response to growth factor and Beta's (TGF-beta) growth suppressor effect on tumor cells may become important as well.

Clinical Photodetection

Photodynamic therapy, also known as PDT, and photodetection of cancer may be useful in the oral cavity. Two important variables that must be considered are the uptake of the dye and the dye contrast by normal and neoplastic tissue after injection.[26]

C. Opportunities and Barriers to Progress

Early Detection

The role that health care professionals who are not physicians or dentists play in oral cancer screening is poorly defined. Potential participants include dental hygienists, physician's assistants, and nurses. There has been some assessment of the role of hygienists, but very little for physician's assistants or nurses. The medical and dental professions need additional information on the most effective ways to provide early detection screening for all patients, including medically underserved populations. In addition, health care professionals need to know how to instruct patients on oral self-examination techniques. Most practitioners are aware that such instruction is reasonable and practical for breast cancer but are unaware of its role in the early detection of oral cancer.

Similarly, most of the general public is poorly informed about the risk of oral cancer and ways to prevent this disease. In a recent NIH study, only 25% of surveyed adults could identify one sign of oral cancer.[27] Much public attention is paid to the dangers of cigarette smoking, where the major emphasis is on lung cancer and cardiovascular disease, less on increased cancer risk in the upper airways and oral cavity. In recent years more information has been directed toward oral cancer risks in smokeless tobacco abusers than in cigarette smokers.

Most people have little interest in estimating their oral cancer risk based on age, sex, race, or even habits such as drinking or smoking. The portion of the public that regularly receives medical and dental care tends to assume it is routinely and adequately screened for all types of disease, including all forms of cancer. These people are generally unaware that to screen properly for oral cancer requires a head, neck, and oral examination. Thus, the failure of a primary care doctor to perform those procedures would likely go unnoticed by the average patient. Similarly, many patients are no doubt unclear as to who should be responsible for screening them for oral cancer.

Although members of the public have been informed to some degree regarding the general warning signs of cancer, they may not know the early signs of oral cancer. Not surprisingly, far too many oral cancer patients do not seek care until their tumors are advanced, which suggests that a much better job must be done of informing patients when and how to seek help.

Diagnosis

Fine needle aspiration biopsy is an accepted procedure for diagnosing many subsurface lesions such as salivary gland tumors and nodal disease. However, it is often used inappropriately; on many other occasions the clinician retrieves nondiagnostic tissue. Increased practitioner training on properly

applying the procedure and using CT scanning to guide tissue retrieval is needed.

Another problem is that many clinicians lack a clear understanding of the criteria for ordering the various types of imaging available today, many of them quite costly. Inappropriate and indiscriminate use of imaging results in millions of dollars wasted annually. In general, except for unusual and occult lesions, sophisticated imaging is not required for early detection, but it may be essential later to enhance clinical staging and treatment. Clinicians also frequently order CTs and MRIs but do not indicate the extent of anatomy essential for staging; thus, the study needs to be repeated.

Because of the well-recognized phenomenon of "field cancerization" in the head and neck region, it is important to refer patients who are diagnosed with a primary squamous cell carcinoma or epithelial dysplasia of the oral cavity for evaluation of a synchronous tumor. In addition, an annual evaluation for detection of metachronous disease should be reinforced for these patients. Such patients should be monitored routinely for high-risk behaviors, including continued tobacco and alcohol consumption, because these behaviors adversely influence survival after the occurrence of a second cancer. Finally, the use of consultations and tumor board services is essential, even in what may be deemed "early cancer."[28]

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ORAL CANCER BACKGROUND PAPERS

Chapter VI: Treatment

Working Draft

A. State of the Science

Multidisciplinary Tumor Board Concept

Patients with head and neck cancer should be evaluated before initiation of therapy by representatives of each discipline responsible for administering cancer care. Having a multidisciplinary tumor board composed of otolaryngologists, plastic surgeons, oral and maxillofacial surgeons, radiation oncologists, medical oncologists, dental oncologists, pathologists, radiologists, and allied health professionals facilitates this approach. Patients and their family members should attend this tumor board or conference.

After they review the case histories, microscopic slides, and pertinent studies from diagnostic imaging (e.g., computed tomography, magnetic resonance imaging, plain X-ray films), representatives of each discipline should examine the patient. The tumor board process is useful in establishing a correct pathologic diagnosis, determining the extent of disease, detecting other simultaneous head and neck primary cancers that might have escaped detection, and facilitating dental evaluation, which is particularly important in patients whose treatment will include irradiation, chemotherapy, or resection of oral or oropharyngeal tissues.

After examination of the patient, the board should reconvene to discuss therapeutic alternatives and to formulate a recommendation for treatment based on expected outcome (function, cosmesis, impact of treatment on lifestyle and career) and the expertise available at the treating institution. If the board believes that either the necessary expertise or technology is not available at its institution, or if the patient and family so desire, the board may recommend referral to another institution or physician. If no curative option exists, the board may recommend treatment with palliative intent. If further workup is indicated, there may be a recommendation to obtain other tests and re-present the patient's case to the board once additional information becomes available. Members of the board discuss these alternatives and recommendations with the patient and family, and in many instances, the patient and family are active participants in the decision-making process about the case. Patients are routinely advised to discontinue use of all tobacco products and alcohol.

Secondary benefits that accrue to patients and physicians from a multidisciplinary tumor board include the efficiency of: having multiple consultations by a number of specialists in a short period of time without having the patient travel from one office to the next; avoiding delays in obtaining consultative appointments; providing patient, family, and physician education; and assuring that the most appropriate therapy is applied first (as opposed to the commonplace situation in which the first practitioner to evaluate the patient provides the treatment as well).

Treatment Selection for the Primary Site: General Principles

Surgery or radiotherapy is curative for most early carcinomas of the oral cavity and oropharynx; cure rates for the two modalities are similar. Chemotherapy is not curative and is used only as an adjunct. Selection of the treatment modality must be based on factors such as functional outcome, cost, length of treatment, risk of complications, the patient's general medical condition, and patient preference. Choices are also influenced by clinicians' skills, experience and philosophies, and by available facilities.

More advanced lesions typically require combined radiotherapy and surgery to obtain optimal cure rates. In the past, preoperative radiotherapy of the primary site was common, but in recent years most centers have preferred to use postoperative radiotherapy, primarily because surgical complication rates are lower if irradiation is withheld until then. Postoperative radiotherapy is also used when the primary surgical specimen is found to have vascular or perineural invasion or close surgical margins.

Management of the Neck: General Principles

The incidence of cervical nodal metastases for each oral primary site increases with increasing local stage of disease. The patient with no neck disease or very early stage positive neck disease (N1) may be treated electively by radiotherapy or neck dissection. Because cure rates are the same, the neck is generally treated with the same modality selected for the primary site. If the risk of lymph node metastases is believed to be less than 15%, the clinician may simply observe the neck for the occurrence of metastases.

More advanced neck disease generally requires combined treatment for optimal regional disease control. Combined therapy is essential if there is extranodal spread of cancer or multiple positive nodes are identified. If surgery was used to treat the primary site, postoperative radiotherapy is appropriate. The only exceptions are when the nodal mass is fixed to the carotid artery or the cervical fascia; then preoperative radiotherapy is given. When radiotherapy is selected for the primary tumor, the neck dissection is generally performed 4-6 weeks after radiotherapy has been completed.

Oral Cavity

Most centers advocate surgical excision for early-stage primary disease (T1-T2) of the lip, floor of mouth, oral tongue, alveolar ridge, retromolar trigone, hard palate, or buccal mucosa. The CO_2 laser may also be used as a cutting tool in removing oral cavity cancers.[1] In addition, this laser may be useful in removing dysplastic lesions without scarring the area significantly. However, clinicians must still observe the patient closely after the lesions are removed, as there is a significant likelihood of recurrence.

Although radiotherapy may work as well as surgery for early malignant lesions in several of these

subsites, such as the floor of mouth, concern about complication rates has made surgery the choice for most of these lesions. However, more advanced primary tumors in any of these sites typically require a combination of surgery and radiotherapy. Advanced primary tumors adjacent to the mandible may require a rim mandibulectomy, and those tumors that frankly invade the mandible are treated with a segmental mandibulectomy. The plan for surgical resection must also include reconstructive options; reconstructive teams composed of head and neck surgeons, oral surgeons, and prosthodontists are most successful at achieving the best functional and cosmetic result. (Chapter VIII contains a full discussion of reconstruction and rehabilitation.)

Most radiotherapy for carcinoma of the oral cavity uses an interstitial implant either alone or combined with external beam. For carcinoma of the oral tongue and buccal mucosa, the results of an interstitial implant alone or combined with external beam radiotherapy are generally better than those achieved with external beam radiotherapy alone.

Recurrence rates vary by primary site and increase with increasing primary stage. For lesions on the floor of the mouth, 5-year cause-specific survival rates by stage are as follows: I: 90%, II: 80%, III: 70%, favorable IV: 40-50%, and unfavorable IV: 20%. Five-year cause-specific survival rates for oral tongue cancers by stage approximate the following: I and II: 70-80%, III: 40%, and IV: 15-20%.[2]

Oropharynx

The main goals in treating patients with oropharyngeal cancer are achieving a cure and preserving both speech and swallowing functions. Although some institutions favor surgery[3] alone or in combination with radiotherapy, a review of the literature showed no definite advantage for surgery over radiotherapy in either tumor control or survival;[4] surgery has the added disadvantage of causing losses (e.g., of velopharyngeal competency, of tongue musculature or tongue mobility, of all or part of the mandible, or of the larynx) that are not always fully compensated by reconstructive procedures. Thus, in a great many institutions, treatment consists of radiotherapy to the primary site, with or without subsequent neck dissection.

Base of Tongue

Because it responds strongly to irradiation, frequently metastasizes to the lymph nodes, and has poorly differentiated histology, carcinoma of the base of the tongue is usually treated by radiotherapy. Surgery for more advanced lesions usually results in a loss of major organ function. However, there remains disagreement about the optimal radiotherapy technique; similar results have been obtained by external beam irradiation followed by an interstitial implant boost and by external beam irradiation alone.[5] Local control rates are 90% for stage T1, 78% for T2, 79% for T3, and 47% for T4 lesions treated by external beam alone; and 88%, 70%, 74%, and 70%, respectively, for external beam plus interstitial implant.[3,6]

Extended supraglottic laryngectomy may be used for limited, lateralized vallecular lesions only if one lingual artery can be preserved and the patient is in good medical condition. If the glossectomy is extensive or a total glossectomy is required, a total laryngectomy is also usually necessary to prevent aspiration. Because of the risk of bilateral neck node metastasis, consideration should be given to bilateral neck dissections or postoperative radiotherapy if there are no clinically positive lymph node metastases.

Tonsillar Region

Occasional, discrete, superficial lesions of the anterior tonsillar pillar can be managed by wide local excision. More advanced tumors usually require resection of the tonsillar region (which includes the fossa and pillars), part of the soft palate, and frequently part of the tongue; a segmental mandibular resection; and a neck dissection.

Radiotherapy for tonsillar region cancers is highly successful for early and moderately advanced disease. Treatment is given by parallel-opposed portals or, in patients with well-lateralized tumors, by either a wedged-pair technique or a mixture of high-energy electrons and photons so that the contralateral salivary tissue is spared. An interstitial (cesium or iridium) boost dose is sometimes administered when the primary cancer invades the tongue. For tonsillar pillar primaries, treatment can be initiated with an intraoral cone using orthovoltage x-rays or electrons as a “reverse boost” to the primary. External beam radiotherapy is then directed to a more generous field encompassing the primary tumor and the regional lymph nodes. The intraoral cone technique allows administration of a high radiation dose confined to a limited volume of tissue—a technique that not only improves the control rate but also reduces the risk of serious late radiation injury.

The overall rate of tumor control at the primary site for early (T1-T2) tonsillar fossa primaries is 95%, compared with 70% for T1-T2 tonsillar pillar primaries. T3 tumors at either site are controlled approximately 70% of the time, and T4 lesions have a 40-50% chance of local control.[7] Treatment of tonsillar pillar cancers should be intensified with intraoral cone or implant therapy or other suitable approach.

Conventional standard fractionated radiotherapy consists of 1.8-2.0 Gy per fraction, once a day, 5 days per week, for a total weekly dose of 70-75 Gy. However, hyperfractionated and accelerated fractionated radiotherapy employing using smaller doses per fraction, twice a day, 5 days per week, has recently been used in the treatment of head and neck cancer. A randomized trial by the European Organization of Research on Treatment of Cancer (EORTC) showed improved local control using hyperfractionated radiotherapy compared with conventional fractionated radiotherapy for stage II and III oropharyngeal carcinoma. The survival was also better for the hyperfractionation arm, although the difference was not statistically different.[8]

Hyperfractionation has been used at the University of Florida,[7,9] split-course accelerated fractionation at the Massachusetts General Hospital,[10] and accelerated fractionation with a concomitant boost

technique at the M.D. Anderson Cancer Center.[11] In contrast to the EORTC trial, University of Florida results showed no significant improvement in local control of carcinoma of the oropharynx by hyperfractionated radiotherapy compared with that achieved for historical controls treated by conventional fractionated radiotherapy.[9] However, Massachusetts General Hospital and M.D. Anderson Cancer Center results suggest improved local control with the regimens used at those institutions compared with historical controls treated with conventional fractionation.[10,11] The results of hyperfractionated or accelerated fractionated radiotherapy may depend on primary site and stage. The Radiation Therapy Oncology Group (RTOG) is investigating through a Phase III randomized trial the relative efficacy of standard fractionation, hyperfractionation, and the two variants of accelerated fractionation in the radiotherapy of stage III and IV carcinoma of the oral cavity, oropharynx, supraglottic larynx, and hypopharynx.

Five-year survival is achieved in 50-55% of patients with early or moderately advanced (stages I, II, III) cancer of the tonsillar region and in approximately one-third of patients with stage IV disease.[7]

Soft Palate

Small, well-defined lesions of the soft palate may be excised, but because these lesions are multifocal, recurrence of soft palate tissues at the margin will likely occur unless patients are carefully selected. Radiotherapy is commonly used because it leaves the patient functionally intact with no need for a prosthesis or elaborate reconstruction.

Morbidity associated with surgery is minimal if the full thickness of the palate is not removed. Moderate-sized through-and-through defects are usually closed with local flaps, although velopharyngeal incompetence is a potential hazard with this approach. If a major resection is required, a prosthesis is necessary.

The basic radiotherapy technique for soft palate cancer involves parallel-opposed portals to the primary site and neck. If the lesion is located very much to one side of the mouth, it can sometimes be treated with a single ipsilateral portal arrangement or other field arrangements using 3-D treatment planning, so that contralateral salivary tissue is spared. Often the initial 15-20 Gy is administered via an intraoral cone as a reverse boost to limit the volume of tissues receiving high-dose radiotherapy.

Local control with radiotherapy is achieved in approximately 85% of T1, 75% of T2, 60% of T3, and 20% of T4 tumors.[9] Five-year survival rates of about 80% are achieved for stage I-II cancers; stage III-IV patients have 5-year survival rates of about 30-40%.

Chemotherapy

Although improvements in radiation therapy and surgery have led to modest improvements in survival and relapse-free survival rates, there is still considerable room for improvement, particularly for

patients with advanced-stage disease. Chemotherapy has been used in attempts to improve survival or to reduce the incidence of distant metastases, to serve as an adjunct to radiotherapy for organ preservation, and to select patients for subsequent therapy based on their response to chemotherapy. However, how much chemotherapy actually contributes to achieving these goals remains controversial.

Chemotherapy has been applied as induction (so-called neoadjuvant therapy), concurrently with radiotherapy and as post-treatment adjuvant therapy. Neoadjuvant therapy has been widely studied in recent years; a number of drug regimens have been used. The combination of cisplatin and fluorouracil (5-FU) has achieved considerable popularity because of high rates of response with acceptable rates of toxicity. In previously untreated patients, response rates of 60-90% have been reported—with a complete clinical response in 20-40% of patients.[12] (Patients who experience a complete clinical response have a favorable prognosis compared with patients having partial or no response.) Unfortunately, randomized studies have shown no significant impact on survival rates.[12,13]

Concomitant chemotherapy and radiotherapy has been used to try to increase the rate of local-regional control, on the theory that these might be either an additive or synergistic interaction between the two treatments. Both single and multiagent chemotherapy have been used. Several randomized trials have shown an improvement in local-regional control and disease-free survival with concurrent single-agent chemotherapy and radiotherapy compared with radiotherapy alone.[12] Unfortunately, the toxicity of concurrent multiagent chemotherapy and radiotherapy is significant.

Adjuvant chemotherapy, given after radiation or surgery, has received less attention, mostly because patients are reluctant to continue prolonged treatment after extensive, sometimes debilitating local-regional therapy. Results have generally been discouraging.

B. Emerging Trends

Immunologic response modifiers such as alpha interferon and interleukin have been used in combination with other therapies to boost the patient's own immune response against oral carcinoma. In addition, monoclonal antibodies to an individual tumor are being used in an attempt to image the lesion better and to deliver specific toxic substances, including radiolabeled substances, directly to the tumor. Efforts continue to develop antibodies capable of reaching the entire tumor cell population while avoiding systemic toxicity.

Twice-a-day radiotherapy is being used increasingly in a variety of head and neck sites to improve

outcomes. However, the relative efficacy of twice-a-day hyperfractionated or accelerated fractionated radiotherapy compared with conventional fractionated radiotherapy for the various head and neck primary sites other than stage II and III oral carcinoma (excluding base of tongue) remains to be established by ongoing randomized clinical trials. Another new technique, stereotactic radiosurgery, is being considered in patients for whom radiotherapy or surgery (or both) has failed.

Tumor markers, such as oncogene and tumor suppressor mutations and specific allelic losses in the genome of a carcinoma, are being investigated to determine the relationship of such molecular alterations to clinical outcome. The development of such markers would allow treatment to be more properly tailored to the individual tumor. To date, however, no specific marker has been identified that correlates for all sites with tumor response to treatment.

Gene therapy has been used to treat other tumors, particularly hematologic tumors. In this approach, investigators or clinicians try to introduce new molecular material into human cells. They may be trying to alter the tumor's immunogenicity, activate the host response, modulate the tumor's sensitivity to chemotherapy or radiotherapy, insert tumor suppressor genes, inhibit oncogenes, prevent malignant transformation, or introduce lethal genes. Despite a number of potential obstacles, there may be a future for gene therapy in the treatment of squamous cell carcinoma of the head and neck.

In surgical therapy, the use of microvascular free flaps permits resection of larger areas because of the ease of reconstructing such defects; suitable soft tissue or bone can be moved from a variety of different sites to fill the defect. For example, fibular reconstruction at the time of mandibular resection has improved rehabilitation in some patients. Neural reanastomoses are attempted to try to improve swallowing after free flap reconstruction. The advent of osseointegrated dental implants as part of the reconstructive technique has allowed for more aggressive tumor removal, since oral rehabilitation is now more feasible.

C. Opportunities and Barriers to Progress

Initial Diagnostic Steps

One frequent misunderstanding about the treatment of patients with carcinomas of the oral cavity concerns the first diagnostic steps. Initially, only an incisional biopsy of the primary lesion should be performed, not an excisional biopsy. Inadequate excisional biopsies only cause confusion about the initial extent of the tumor and add an unnecessary procedure. Of greater concern is that excisional neck node biopsies are frequently used to establish a diagnosis of head and neck carcinoma. A physical examination combined with imaging of the mucosa of the upper aerodigestive tract will

usually reveal the source of suspicious adenopathy. If the relationship of lymphadenopathy to primary oral cavity tumors remains uncertain, a fine needle aspiration biopsy will almost always provide a tissue diagnosis from the lymph node. Removing a lymph node during diagnosis complicates management, as radiotherapy then must be the next treatment step to have the usual chance of a successful outcome.

Imaging

Successful treatment depends on precise delineation of tumor extent. Computed tomography (CT) and magnetic resonance imaging (MRI) are both useful. Unfortunately, these technologies require strict physician monitoring if optimal images are to be obtained. All too often, the techniques used for CT, the manner in which intravenous contrast was utilized for this modality, or poor patient positioning limits the clinician's ability to obtain useful diagnostic information. In many cases, carelessly performed studies have to be repeated at additional cost, inconvenience, and sometimes additional risk to the patient.

New imaging techniques such as positron emission tomography (PET), single photon emission computed tomography (SPECT) scanning, and imaging with fluorodeoxyglucose (FDG) may help to diagnose new cancers and detect tumor recurrences.[14] Both the scarcity and expense of the equipment are problems, but early results look promising. However, confirmatory data are needed.

Radiation Therapy

Not all cancers need the same type of fractionation schedule; already the groundwork has been laid for new fractionation methods. Hyperfractionated radiotherapy[8] and accelerated fractionated radiotherapy[10,11] may offer better local-regional control for some primary sites and stages of head and neck cancer; their relative efficacy is currently being investigated in randomized clinical trials. Cell kinetic parameters may help determine the best means of fractionating treatment in the individual patient.[15] Improved tumor control and reduced long-term morbidity are the goals.

New treatment planning and delivery systems in radiation therapy using 3-dimensional computer treatment planning programs and computer-driven multi-leaf collimator systems can provide better confirmation of the high-dose radiation volume to the tumor while sparing normal structures. More widespread availability of these technologies can be anticipated in the very near future. Major barriers to their widespread use are that they are very time- and labor-intensive, require sophisticated computer programming capabilities, and are expensive.

Chemotherapy

Chemotherapy has been shown to have positive effect in squamous cell carcinomas of the head and

neck. There appears to be an opportunity to integrate chemotherapy into therapeutic strategies, although there is an issue of how it should be timed in relation to other therapies (surgery or radiation therapy). However, the benefits of chemotherapy should not be measured only by survival, but also by organ preservation and quality of life. Continued support for randomized trials and new drug discovery and development is essential.

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ORAL CANCER BACKGROUND PAPERS

Chapter VII: Sequelae of Treatment

Working Draft

Introduction

Administration of cancer therapy is designed to eliminate or reduce tumor burden. A number of variables, including tumor cell kinetics, site of the tumor, and extent of tissue involvement affect outcome of such treatment. Depending on these and related variables, single or multi-modality therapy may be indicated. Principal forms of therapy include ionizing radiation, surgery, and chemotherapy.

Depending on the extent of the tumor, treatments may not be specific to the tumor; if they are not, normal tissue included within the surgical wound or rapidly replicating normal tissues can be profoundly affected. Injury can be either reversible or irreversible. Because oral epithelium is highly active tissue with replacement times estimated at 9-16 days, chemotherapy and radiation may be directly toxic to the oral mucosa, resulting in dysgeusia, extensive ulceration, pain, bleeding, and compromised normal function.[1,2] The dental/periapical, periodontal, or salivary gland tissues may suffer acute injury. Radiotherapy can cause both serious destruction to bone and permanent salivary gland disturbances.[3-5] Because the sequelae associated with cancer therapy may have a profound psychosocial impact on the patient, a multidisciplinary team approach that reviews all aspects of patient care is necessary.

A. State of the Science

Complications of therapy depend on the cancer treatment protocol of choice. Table 1 offers a selected list of oral sequelae associated with therapy.

Surgical Risks and Complications

Surgical management of intraoral lesions typically includes both the primary lesion and the cervical lymph nodes. Ideally, surgery is selected when permanent control of the tumor is likely. Staging of the patient is essential to determine whether surgery alone is indicated or whether radiation or chemotherapy is also needed.

The risks and sequelae of surgery develop directly from and are primarily based on the extent of the tumor and its relationship to contiguous oral structures. Sequelae may include disfigurement and compromise of vascularity and nerve tissue as well as gustatory, masticatory, speech, and swallowing functions (see Chapter VIII).

Table 1:
Selected List of Oral Sequelae Related to Treatment

Surgery: Acute Sequelae	**Ionizing Radiation: Chronic Sequelae**
functional disturbances	salivary gland pathoses
speaking	acute parotitis
mastication	irreversible changes (flow rates, compositional alterations)
swallowing	dental alterations
vascular compromise	rampant caries
	demineralization
Surgery: Chronic Sequelae	osteoradionecrosis
cosmetic alterations	dysgeusia
functional disturbances	trismus
speaking	laryngeal alterations
mastication	
swallowing	**Chemotherapy**
vascular compromise	oral mucositis
nerve damage	dysgeusia
muscular atrophy	immune dysfunction
	dentition
Ionizing Radiation: Acute Sequelae	infections
salivary gland pathoses	mucosa
acute parotitis	periodontium
irreversible changes (flow rates, compositional alterations)	hemorrhage
oral mucositis	salivary dysfunction (variable)
infections	
mucosa	
periodontium	
dysgeusia	

Risks and Sequelae of Radiation or Chemotherapy

Mucositis and Infection

Mucositis can be caused by either radiation or chemotherapy; the severity and extent of lesions are correlated with the treatment protocol being administered. Radiation-induced mucositis depends on absorbed radiation dose, fractionation, delivery modality, and soft tissue status. The patient may feel a mucosal "burning" sensation 1-2 weeks after initiation of therapy; the mucosa may be edematous and leukoplakic or erythematous on clinical examination. Depending on the intensity of the therapy and patient variables, extensive ulcerations may develop following initial clinical signs and symptoms. With chemotherapy, outcomes are specifically related to the pharmacologic class of drug selected as well as its dose concentration and the extent of neutrophil depletion or leukopenia.

Strategies for preventing mucositis are limited, but the problem can be partially minimized by fractionation techniques, shielding, and modifying modes of delivery. Supportive care for the acute

components of mucositis (bleeding, pain, and infection) is the mainstay of treatment. Although not directed principally at preventing mucositis, comprehensive oral care, including mechanical plaque removal supplemented by an antimicrobial rinse if indicated and frequent rinsing with saline bicarbonate solutions, can reduce the severity of secondary complications. Topical anesthetics or systemic analgesics are administered frequently for palliation of pain. Smoking can exacerbate mucositis; patients should be assisted with cessation using nicotine replacement therapy if indicated.[6]

Candidiasis is the most common oral infection during treatment for oral cancer, although other mycotic, bacterial, or viral infections are possible. Prophylactic or therapeutic topical and/or systemic antifungal agents are necessary to control candidiasis. Selection of an antifungal agent must consider the patient's degree of xerostomia and possible inability to dissolve a troche. Also of concern is the patient's level of oral hygiene and the risk associated with high levels of sucrose in topical preparations. The addition of chemotherapy to the treatment protocol may increase the severity of mucositis, xerostomia, and infection; it also increases the risk of bacterial and herpetic infections.

Because of the high probability of mucositis and infection, their potential severity, and their nutritional consequences, the radiation or chemotherapy patient needs comprehensive management protocols, particularly during periods of highest infection risk. Some cancer centers prescribe a "cocktail" preparation of antimicrobials, a steroid, a coating agent, and a topical anesthetic. However, the effectiveness of such preparations is empirically based and needs to be examined in a well-controlled clinical study.

Salivary Gland Dysfunction

Directing radiation therapy to the salivary glands or administering chemotherapeutic, antiemetic, or psychotropic drugs may alter salivary gland function. Chemotherapy does not typically cause chronic salivary gland changes; in contrast, high-dose ionizing radiation delivered to major glandular sites can cause permanent salivary gland dysfunction. The degree of oral dryness (xerostomia) will vary by the extent of salivary gland injury. These changes can exacerbate oral infection risk at various sites, including the mucosa and periodontium. Xerostomia may also affect mastication, speech, and the patient's overall quality of life.

Unfortunately, there are few effective preventive or palliative interventions for xerostomia. Frequent oral rinses with water or saline and commercial saliva substitutes may be minimally helpful, as may salivary stimulants such as sugarless candies and gum. Currently, no saliva substitute exists that can adequately replace the organic and biologic constituents of saliva. However, two studies[7-9] that examined the effectiveness of oral pilocarpine as a sialogogue in irradiated patients with residual functional salivary gland tissue demonstrated its efficacy and safety; pilocarpine is now approved by the FDA for treating hyposalivation. However, the practitioner must be aware of its potential side effects and contraindications.

Symptoms of dry mouth do not necessarily correlate with quantitative or qualitative changes in saliva.

Some patients receiving high-dose radiotherapy to major salivary glands may experience reduced saliva production but perceive an improvement in function over time after cessation of therapy. Despite improvement in symptoms, however, saliva production in these patients may continue to be impaired, with reduced levels of antimicrobial proteins secreted.[10,11] Thus, these patients will be at high risk for aggressive caries formation, demineralization, and periodontal disease for the balance of their lives. In addition, because mucous secretions from minor salivary glands are often unaffected, patients frequently complain of thick, ropey saliva. Comprehensive long-term preventive oral hygiene and dental follow-up are needed.[12,13]

Dysgeusia

Both chemotherapy and radiation therapy patients can experience disturbances in taste. Mechanisms for this sensory disturbance are often complex and range from direct molecular effects on acinar cell function to conditioned aversions to selected foods. Compositional and/or flow rate changes in saliva may also contribute to the symptom, although underlying mechanisms are not clearly established.

Direct chemotherapy or radiotherapy injury to taste buds may produce partial (hypogeusia) or absolute (ageusia) taste loss. Taste buds may regenerate about 4 months after cessation of therapy, and normal taste function may resume. Given the complex interplay between physico-chemical and psychologic alterations, however, this recovery may not occur. Patients should be counseled as to realistic outcomes and give ongoing dietary consultation as well as programs to resolve food aversions that may have emerged during cancer therapy.[14] High-dose zinc supplementation has helped some patients.

Nutritional Complications

Radiation, chemotherapy, or surgery can impair nutrition through a variety of mechanisms.[15] Maintenance of appropriate levels of nutritional support is essential; indeed, many cancer patients are underweight at diagnosis and lose weight during therapy.

Nutritional complications stem from altered taste sensations, ageusia, anorexia, food aversion, pain, xerostomia, and dysphagia. Inadequate intake of calories leads to weight loss, weakness, and malaise.[16] Tumor factors responsible for anorexia include direct tumor utilization of metabolites. Release by the tumor of chemical moieties that produce protein loss and negative nitrogen balance has also been hypothesized to contribute to cachexia.

Finally, nutritional complications may be caused by lack of access to appropriate reconstructive techniques and rehabilitation, leaving the patient without complete masticatory restoration.

Dental Caries and Periodontal Disease

Patients receiving adjuvant chemotherapy for management of disseminated oral cancer are not typically at high risk for chemotherapy-induced progressive compromise of the dentition and periodontium. However, the compliance of such patients with oral hygiene protocols and nutrition

guidelines may be deficient. Such limitations can produce extensive oral disease patterns.

Patients whose major and minor salivary glands have been exposed to therapeutic doses of ionizing radiation are at significant risk for progression of oral infections and demineralization, even if routine oral management strategies are utilized. Several covariates, including salivary function, nutrition, medications, parafunctional habits, tobacco habits, and compliance with comprehensive oral care protocols that include remineralizing solutions and fluoride use, collectively interact and produce either a stable or regressive oral disease profile. These diseases are caused by infecting pathogens, with consequences that include hard or soft oral tissue destruction, pain and bleeding, and systemic sequelae consistent with infection progression.

Osteoradionecrosis

Ionizing radiation can lead to osteoradionecrosis (ORN), a complication that results from compromised vascularity following surgery or from radiation-induced hypovascularity, as well as from cytotoxic effects on bone-forming cells and tissue, hypocellularity, and hypoxia of affected bone.[17-21] The risk of ORN increases over time following completion of radiation dosing and is present through the lifespan. Complications associated with ORN include intractable pain, drug dependency, pathologic fractures, oral and cutaneous fistulas, and loss of large areas of bone and soft tissue.[22]

The incidence of ORN is quite variable and depends mostly on the aggressiveness of radiation therapy; reported incidence ranges from 2% to 40%.[17] Although trauma (e.g., dental extraction or scaling, denture irritation, periodontal disease) can initiate ORN, the etiologies of many cases are not identified. Managed unsuccessfully, ORN can have serious consequences, including progressive pain, trismus, and, eventually, loss of major segments of the jaw bone.

Ideal management of ORN calls for eliminating potentially riskful foci of oral disease prior to instituting radiation therapy. This approach requires a multidisciplinary team, which conducts comprehensive treatment planning well in advance of the cancer therapy. (See Table 2 for a list of evaluation and management issues.) Intact teeth can be preserved under certain conditions, such as when the patient is highly motivated toward maintaining ideal oral health and receiving comprehensive dental care. Conversely, compromised teeth in the poorly compliant patient should be extracted at least 10 days prior to radiation. However, the patient's disease state may change the timing of extraction.[23] Realistic clinical judgment combined with comprehensive management is the best tool for preventing osteoradionecrosis.

Table 2: Evaluation and Management Issues
Prior to Surgery and Radiotherapy

extraoral head and neck exam
complete intraoral exam
proposed surgical defects
radiographic evaluation
oral hygiene
previous dental or oral hygiene compliance
status of dentition and periodontium
temporomandibular dysfunction
parafunctional habits
baseline salivary flow
diet and medication analysis
tobacco and alcohol habits
psychosocial impact of treatment

Management of ORN with antibiotics and surgical debridement is not always successful. Courses of hyperbaric oxygen to facilitate healing of compromised bone may be helpful when combined with appropriate surgery and antibiotics. However, because this treatment is expensive and offered by only a limited number of facilities, many patients will not be able to take advantage of it.

Trismus Alterations

Ionizing radiation can also cause obliterative endoarteritis with associated tissue ischemia and fibrosis. This process can contribute to development of trismus if the masticatory muscles are within the portals of radiation. As treatment of trismus can be very difficult, preventive management with jaw exercises using tongue blades and other devices is recommended when signs of this disorder occur.

Psychosocial Impact

Functional and aesthetic changes may profoundly affect a patient's psychic and social status. The clinician should give these factors serious consideration in pre-treatment consultation and post-operative rehabilitation. Failure to do so may have critical consequences for the patient's later quality of life in socioeconomic areas as well as in personal relationships and lifestyles.[24]

B. Emerging Trends

A number of emerging trends in the management of head and neck cancer may directly affect complications of therapy by altering treatment approaches in ways that will selectively protect normally functioning tissues. To assure effetive use of new approaches, organizations such as the American Cancer Society (ACS) have for years promulgated the principle of multidisciplinary care for the cancer patient, including those with head and neck malignancies (see the discussion of

treatment and the multidisciplinary tumor board concept in Chapter VI).

C. Opportunities and Barriers to Progress

There are several approaches to improving the management of patients with oral cancer, including professional and public education, increased multidisciplinary management, and applied and laboratory-based research. However, the current situation is not promising because of:

- limited attention in medical, dental, dental hygiene, and nursing curricula to the oral complications of cancer therapy
- limited patient education about the need to comply with preventive or therapeutic oral interventions
- declining availability of both public and private research funding
- lack of trained basic and applied research directed specifically at management of oral complications.

Currently, there is a great need to develop tools to assess and prevent oral mucositis. Over the past 5 years, the standard for oral mucosa assessment tools has changed from a simplified, global scale to a more complex scale that assesses changes in multiple qualities of oral status that collectively contribute to mucositis severity. Future research must be directed to developing instruments that: (1) eliminate subjectivity in assessing and classifying oral complications; (2) measure oral toxicities with high degrees of specificity and sensitivity relative to the pathologic process under investigation; (3) take little time and are cost-effective to administer; and (4) can be tolerated by the patient with severe mucositis. Such instruments are essential to assess whether new technologies can reduce the severity of radiation- or chemotherapy-induced mucositis.

At present, clinical studies are needed to develop mechanisms for increasing patient compliance with recommended long-term care and preventive measures. The effect that cultural, sociologic, and psychologic factors have on compliance also needs investigation (see Chapter IX).

Current deficits in professional knowledge frequently stem from a failure to understand that communication between the medical and dental teams is essential. Although some cancer centers have integrated medical, nursing, dental, and dental hygiene management of the patient, a number of university-based and most community-based oncology programs have not done so. Yet, the complex management of the oral cancer patient mandates multidisciplinary care; unless the relevant professional groups communicate successfully, patient care may suffer.

More research on managing the patient with mucositis and xerostomia is also needed. Protocols to manage mucositis should be tested in clinical studies. Additional research is also needed on slow-release techniques for the drug oral pilocarpine that might minimize its side effects while maximizing its therapeutic effect.

Long-term studies are also needed to evaluate reconstructive techniques, including their effect on dental function, to prevent nutritional complications and ensure full rehabilitation (see Chapter VIII).

Finally, outcome assessments are necessary to evaluate the impact of treatment and non-treatment on long-term results and quality of life. Information from these assessments will be useful in allocating research dollars and establishing protocols for care.

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ORAL CANCER BACKGROUND PAPERS

Chapter VIII: Functional Rehabilitation

Working Draft

Introduction

The cosmetic, functional, and psychosocial results of oral cancer treatment may combine to produce devastating effects on patients, especially if the tumor is extensive or the treatment particularly aggressive. Indeed, oral cancer is noted for the toll it exacts from patients, from both the disease itself and the effects of its treatment. A variety of functions can be affected, including speech, deglutition, management of oral secretions, and mastication. Thus, maxillofacial prosthetic rehabilitation is a cornerstone of efforts to restore the head and neck cancer patient's oral functions and cosmesis following surgery to pre-treatment baselines.

Each year a proportion of new head and neck cancer patients will require maxillofacial prosthetic intervention. Most of these patients will be rehabilitated at major teaching institutions or designated cancer centers that include a multidisciplinary team. Perhaps half of new patients will be treated with definitive radiation without surgical intervention, but these patients also will require dental intervention (see Chapter VII) and follow-up throughout their lifetime. Thus, multidisciplinary teams are essential for head and neck cancer patients, especially as their treatment may result in loss of oral functions and cosmetic deformities.

With recent changes in the modalities of cancer treatment and reconstruction (e.g., the introduction of brachytherapy and microvascular free flap transfers), rehabilitation of the oral tissues takes on a new dimension. Conventional maxillofacial prosthetic rehabilitation usually will not be enough to restore the resultant hard or soft tissue defects. Thus, a multidisciplinary surgical team that includes dentists will increasingly be instrumental in the reconstruction of head and neck patients. The ultimate goal of rehabilitation, however, will remain the restoration of oral functions and cosmesis with the aim of providing an acceptable quality of life.

Successful rehabilitation and quality of life go hand in hand. Because patients vary in attitudes and adaptation, it is very difficult to predict the patient's eventual quality of life prior to initiating treatment for an oral tumor. Furthermore, the use of newer techniques at surgical reconstruction makes the maxillofacial prosthodontist's task even more challenging. It is important for the dental team to be experienced and to identify for the medical and surgical oncologists realistic goals and objectives for rehabilitation. At major cancer centers with rehabilitative teaching programs, it is not uncommon for the surgically resected head and neck patient to require 20-25 appointments for appropriate rehabilitative care in a 1-year period.

With multidisciplinary cancer therapy (ablative surgery, reconstructive surgery, radiation therapy, and/or chemotherapy) available, rehabilitative dentistry is essential for improving quality of life. Treatment plans for rehabilitative dentistry should be included in the overall cancer treatment plan; in many instances, the sequelae of ablative head and neck surgery and radiation therapy could be alleviated, minimized, or even eliminated altogether if there were appropriate planning for

maxillofacial prosthetic and other dental interventions before treatment begins.

A. State of the Science

The strategy and techniques of rehabilitation of a head and neck cancer patient are directly related to the location of the cancer and to the extent and type of surgical intervention and radiation modalities used. Oral carcinomas not detected and evaluated in their early clinical stages usually invade contiguous structures, thereby setting the stage for extensive surgical procedures that are generally followed by radiation therapy.

Removal of extensive segments of the tongue, floor of mouth, mandible, and hard and soft palate as well as the regional lymphatics usually mandates extensive rehabilitative management.[1,2] Generally, maxillofacial prosthodontists restore maxillary resections with obturator prostheses. However, in many instances a soft palate speech bulb-obturator retained in the maxillae (for restoration of velopharyngeal function) or a palatal augmentation prosthesis (if tongue function is lost) is required for optimal rehabilitation. Currently, rehabilitation of a maxillectomy and/or soft palate defect via an obturator prosthesis is most effective in restoring function. Recent advances in microsvascular free flap tissue transfers have been used successfully to reconstruct composite defects of the mandible, buccal mucosa, and tongue.[3]

Current rehabilitative practice is centered in five principles:[4,5]

1. The process of rehabilitation begins at time of initial diagnosis and treatment planning.
2. The dentition should be preserved if possible.
3. Rehabilitative treatment plans should be based on fundamental principles of prosthodontics, including a philosophy of preventive dentistry and conservative restorative dentistry.
4. Surgery before prosthetic rehabilitation may be indicated to improve the existing anatomic configuration after ablative cancer surgery, reconstructive surgery, and/or radiation therapy.
5. Multidisciplinary cancer care is required to achieve the best functional, physical, and psychologic outcomes.

The need to treat tumors expediently often delays planning for rehabilitation. However, without a highly interactive and dynamic dialogue among health care providers during the initial treatment planning process, efforts to provide optimal rehabilitative care are impaired. Other health professionals—including social workers, vocational rehabilitation counselors, nurses, nutritionists, occupational therapists, physical therapists, speech pathologists, and dental hygienists—are also vital members of the team.[5] Because a team of this breadth is not typically encountered in the community setting, comprehensive rehabilitation is best managed in a medical center venue.

Factors affecting the cancer surgical treatment plan for oral cancer patients include the following:[1]

- prognosis and systemic status of patient;
- potential size and site of defect;
- potential nature of functional and/or cosmetic defect;
- adjunctive therapy (e.g., chemotherapy or radiation) that may compromise the surgical result; and
- anticipated changes to function and cosmesis, based on the cancer surgery and the availability, accessibility, and cost of rehabilitative procedures.

Planning for patients who need rehabilitation of the maxillofacial complex includes consideration of surgical defects associated with the maxilla, mandible, tongue, soft palate, and facial region, including the patient with a combined orofacial abnormality. The role and impact of radiation and chemotherapy also need consideration (see Chapter VII).[4]

Specific abnormalities result directly from the extent and nature of cancer treatment as well as the patient's functional and psychological ability to respond to changes induced by therapy.[6] Thus, rehabilitation may be directed to hypernasality, mastication and deglutition dysfunction, control of oral secretions, compromised interarch relations, speech deficits (tongue disarticulation), salivary gland dysfunction, and/or cosmetics.

In recent years there have been significant advances in some of the strategies for rehabilitating the oral cancer patient. These include fundamental qualitative improvements in biomaterials (including osseointegrated implants), microvascular free flap tissue transfers, and hyperbaric oxygen technology (by which gas highly concentrated in oxygen is delivered under increased pressure to patients).

Still, long-term success depends in large measure on effective follow-up protocols. The traditional idea that a patient's original maxillofacial prosthesis will adequately support his or her lifelong needs is no longer valid.[7] The prosthesis needs ongoing evaluation, adjustment, and usually replacement over time. Most removable extraoral prostheses need to be remade every 2 to 3 years; removable intraoral maxillofacial prostheses require regular maintenance and generally need replacement every 5 to 7 years. In addition, the ongoing long-term sequelae of radiation therapy for head and neck cancer require the dentist to keep the periodontium in optimal condition. Furthermore, restorations of abutment teeth used to retain an intraoral maxillofacial prosthesis must be sound and noncarious, and implant prostheses in this population require extensive maintenance for optimal functional results.

The standard of care for patients receiving a palatal resection (maxillectomy, palatectomy and/or soft palate resection) includes three stages of maxillofacial prosthetic intervention:

1. Immediate placement of a surgical obturator prosthesis (inserted in the operating room, usually by the maxillofacial prosthodontist, at completion of surgery to separate the oral cavity from

nasal cavities created by cancer surgery).

2. Placement of a provisional or interim postsurgical obturator prosthesis (inserted after the surgical obturator and packing is removed 7 days postoperatively, worn in the postoperative healing period).
3. Placement of a definitive postsurgical obturator prosthesis.

Major technologic advances have occurred in recent years in osseointegration[8] (the process by which natural bone attaches to the metal or ceramic component of an implant), thereby facilitating the use of dental implants. Brånemark et al. have pioneered the modern-day use of this technology,[9] in which implant materials capable of bearing forces produced during normal function interface both structurally and functionally with bone. Dental implants are now being used in both oral and extraoral settings and have significantly improved the restoration of both form and function to the oral and craniofacial region. Potentially, implant-borne prostheses can be used in the majority of intraoral and extraoral defects. However, in patients with intraoral defects, the most useful implant sites usually are not within the radiation treatment volume. An emerging exception appears to be the case of fibula free flaps, where implants are used to restore segmentally resected mandibles prior to post-surgical radiation. For extraoral prostheses, bioadhesives have traditionally been used to enhance retention, but they have considerable limitations.[8,10] Indeed, patients and clinicians often become frustrated by the difficulty of achieving optimal effects with adhesives. Both experience and specialized education can improve the clinician's ability to provide these components of extraoral and intraoral rehabilitative care.

The characteristics of successful osseointegration include: (1) biocompatible implant materials; (2) non-traumatic, aseptic surgical procedures; (3) an initial healing period in which functional loading of forces is deferred; and (4) stress-reducing prosthodontic procedures.[8,11] Patients should be selected with great care, and proper maintenance and follow-up are imperative. Successful osseointegration can permit the restoration of masticatory function following mandibular fibula free flap microvascular transfers.[12,13] Osseointegration in the maxillary-resected patient[14] and implant-retained facial prostheses have become acceptable in major cancer centers worldwide.[15-21]

B. Emerging Trends

Rehabilitative practices for oral and maxillofacial surgery patients have made important advances during the past several decades.[22] Relevant research on biomaterials has been transferred directly to the clinical setting;[23] these materials permit effective functional and cosmetic management of many patients with facial and intraoral defects who would otherwise experience lifelong disfigurement and dysfunction. In addition, important advances in imaging modalities, adhesives, implant materials, bone grafting, microvascular free flap tissue transfers, and hyperbaric oxygen have collectively

enhanced rehabilitation outcomes. Still, these new modalities require outcome assessments to measure their effects on patient rehabilitation.

Both the 1989 National Institutes of Health (NIH) consensus development conference on oral complications and its therapies[24] and the First International Congress on Maxillofacial Prosthetics (1994)[25] emphasized multidisciplinary cancer treatment, including specialists in maxillofacial prosthetics, oral medicine, and oral and maxillofacial surgery. Professionals and the public need to be educated about multidisciplinary cancer treatment, through additions to dental and medical curricula, postgraduate training, and continuing education programs; and educational programs delivered by public health agencies at local, state and national levels.

Future clinical and laboratory research on the use of osseointegrated implants and other prostheses in the presence of irradiated bone is expected to continue to refine the selection criteria for patients.[6] Although the concern about osteoradionecrosis as a theoretic risk in such settings is real, risk is minimal in the maxilla, even in segments receiving more than 6,000 cGy. Even in the mandible, the prime implant site (symphysis) is not usually included in the high-dose field; if it is included, the dose is generally limited in the setting of field size reductions or use of brachytherapy.

A history of high-dose radiation to oral bone does not per se eliminate prosthetic placement of osseoimplants at irradiated sites. Patients who have previously undergone head and neck irradiation still may be candidates for osseointegrated implants. The most likely limiting factors appear to be the ability to maintain viable appositional bone associated with the implant and the problem of the patient with a poor prognosis for tumor control. Selection of patients for osseointegrated systems must be based on careful consideration of their biologic and psychologic status. Because long-term, comprehensive monitoring of patient status is essential, the patient must commit to periodic comprehensive oral evaluations.

Both basic research and clinical experimentation with osseointegrated implants in irradiated bone must be priorities. In addition, planning for the future must include training adequate numbers of experienced professionals to meet the growing need for osseointegrated systems. It is important that educational training programs include the use of osseoimplants in irradiated bone to meet the evolving needs of the head and neck cancer patient.

C. Opportunities and Barriers to Progress

Strategies for improving the rehabilitation of the oral cancer patient and reducing the volume of rehabilitative services needed include addressing risk behavior and detecting oral malignancies early. Opportunities exist to do the following:

- enhance primary cancer management by adding new radiation protocols, using combined-modality therapy, and reducing acute or chronic injury to normal, contiguous tissues (see Chapters VI and VII);

- continue to foster research related to the complete rehabilitation of the patient, including investigations on reconstructive techniques, timing of the rehabilitation process, implants, and prostheses;

- enhance professional education at the predoctoral and postdoctoral levels, so that the gold standard of multidisciplinary management becomes available to more patients; and

- establish graduate training programs that combine traditional specialties for more comprehensive rehabilitation of the head and neck cancer patient, e.g., maxillofacial prosthetics and clinical oral medicine.

Major barriers to capturing the opportunities described above are as follows:

- limited technology and standards of care to protect normal tissues while maximizing direct exposure of the tumor to cytoreductive interventions.

- increasing demands on health center faculty to model and deliver new educational programs that are both didactically and cost effective.

- limited national fiscal resources to extend reimbursement coverage for rehabilitative care; prevailing trends are to maintain or even reduce the scope of current reimbursement.

- limitations in the National Cancer Institute's Cancer Education Program and the American Cancer Society's Advanced Clinical Oncology Fellowship Awards.

- inadequate exposure to oncology principles in undergraduate dental and medical school curricula.

- limited funding for graduate dental education in major cancer institutes to train future members of the dental oncology team.

Several university-based cancer centers include dentists in rehabilitative services during the initial treatment planning phase, as cancer treatment is being rendered, and during an appropriate follow-up period. This strategy capitalizes on traditional dental graduate training programs that are hospital-based and usually permits restoration of head and neck cancer patients to near-normal form and function. In private practice, however, it is difficult to create such dental teams and the interaction they require. Thus, the gap between the level of care offered in institutional settings and that offered

in private offices continues to widen. Unfortunately, this gap threatens the long-term quality of life of many patients.

In specialized private practice settings, patients are frequently not informed that they need oral rehabilitation services independent of their primary oncology care. However, if patients are managed by a multidisciplinary cancer team, they can easily be directed to the rehabilitation services they require.

Effective management of the acute and chronic sequelae of oral cancer, including its biologic, psychologic, social, and economic components, should be centered in prevention rather than in crisis-oriented responses.[2,26,27] Unfortunately, except at selected health centers, comprehensive management is not routinely implemented for long-term patient care. Dental generalists can manage some oral sequelae to head and neck cancer treatment, but they should have specific education and experience in managing the survivor of head and neck cancer.

Many of the major health care programs currently reimburse only a fraction of the costs of these medically based rehabilitative services, regardless of the professional qualifications of the provider. Whether reimbursement for maxillofacial prosthetic rehabilitative services will be better in the future remains uncertain. Development of more analyses that address the cost of prevention of complications versus management of acute lesions, analogous to models proposed for oral management of patients with hematologic malignancies,[22,28] might be useful. In most instances, medically necessary dentistry (prophylaxis, endodontics, extractions, and restorations) for the head and neck cancer patient is essential to prevent long-term sequelae from radiation to oral hard and soft tissues. Patients also need their dentists to maintain or provide optimal conditions and support for the abutments required to retain a maxillofacial prosthesis. Finally, they require periodic oral examinations and other medically necessary dental treatment.

Osseointegration, which emerged in the 1970s and 1980s as an effective alternative for patients who otherwise would have relied upon adhesives or nonimplant retentive designs, is also affected by its low reimbursement and high cost. Thus, few patients with modest or low incomes can benefit from procedures that use osseointegration. However, many insurance carriers are beginning to recognize the value of osseointegrated implants for retaining and supporting maxillary obturators, as well as the benefits of mandibular dentures in patients who have had mandibular reconstruction with a graft or fibula free flap. Still, insurance approval rates are generally low at present and are uncertain in the future.

Considerations for the research agenda include the following:

- improved radiation delivery systems that protect an increased percentage of normal oral

hard and soft tissues (see Chapter VI);

- topical or systemic interventions to protect normal tissues or enhance healing of damaged tissues;
- improved technology for the placement of prostheses, including osseointegration in previously irradiated tissues;
- improved prevention and management of osteoradionecrosis, including enhanced hyperbaric oxygen therapy protocols or new, superior modalities that promote angiogenesis and neovascularization;
- health services research on the cost-effectiveness of current and emerging interventions; and
- oral function assessment designed to determine which strategies are most effective in rehabilitation and medically necessary dentistry.

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ORAL CANCER BACKGROUND PAPERS

Chapter IX: Health Promotion in Oral Cancer Prevention and Early Detection

Working Draft

Introduction

Each year, oral cancer kills more people in the US than does cervical cancer, malignant melanoma, or Hodgkin's disease.[1] Oral cancers usually involve the tongue, lips, floor of the mouth, soft palate, tonsils, salivary glands, or back of the throat. In the US, more than 90% of oral and pharyngeal cancers occur in individuals over 45 years of age; males are more likely than females to develop them[1,2] (see Chapter I). The primary risk factors for oral cancers in this country are tobacco and alcohol use; for lip cancer, exposure to the sun is most important (see Chapter III).[3-6] Advanced oral cancer and its sequelae cause chronic pain, loss of function, and irreparable, socially disfiguring impairment. The functional, cosmetic, and psychological insults suffered by oral cancer patients often result in social isolation, significantly burdening patients, their families and society.[7]

Of all the procedures available to control oral cancer, none has affected survival as much as has early detection.[3] Unlike other parts of the body, the oral cavity is easily accessible and an oral cancer examination poses relatively little discomfort or embarrassment for the patient. Dentists are the provider of choice to perform oral cancer examinations, but about 40% of the population does not visit a dentist in a given year.[8] Furthermore, those who are middle age or older, edentulous, of lower income status, black or Hispanic—the groups at highest risk for oral cancers—are even less likely to visit a dentist.[9] Thus, other health care providers must assume more responsibility to ensure that the public receives oral cancer examinations on a routine basis. Primary care physicians should know that targeting those at high risk is a viable and cost-effective intervention for oral cancer when performed as part of routine practice.[10-12] Oral cancer examinations also offer providers an opportunity to identify patients who use tobacco and alcohol and counsel them about their risk for cancers.[13]

Oral cancer has one of the lowest 5-year survival rates of all major cancers,[14] probably because most lesions are not diagnosed until they are advanced.[15] However, when detected early, the probability of surviving from oral cancer is remarkably better than for most other cancers.[16] Theoretically, morbidity and mortality due to oral cancers can be reduced dramatically with appropriate interventions; because of this potential, 13 of the objectives in *Healthy People 2000* relate to oral cancer prevention and early detection (Table 1).[17]

To achieve these objectives, health care providers and the public need to know the risk factors for oral cancer, as well as their signs and symptoms. Furthermore, health care providers, particularly dentists, physicians, nurse practitioners, nurses and dental hygienists, need to provide oral cancer examinations routinely and competently. Equally important, members of the public need to know that an examination for oral cancer is available and that they can request one routinely. Thus, both health care providers and the general public need to increase their knowledge and change their behaviors or practices. Health promotion is a key to achieving these changes.

Table 1:
Healthy People 2000 Oral Cancer Objectives[17]

2.2	Reverse the rise in cancer deaths to achieve a rate of no more than 130 per 100,000 people.
2.6	Increase complex carbohydrates and fiber containing foods in the diets of adults to 5 or more daily servings for vegetables (including legumes) and fruits, and to 6 or more daily servings for grain products.
3.4	Reduce cigarette smoking to a prevalence of no more than 15% among people aged 20 and older.
3.5	Reduce the initiation of cigarette smoking by children and youth so that no more than 15% have become regular cigarette smokers by age 20.
3.9	Reduce smokeless tobacco use by males aged 12 through 24 to a prevalence of no more than 4%.
3.16	Increase to at least 75% the proportion of primary care and oral health care providers who routinely advise cessation and provide assistance and followup for all of their tobacco-using patients.
4.6	Reduce the proportion of young people who have used alcohol, marijuana and cocaine in the past month.
4.7	Reduce the proportion of high school seniors and college students engaging in recent occasions of heavy drinking of alcoholic beverages to no more than 28% of high school seniors and 32% of college students.
4.8	Reduce alcohol consumption by people aged 14 and older to an annual average of no more than 2 gallons of ethanol per person.
4.19	Increase to at least 75% the proportion of primary care providers who screen for alcohol and other drug use problems and provide counseling and referral as needed.
13.7	Reduce deaths due to cancer of the oral cavity and pharynx to no more than 10.5 per 100,000 men aged 45 through 74 and 4.1 per 100,000 women aged 45 through 74.
13.14	Increase to at least 70% the proportion of people aged 35 and older using the oral health care system during each year.
16.14	Increase to at least 40% the proportion of people aged 50 and older visiting a primary care provider in the preceding year who have received oral, skin, and digital rectal examinations during one such visit.

It is widely accepted that health promotion influences knowledge and behaviors at all levels of social organization. Health promotion is defined as follows: "Any planned combination of educational, political, regulatory, and organizational supports for actions and conditions of living conducive to the health of individuals, groups, or communities."[18] These actions or behaviors may be those of individuals, groups or communities of policy makers, employers, teachers, or others whose actions influence the determinants of health. This use of the term "promotion" differs from a common usage that is frequently associated only with public relations, advertising, and other marketing activities. Although marketing activities play an important role in health promotion, the term as used here refers to actions intended either to alter a person's environments in a way that will improve health in the absence of individual actions or to enable individuals to take advantage of preventive procedures by removing or mitigating barriers to their use.[19] Education is the essential, common denominator of health promotion. Educating a variety of publics, including consumers, health care providers, legislators and other decision makers is necessary to improve awareness of preventive and early detection methods and procedures, gain their acceptance by these groups, and increase their use.[19,20] Education, alone, however, is insufficient to prevent diseases or conditions;[20] simply having knowledge or information does not mean that appropriate behaviors or actions will follow. Still, knowledge is an important aspect of empowerment—without appropriate knowledge, individuals can

neither make nor be expected to make intelligent decisions about their health.[21]

Among other factors that influence behavior are beliefs, values, and attitudes. These factors influence decisions to consult health care providers about obtaining cancer examinations or to use tobacco and alcohol.[19-20]

A. State of the Science

Knowledge, Opinions, and Practices of Physicians and Dentists

A review of several studies that assessed oral cancer knowledge, opinions, and practices of health care providers suggests that many physicians and dentists do not detect oral lesions in their early stages because of inappropriate attitudes or lack of knowledge.[22-27] For example, physicians in Great Britain believed that dentists were primarily responsible for detecting oral cancer.[28] In the U.S., Crissman et al. found that physicians delayed diagnosis of cancers of the floor of the mouth because they confused them with traumatic, inflammatory, or infectious lesions.[29]

Although practitioners' knowledge, opinions, and practices relative to many types of cancers have been investigated,[30] no US national surveys on oral cancers have been conducted among dentists or physicians. However, a recent pilot survey of physicians' and dentists' knowledge, opinions and practices related to oral cancers found that 34% of dentists and 37% of physicians did not recognize the importance of early detection as a means of reducing morbidity and mortality from these diseases.[31] The survey found that a significantly higher proportion of dentists (73%) than physicians (33%) believed that their oral cancer knowledge was current. Furthermore, physicians who believed they were inadequately trained to provide oral cancer examinations were less likely to provide them.

Physicians, dentists, and other providers have a unique opportunity to detect malignant oral neoplasias while they are asymptomatic. Yet, studies have reported that physicians do not routinely examine their patients to identify early, suspicious oral lesions.[32-37] Prout et al. found that more than 77% of patients first diagnosed with oral cancer at an advanced stage had been under the routine care of a physician within the past 3-24 months.[33] Elwood et al. reported that 94% of patients with advanced oral cancer had been seen by a physician within 1 year of their diagnosis.[32] Finally, Lynch and Prout found that only 3% of internal medicine residents documented that they completed an oral cancer screening examination of their patients at high risk for oral cancer.[36]

Studies reporting that physicians are more likely to refer head and neck cancer at an advanced stage than dentists[34,35] suggest that physicians are relatively less aware of signs and symptoms of oral cancer and, as a result, are not fulfilling their responsibilities for early detection.[38-41] When asked about barriers to completing cancer screenings in general (in surveys that did not mention oral cancer),

physicians have reported a treatment-based orientation, time constraints, lack of financial reimbursement, poor patient compliance, and lack of immediate results.[39,42,43]

Dentists also have been found to be remiss in early diagnosis and referral for oral cancers. [24,28,44,45] Schnetler found dentists to be less adept at diagnosis and early referral than physicians.[24] Maguire et al. reported that only 14% of dentists performed all aspects of an intra-oral examination.[28] In an older report from Scotland, Pogrel noted that dentists missed approximately twice as many asymptomatic oral cancer cases as they found.[44] And in 1964, Coffin reported that dentists failed to recognize oral cancer in 69% of the cases presented to them.[45] Still another study, which focused on both dentists and physicians, found that 15% of their patients experienced either significant mismanagement or delayed diagnosis of oral cancer.[25]

Recent studies report that clinicians frequently either do not assess or are unaware of their patients' high-risk behaviors. For example, Maguire et al. reported that 64% of dentists were unaware of their patients' tobacco habits and 40% did not know their alcohol habits.[28] Dolan et al. reported that only 35% of 1,746 randomly selected US dentists asked all or nearly all of their patients whether they smoked. Even fewer dentists (15%) asked about use of smokeless tobacco.[46]

Knowledge, Opinions, and Practices of US Adults

Only a few studies have assessed the US public's knowledge, opinions, and practices relative to oral cancer. The 1990 National Health Interview Survey (NHIS), Health Promotion and Disease Prevention Supplement (HPDP) included four questions about oral cancers.[47] Findings from this study indicate that US adults are not well informed about the signs of oral cancers. There was a great lack of information (or misinformation) regardless of age, race, or ethnicity. Forty-four percent of adults did not know any signs of oral cancer; another 25% correctly identified only one. Just 13% answered correctly that regular alcohol drinking increases one's risk of oral cancer. Although two-thirds identified tobacco use as a risk factor for oral cancer, more people correctly identified smoking as a risk factor for heart disease, emphysema, or lung cancer than for oral cancer. Similarly, few knew that heavy drinking is a risk factor for throat and mouth cancer, although 83% knew that it definitely increases one's chance of getting cirrhosis of the liver.

The 1992 National Center for Health Statistics (NCHS) Cancer Supplement Survey also looked at oral cancer and found that only 14% of the public had ever been examined for the disease.[48] The question of interest actually described the oral cancer screening examination: "in which the doctor or dentist pulls on your tongue, sometimes with gauze wrapped around it, and feels under the tongue and inside the cheeks." Given this description and the nature of the examination, it is unlikely that many patients answered the question incorrectly. Groups least likely to have been examined were: African-Americans or Hispanics; those with low levels of education; persons 65 years of age or older; current users of tobacco products;[48] and respondents with a low level of knowledge about risk factors

for oral cancer.[49] Of individuals receiving an oral cancer examination, 67% received it from a dentist and 24% from a physician.[48]

The 1992 survey generally corroborated the 1990 findings; both, for example, found that the overall level of knowledge about risk factors for oral cancers was low and that a higher level of knowledge of risk factors for oral cancer was associated with a report of having had an oral cancer examination. The latter finding is consistent with results from surveys about cervical, breast, and colorectal cancer.[50-53]

Oral cancer questions also were part of a recent pilot study about oral health among 700 adults.[54] Again, a significant percentage of respondents did not correctly identify oral cancer risk factors. When asked, "which of the following are early warning signs of mouth or lip cancer," only 63% correctly identified "a white or red patch in the mouth that does not go away;" 20% responded "don't know/ not sure" on this question. Only 49% indicated that regular use of both alcohol and tobacco were risk factors; 29% incorrectly responded that having a relative who has had mouth or lip cancer was a risk factor.

Eighty-six percent recognized that regular use of chewing tobacco or snuff can increase the risk of oral cancer. However, 38% of the respondents in this survey were young adults and may have been exposed to anti-tobacco use education. (Of the few educational efforts targeting oral cancer, the majority have been directed to youths and young adults on the use of snuff or chewing tobacco.)

B. Emerging Trends

Over the last two decades, interest in health promotion and disease prevention has increased significantly. At least three factors are responsible for this trend: First, ever-increasing expenditures for health care, most of which pay for the treatment of diseases or conditions, have taken an ever larger proportion of the US gross national product. Second, a growing body of data has confirmed that many chronic diseases result from lifestyle factors that, theoretically, could be changed. Third, and very important, a body of scientific literature in health education and promotion has accumulated. Today, health promotion is recognized as a viable approach to preventing diseases and disorders and promoting health.

A variety of educational campaigns have been mounted to urge people not to start using tobacco products or to stop if they have already started. Today, school-based interventions frequently begin in primary grades; they may focus on developing self-esteem, on building skills to resist peer pressure, or on urging children to remain smoke-free. These efforts are often implemented in conjunction with other community-based activities aimed at preventing children and youth from starting the habit and urging users to stop.[55] Unfortunately, these programs often do not identify tobacco products as risk

factors for oral cancers. Similarly, efforts focusing on alcohol use as a risk factor for cirrhosis of the liver, liver cancer and fetal alcohol syndrome rarely identify alcohol as a risk factor for oral cancers. However, recent intervention strategies for decreasing the use of tobacco products and alcohol bode well for reducing cancer incidence, including oral cancers. For example, many health institutions, businesses, airports, airlines, and schools have implemented smoke-free policies or provided only limited indoor space for smoking. Overall, there is a growing trend in the US to consider smoking socially unacceptable, especially among more highly educated people.[56]

Although not as prominent as anti-smoking activities, there has been an increase in recent years of educational efforts about self-protection from exposure to the sun by using sun and lip screens, hats, and other coverings. In addition, the public is being urged to obtain skin cancer examinations on a routine basis.

There is a clear trend to use public policy to help decrease or prevent behaviors that contribute to diseases.[57] For example, some states and communities have taken steps to prevent or reduce the availability of tobacco products or alcohol for underage youths. Approaches have included increasing taxes on tobacco products and enforcing laws prohibiting sales to minors.[58,59] Also, as a result of lawsuits against tobacco companies by states and individuals, there have been modifications of tobacco advertising, especially that directed at youth. Lawsuits and public policy initiatives frequently result from community action on the part of partnerships of organizations and individuals or coalitions.

On another level, health care professionals are being urged to train themselves in methods of tobacco cessation and to implement them in their practices.[60,61] Dolan et al. found that nearly 19% of dentists they surveyed reported they had completed formal training in tobacco use cessation, and over 19% felt very well or well prepared to assist patients in tobacco use cessation.[46] However, these efforts are not primarily directed at reducing oral cancers. In fact, oral cancers frequently are not mentioned as part of the rationale for discontinuing tobacco use. Still, dentists and physicians have the opportunity to make this point.

Several government and private agencies are urging the increased consumption of fruits and vegetables to help prevent cancers and other diseases. The National Cancer Institute's Five A Day program is a good example; it has encouraged many restaurants, schools and supermarkets to join in this effort. Because consuming of fruits and vegetables may provide protection against oral cancers, such initiatives may be beneficial.[62]

In addition, the Food and Drug Administration has changed its requirement for labeling. The agency's intent is to give the consumer a standardized and understandable approach to assess the nutrients in packaged foods. For example, alcohol is now labeled with a US government warning, a positive step although the labels, as are those on cigarettes, are inconspicuous and do not mention oral cancers.

C. Opportunities and Barriers to Progress

Knowledge, Opinions, and Practices of Health Care Providers

Education and Licensing

How clinicians practice is determined in large part by their training and education. For example, dental sealants (also a preventive procedure) are under used by practitioners. Yet, dental students who are well trained in, and expected to be competent in, the use of sealants do use them once in private practice.[63,64] Early and comprehensive exposure of undergraduate medical and dental students to cancer prevention methods is necessary to predispose them to provide oral cancer examinations effectively and routinely.[22,65-67] However, emphasis on prevention has never equaled emphasis on treatment in most U.S. dental and medical schools.[68] Furthermore, our knowledge of social and behavioral risk factors for disease has increased, but developing the skills to communicate this information to the public has not been addressed as well as it might be in most dental school curricula. In fact, after an upswing in the 1970s, emphasis on community health and prevention has declined.[69,70] Furthermore, preliminary findings from a recent study found that the oral cancer examination content of medical school curricula lacked comprehensiveness and consistency. In addition, medical schools do not require students to evaluate oral cancer signs and symptoms and do not train their students in thorough oral examination techniques.[71]

Although curricular guidelines exist for teaching undergraduate and graduate dental students how to provide an oral cancer examination,[72-75] there is no mechanism for enforcing them. Regulatory guidance for educational curricula is essential to ensure proficiency. These guidelines should include requirements for student clinicians to complete a specific number of oral cancer screening examinations; such a standard could serve as a catalyst for clinical licensing examination boards to assess competency in conducting oral cancer examinations.

State, regional, and national licensing dental board examinations all contain some questions related to oral cancer. No state dental board, however, requires that applicants perform an oral cancer examination to obtain a license to practice. Because some states already assess expertise in other content areas before granting a license, it is reasonable to insist that all licensing boards require practitioners to demonstrate their expertise in oral cancer examinations. In addition, licensed practitioners should be required for relicensure to complete a continuing education course in oral cancer. Although some dental schools have a rigorous cancer education curriculum,[66] the fact that students do not have to perform an oral cancer examination to obtain their license sends a message that the oral cancer examination is not as important to the health of the patient as are other procedures, such as the proper placement of an amalgam restoration. Overall, there are numerous opportunities for licensing agencies and dental schools to increase their focus on oral cancer prevention and early detection.

Although national survey information on oral cancers does not exist,[60] this type of information would be very helpful in identifying educational and training shortcomings and subsequently in developing and implementing educational and clinical interventions. Research is also needed to determine knowledge levels, opinions, and practices related to oral cancer and its prevention among other health care providers, including dental hygienists, nurses, nurse practitioners, and physician assistants. In addition, curricula and continuing education courses for these providers should be assessed relative to oral cancer prevention and early detection. Ultimately, the results of this research can be used to increase the volume of oral cancer examinations and thereby promote early detection of these diseases.

Continuing Medical and Dental Education

Continuing education courses provide opportunities to advance practitioners' knowledge and skills. Yet, relatively few continuing education courses for dentists deal with oral cancer.[76,77] Continuing education should be simple, valid, acceptable, and concise in order to enhance providers' attitudes and behaviors.[42] Although educational guides for both physicians and nurses regarding early detection of oral cancer are available, their use may be limited and their effectiveness has yet to be assessed.[39,78-80] An early study suggested that self-instructional courses are effective in enhancing awareness in early detection of oral cancer among medical and dental professionals;[81] but few have used this approach to date. However, the increased use of computers brings with it unique opportunities for self-study in pre-doctoral as well as continuing education.

Educational interventions to inform, train, and prepare health care professionals to diagnose and manage oral cancers properly are needed.[82] More recently another approach to providing continuing education—academic detailing—has been used to teach practitioners to change their prescribing practices.[83,84] Academic detailing, which is patterned after drug detailing, uses educational detailers who visit physicians in their offices or clinics and provide them with education. Currently, this method is not used to educate providers about oral cancer prevention and early detection. Ironically, one of the earliest uses of detailing to educate health care providers was the initiative decades ago to introduce dental practitioners to oral cytology testing as a means of detecting early oral cancer lesions.[85]

Sensitivity and Specificity of Oral Cancer Examination[1]

Theoretically, when health care providers understand the oral cancer exam procedure and know the clinical appearance of oral precancerous and cancerous lesions, they can routinely perform a systematic oral cancer examination for all their patients.[16,86-88] To date, however, no study to measure

[1] Sensitivity is the proportion of truly diseased persons in the screened population who are identified as diseased by the screening test, i.e., the probability of correctly diagnosing a case, or the true positive rate. Specificity is the proportion of truly nondiseased persons who are so identified by the screening test, i.e., the probability of correctly identifying a nondiseased person with a screening test, or the true negative rate. (From JM Last's *A Dictionary of Epidemiology*, Oxford Press, 1988).

the sensitivity and specificity of the oral cancer examination has been conducted in the United States. However, studies conducted in other countries have reported sensitivity and specificity rates ranging from 58-99%.[82,89-91] Jullien et al. suggest that sensitivity will be improved when providers are better trained to recognize specific signs and symptoms of early cancer and pre-cancer.[82] Furthermore, they suggest that if practitioners understand disease progression and regression, they will be more likely to detect disease in its early stages. Still, it would be helpful if one or more research teams would conduct studies to determine the sensitivity and specificity of oral cancer examinations in the US.

Adjunctive Screening Procedures and Tools

The lack of specific adjunctive examination tools such as the Papanicolaou (Pap) smear or vital staining (see Chapter V) may be barriers to the provision of routine oral cancer examinations. Sensitive and specific screening procedures that are reimbursable by third party payers need to be developed to encourage, motivate, and assist health care providers to increase their use of routine and effective oral examinations.[16] For example, toluidine blue rinse (vital staining) has been used in other countries as a diagnostic adjunct to oral cancer exams but not in the US. This easy and expeditious office procedure may be valuable in identifying lesions that are cancerous, although its potential for false positives warrants concern (see Chapter V).[92] Further research is needed to develop and test valid and reliable screening tools that could be identified as warranting insurance coverage.

Current Guidelines: A Lack of Consensus

Preventive care guidelines have been developed by governmental agencies, private enterprises, insurers, hospitals, academic centers and nearly 40 medical and dental societies.[93] Unfortunately, the lack of consensus among these guidelines not only fails to provide guidance to make informed clinical decisions but also may serve as a rationale for not providing oral cancer examinations. Because patients at highest risk for oral cancer are more likely to receive medical care than dental care, it is important that policies advocate the integration of oral cancer screening into routine health care. Most physician organizations do not consider recommendations for oral cancer within their periodic health examination guidelines. As shown in Table 2, the American Cancer Society, but not the US Preventive Task Force or the Canadian Task Force, recommends routine oral cancer examinations for adults.

Table 2:
Guidelines for Oral Cancer Screening Examinations

Organization	Routine	High-Risk Group Only	Screening Recommendations

American Cancer Society	yes	no	Examination for cancer of the oral region every 3 years for persons 21 years of age and older and annually for those 40 years of age and older.
US Preventive Task Force	no	yes	All patients should be counseled to discontinue the use of all forms of tobacco and to limit consumption of alcohol. Clinician should remain alert to signs and symptoms of oral cancer and premalignancy in persons who use tobacco or alcohol.
Canadian Task Force	no	yes	There is insufficient evidence to include or exclude screening for oral cancer from the periodic health examination in the general population. Only high-risk people warrant an annual oral examination by a physician or dentist.

According to Frame, who has played an important role in developing clinical preventive guidelines, "the incidence of the condition must be sufficient to justify the cost of screening."[96] This criterion was used to justify objections to guidelines advocating routine oral cancer examinations.[96,97] Yet, that oral cancer has a relatively low incidence and prevalence remains open to debate, as it reportedly often coexists with other upper aerodigestive cancers. Regardless, the examination requires only a few minutes and ultimately benefits many patients. Inasmuch as the scientific and economic justifications for preventive guidelines are still being defined, it seems inappropriate for current guidelines to deter the application of available, effective measures such as oral cancer examination. One encouraging piece of evidence comes from Prout et al., who found that early detection increased the number of *early* stage oral lesions found by physicians from 20% to 33% during a 3-4-year period.[98]

The US Preventive Services Task Force suggests that "All patients should be counseled to discontinue the use of all forms of tobacco and to limit consumption of alcohol."[99] In effect, the clinician must determine the patient's present and past use of alcohol and tobacco products. Thus, this recommendation tacitly assumes that practitioners routinely determine their patients' use of tobacco products and alcohol; it also assumes they are trained to counsel their patients.

Assessment of Patients Use of Tobacco and Alcohol

As previously noted, only 35% of US dentists ask their patients whether they smoke; even fewer ask about their use of smokeless tobacco.[46] Correspondingly, US and Canadian dental schools use health history forms that are often severely deficient in determining a patient's high risk behaviors associated with oral cancer.[100] Nearly 25% of the schools do not include any questions on tobacco and alcohol

use and 37% fail to include both tobacco and alcohol questions on these forms. There is also extensive variability in the questions about the history, quantity, duration, and types of tobacco or alcohol use.

A recent study of health history forms used in of dental hygiene schools showed that 36% of the schools failed to ask about alcohol and tobacco use.[101] Finally, a survey of 126 US medical schools found that the topic least likely to be covered in their cancer prevention curriculum was prevention and cessation of smoking.[102]

Health history forms used in medical and dental schools are critical documents not only to determine patients' health risk factors but also as teaching tools to influence future practitioner behaviors.[103] Thus, in assessing an individual's risks, a health history form should ask about tobacco, alcohol, and sunscreen use.

In addition to using health history forms, clinicians must engage directly those of their patients who smoke. Indeed, Fiore has suggested that health care practitioners practice "bad medicine" when they do not address tobacco use in a timely and appropriate fashion with these patients.[104]

Educational Materials for Providers

Educational materials about oral cancer and related examination techniques recently developed for health care providers have included an overview of the literature on oral cancers, a video, leaflets, and a poster that shows how to perform an oral cancer examination. However, to our knowledge, a survey has not been conducted to determine what is available for US providers and to systematically assess whether the content of available materials is valid and effective. Also, although there are many educational materials for health care providers on how to assist their patients to become tobacco-free, these materials do not always specifically link use of tobacco products with oral cancers.

Knowledge, Opinions, and Practices of The Public

Oral Cancer Examinations

Just as health care providers need basic knowledge and skills to complete an oral cancer examination and to assess the risk behaviors of their patients, the public has its own needs for knowledge about oral cancers. Specifically, the public needs to know the risk factors for these diseases and their signs and symptoms. Because some oral cancer risk factors may be synergistic, eliminating just one risk factor might produce very substantial benefits, as its absence might greatly affect the overall risk for these cancers (see Chapter III).[101] In addition, the public needs to know there is an oral cancer examination and what it entails.[82,102] With this information, patients can assess whether their practitioners are routinely providing a comprehensive examination and, if not, to request that they do so.

Unfortunately, relatively little attention has been paid to educating the general public about oral cancer. Yet, without accurate and appropriate information, members of the public can neither make nor be expected to make informed decisions about their own health, including the need to seek oral cancer examinations.[21] Unfortunately, a lack of knowledge can result in an individual's simply ignoring a sign or symptom of oral cancer, a response that could have grave consequences. Research suggests that knowledge is important relative to cancer screening practices. Indeed, studies of other cancers have shown that a lower level of knowledge tends to increase fatalistic attitudes toward cancer and other diseases and fosters misinformation. This lack of information can lead to delay in seeking care for symptoms[50] or to foregoing screening examinations.[51] In fact, one study found that most oral cancer patients had delayed seeking professional advice for more than 3 months after becoming aware of an oral sign or symptom.[103] Still, simply "holding knowledge" about a risk factor does not translate into behavior change, but having appropriate knowledge enables one to make an intelligent decision upon which to act.[18,20]

Many people do not practice preventive procedures, not by informed choice, but because they may never have been taught about them, may not have necessary information-seeking skills, or may not have access to the information.[18,102] For example, the two most common reasons women give for never having had a mammogram or a Pap smear are the following: (1) they did not know they needed it (lack of knowledge); and (2) their physician had not recommended the procedure.[51-53] Yet, the public has the right to this information for its self-protection.

Access to Health Services

Unfortunately, few systems are in place to ensure the provision of routine (annual) oral cancer screening examinations. Not surprisingly, mortality rates from oral cancer are high in populations with poor access to the health care system.[5,8,32,104,105] Groups with low utilization of the medical (non-dental) care system include those who have low incomes, lack private insurance, have less than a high school education, are 65 years of age or older, or are members of a minority group.[106] Access to oral

health care is even more restrictive.[8] Although Medicare reimburses the treatment of oral cancers in a hospital setting, it does not cover routine or preventive oral health care, including examinations for oral cancers. Furthermore, Medicaid programs do not reimburse adult oral health care, thereby limiting access for low socioeconomic groups.

Persons of low socioeconomic status are more likely to engage in high-risk behaviors, such as tobacco or alcohol use,[56,107] a fact that may explain some of their poor performance on oral cancer indicators. However, another group with below-average use of oral health services, the edentulous elderly, were found in one study to have a higher oral cancer risk independent of tobacco and alcohol use.[108]

Opportunities should be explored to develop new strategies for providing oral cancer examinations. For example, oral cancer exams could be provided by physicians in conjunction with other cancer screening procedures. In addition, these exams might be offered in hospital emergency departments to those persons who go there for routine primary care. In addition, non-medical personnel in health-related programs who work with individuals who are at high risk can be trained to provide screening exams and to make follow-up referrals when necessary.

Educational Materials for the Public

Relatively few oral cancer educational materials have been produced for the public, far less than the plethora of materials on toothbrushing, flossing, and the need for dental visits. Surveys are needed to determine what educational materials are available for specific target groups and to assess their accuracy, comprehensiveness, reading level, and acceptability.

A review of health education textbooks for students from kindergarten through 12th grade found that the oral cancer coverage was uneven, misleading, sometimes incorrect, but most often omitted altogether.[109] Most of the content about oral cancer dealt with the use of chewing tobacco. Both the lack of content and the incorrect information in health education textbooks may contribute to the public's overall lack of knowledge about oral cancers. Clearly, it is imperative to include correct material about prevention of oral cancers in health textbooks.

Another priority for public education concerns the labeling of alcohol and tobacco products. Although placing warning messages on alcohol and tobacco products is commendable, currently the messages can barely be distinguished from the balance of the label. Warning messages on electrical appliances such as hair dryers are far more obvious. Warning messages need to be clearly visible and distinct from the rest of the label. Furthermore, the content of the messages should be much stronger and clearer.[55]

Self-examination

A first line of defense against oral cancer is an orofacial self-examination.[110,111] A self-examination can help individuals become more aware of their own bodies and involve them in monitoring their own

health. As has happened with other self-examination procedures, the public can be educated to perform oral cancer self-examinations. Although they should not take the place of a professional oral examination, self-examinations can be a secondary preventive technique to detect early lip and mouth lesions.[110,111] The examination includes intraoral and extraoral observations and palpation of the head and neck region; it requires only a few minutes to complete.[110] However, because signs are often difficult to recognize and symptoms may be minimal, professional examinations are still of primary importance. Studies of the effectiveness of oral cancer self-examinations and the public's awareness and use of this tool are needed.

In summary, oral cancer is a disease that frequently has been given low priority by both health care providers and the public.[112] Furthermore, although there is currently great interest in exploring therapeutic modalities for oral cancer, scant attention has been paid to its prevention, early detection, and control. Although there are numerous barriers to prevention and early detection of oral cancers in the US, none is insurmountable. Let us consider the barriers to be opportunities to change the behaviors and practices of health care providers and the public. If we can make these changes, we can achieve the oral health objectives in *Healthy People 2000*.

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