

Oral Cancer and Oral Effects of Anticancer Therapy
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OCTOBER/NOVEMBER 1998 NUMBER 5 & 6 VOLUME
65:370-377

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Abstract

The term "oral cancer" generally refers to squamous cell carcinoma of oral mucosal origin, which accounts for more than 90% of all malignancies of this location. Although a relatively uncommon disease in the United States, this malignancy is nonetheless important, as it accounts for significant morbidity and mortality. Approximately half of the estimated 30 thousand cases diagnosed annually in this country have a fatal outcome. Survivors of the surgical and medical management may suffer from sequelae of treatment ranging from pain and infection to partial or total disfigurement and loss of stomatognathic function. Such high morbidity and mortality are truly regrettable, since many of these malignancies are preventable. This article will review recent developments in the epidemiology, treatment and chemoprevention of oral squamous cell carcinoma as they relate to early diagnosis, and management of the oral cancer patient.

Key Words: Mouth, cancer, chemotherapy, etiology, epidemiology, radiation.

Epidemiology of Oral Cancer

Oral and pharyngeal cancers rank number five in prevalence worldwide, but represent only 3B5% of all malignant neoplasms diagnosed annually in the United States (1B3). The overall survival rate for this disease in 1987 was 50.7%, with incidence and mortality remaining virtually unchanged over the past two decades (1). This relatively high mortality is in part due to the advanced stage of the disease at the time of diagnosis. The 5-year survival rate for patients with localized disease at the time of diagnosis is approximately 75% as compared to less than 10% for those with distant metastases (1). Thus, early diagnosis of this easily identifiable malignancy, alone could drastically reduce mortality, medical costs, pain and suffering. Given the ready accessibility of the oral cavity, knowledgeable clinicians should be adept at recognizing precancerous abnormalities as well as frank carcinomas.

Despite a relatively constant incidence of oral cancer, national trends in the past 50 years show some significant epidemiological changes: the number of affected white males has steadily decreased, while a disturbing increase of this disease among African-American males and all females has been noted (1). In contrast, recent European studies report an alarming overall increased prevalence of oral cancer, particularly in younger adults from the Eastern and Central regions of that continent (4). However, this increase may be due partly to previous underreporting of cases before 1989.

While oral cancer remains predominantly a disease of males (in the United States, the male-to-female ratio was approximately 2.5 for the period 1983B1987) (1), a significant linear trend toward increasing prevalence of this malignancy in females has been reported, with ratios changing from 9.8:1 in 1935 to as low as 2.6:1 in 1985 (5). The number of women with oral cancer increased yearly by 0.5% despite the fact that the total number of reported lesions decreased by 0.4% within the analyzed 15-year period (1). This phenomenon can be explained in part by increased exposure to carcinogenic substances as a result of greater social acceptance of smoking and alcohol use in women. However, other factors may account, at least partially, for this observation, and they remain to be identified or confirmed (5, 6).

Most cases of oral cancer in the United States are diagnosed in the sixth and seventh decades of a person's life, with the highest prevalence noted in 65B74-year-old patients (1, 5). However, younger individuals, including children, may be affected in rare instances (7). In a study of more than 14,000 patients with oral squamous cell carcinoma, 3 were younger than 14 at the time of surgery and another 16 belonged to the 15B19-year-old group. Overall, 7.2% of the patients were younger than 40 (7). A similar report found 53 cases of tongue cancer in males 40 and younger, which represented a nonlinear increase in prevalence of the disease in this age group (8). These findings suggest a trend toward decreasing age at diagnosis of oral cancer. However, other reports do not support this conclusion, mandating further study of the issue (1, 5). Based on these suggestions and the European experience, examining younger patients with this diagnosis in mind is nevertheless advisable.

The majority of intraoral squamous cell carcinomas originate from the non-keratinized

mucosa of the tongue and the floor of the mouth. Recently, a trend toward increased numbers of lesions arising on both the dentate and edentulous gingiva was reported, with the gingiva being the third most common site for intraoral squamous cell carcinoma in several studies (6, 9B13). These results are surprising, since keratinized tissues were traditionally considered to be relatively immune to factors contributing to malignant transformation in the oral cavity.

An explanation for these findings is not readily evident. However, two possible contributory factors can be listed: (a) etiologic agents other than tobacco and alcohol consumption may have more affinity for keratinized tissues; and (b) gingival carcinomas have a predilection for females, who account for an increasing number of oral cancer cases (6, 9). This theory is consistent with recent reports that suggest that alcohol and tobacco have unequal malignant transformation potential on specific oral subsites (floor of the mouth > tongue > gingiva) (6, 12B14). Similarly, gender may be a significant predictor of the oral subsite for development of cancer, with males and females showing predilection for development of floor of the mouth and gingival carcinoma, respectively (5, 6). However, due to lack of uniformity in study methodology in the published reports, solid conclusions regarding these topics are premature. Further study is necessary for confirmation of these findings, as well as for identification of possible mechanisms of carcinogenesis at various oral subsites.

Etiology of Oral Cancer

Many factors probably play a role in the development of oral cancer. Although there is debate with regard to the relative importance of some of these factors, it is widely agreed in Europe and North America that tobacco and alcohol play a significant role in the pathogenesis of carcinoma arising from oral surface epithelium (14, 15), whereas it is clear that ultraviolet radiation is the major cause of cancer of the external lip (16). Betel (areca) nut and toombak chewing are strongly associated with oral cancer in Southeast Asia and Africa (17). Other proposed causative agents include alcohol-containing mouthwashes, syphilis, poor oral hygiene, iron deficiency, chronic trauma and viruses; however, well-designed studies failed to show any consistent association of these factors with malignant transformation.

Another controversial topic in oral cancer etiology is the role of smokeless tobacco. While most authors strongly believe that chewing or pouching tobacco increases chances for oral epithelial malignant transformation (16, 18, 19), recent epidemiological data cast significant doubt on this association (20B22). This doubt is augmented by the fact that tobacco products have not been shown to induce premalignant changes in animal models. Since neither the mechanism of oral carcinogenesis nor the precise role of tobacco and alcohol has been elucidated, and since only approximately 3% of heavy users of these substances ever develop oral cancer, the search for other possible etiologic factors must continue. Recent efforts have been directed toward identification of a possible role of viral agents, particularly the human papilloma and herpes simplex viruses (HPV and HSV) (23, 24). These ubiquitous viruses have been associated with various other cancers and are common inhabitants of the oral cavity. While some studies found an increased presence of viral genome in malignant and premalignant oral lesions, others denied any conclusive evidence (23).

It is worth mentioning that evidence gathering for identification of cellular and molecular

mechanisms of oral carcinogenesis is hampered by the relatively small number of cases in the United States, the large number of possible etiologies, and the lack of an adequate animal model. At this time, it appears safe to conclude that the etiology of oral squamous cell carcinoma is multifactorial and that various oral sites may be selectively affected by these factors.

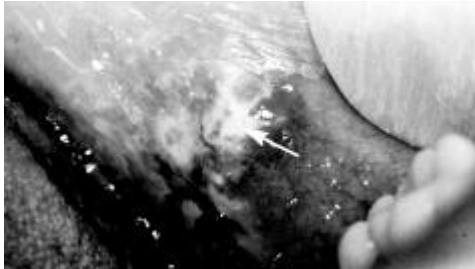


Fig. 1. Erythroleukoplakia of the buccal mucosa in a 74-year-old heavy-smoking female. This lesion was moderately dysplastic on microscopic examination.

Clinical Presentation

Premalignant oral lesions typically present as asymptomatic erythroplakia or leukoerythroplakia of the non-keratinized soft tissues (25-27) (Fig. 1). Any such lesion without obvious cause, such as mechanical or chemical irritation, particularly if found in an elderly tobacco and/or alcohol user, should be regarded as suspicious. Submucous fibrosis is a premalignant presentation consisting of epithelial atrophy and induration with loss of elasticity of affected mucosa; it is associated with betel nut use. Patients are generally symptomatic, presenting with limited mouth opening, trismus and inability to eat.

Other clinical presentations of premalignant lesions are possible but uncommon. Leukoplakia, a white patch on the mucosa which cannot be otherwise diagnosed on clinical grounds alone, was thought to be the prototypical oral premalignant presentation in the past (28), but it has been shown to undergo malignant transformation in fewer than 4% of the cases (27). Another controversial lesion in terms of its malignant potential is lichen planus, which is often the subject of confusion with a similar clinical entity, lichenoid dysplasia (29). A recent genetic study provided more evidence that true lichen planus, an autoimmune disease, is most likely not premalignant (30). However, since the clinical presentations of lichen planus and lichenoid dysplasia are similar, a confirmation biopsy should be performed on all lichenoid-appearing lesions.

Clinical presentation of invasive malignancies in the oral cavity is typically in the form of a mass, nodule or an indurated ulcer (Figs. 2 and 3). Color changes are common and consist of red,

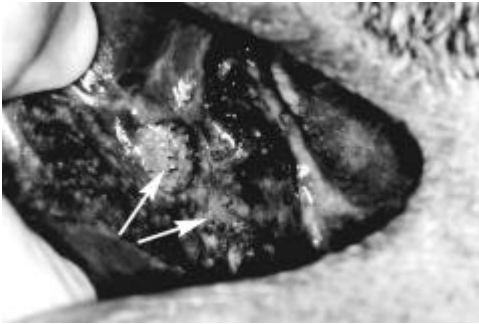


Fig. 2. Second primary squamous cell carcinoma on the buccal mucosa of a 91-year-old male.



Fig. 3. Squamous cell carcinoma of the lateral tongue. An ideal biopsy should include the ulcerated area.

or red and white hues. Attachment to adjacent tissues is possible, though not necessary, and represents local invasion of the tumor. Systemic spread occurs through the submandibular, cervical and jugular lymphatic pathways, and distant metastases most commonly occur in the lungs. Symptoms are uncommon in earlier stages of disease, but become frequent with advanced local invasion. In particular, paresthesia and anesthesia in the absence of a history of trauma are highly suggestive of invasive malignancy.

Since microscopy is the sole definitive means of distinguishing malignant tissues, biopsy is indicated for all suspicious mucosal lesions. Although exfoliative cytology is an invaluable diagnostic tool for cervical malignancies of mucosal origin, it is not a reliable method for diagnosis of suspicious oral mucosal lesions (27). Once oral squamous cell carcinoma has been confirmed by biopsy, extensive upper aerodigestive mucosal examination is mandatory, since synchronous lesions occur in 10B20% of patients (31).

Therapeutic Approaches

Clinical staging of oral cancer is accomplished based on the tumor size, lymph node involvement and metastases (TNM) classification, which is further divided into Stages IBIV (32).

Lymphatic and metastatic spread are best determined by computed tomography (CT) or magnetic resonance (MRI) studies followed by microscopic confirmation. Therapeutic strategies are usually dictated by the stage of the disease and the patient's ability and desire to withstand treatment. Similarly, prognosis is also dependent on the stage of the malignancy at initiation of therapy, the patient's compliance with the therapeutic regimen, and necessary lifestyle changes.

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Stage I and II diseases have a high rate of complete remission, and 60B80% of the patients are disease-free 5 years after surgery or radiation therapy. Stage III and IV oral cancers have poor to dismal prognosis, and any curative attempts must include multitherapeutic approaches (33). Confirmed metastatic disease is typically treated palliatively. Most treatment failures consist of either local recurrence or a second primary tumor which carries a prognosis much worse than the initial disease. Continuation of tobacco and ethanol use, as well as the presence of genetic mutations in adjacent tissues (field cancerization), has been shown to significantly decrease chances for long-term survival.

The time-tested therapeutic approaches to oral cancer are surgery and ionizing radiation. Chemotherapy has been used in research trials as adjuvant or neoadjuvant therapy for the past two decades. While initial results were not encouraging, recent studies of concomitant or alternating chemo-radiation have reported significant therapeutic benefits for patients with advanced disease. These treatments have both benefits and distinct disadvantages.

Surgery is rapid and has few associated late side effects. However, due to the requirement of a 1.0 cm resection margin of normal tissue, it tends to be painful and mutilating, and results in various degrees of oral dysfunction. Compensatory approaches such as free or attached tissue flaps and prosthetic devices are often utilized to alleviate these problems. Additionally, the stress of the surgical procedure under general anesthesia and the lengthy healing process require that the patient be relatively healthy, with few other complicating medical problems.

Radiation therapy, unlike surgical resection, preserves the integrity of tissues with little or no immediate dysfunction. Inconveniences consist of the long duration (5B8 weeks) and the late effects of this therapeutic modality. Additionally, initial use of radiation therapy reduces or precludes the option of using this method for recurrences or second primaries in the same field. Typical radiation protocols consist of 54B72 Gy (Grays, a unit of absorbed radiation dose equal to 100 rads) of gamma irradiation delivered from an external source in 180B220 cGy/day (1 centiGray [cGy] = 1/100 Gy) for 5 days/week. During active radiation, patients experience various degrees of mucositis accompanied by possible dysphagia and/or odynophagia, and dry mouth sensation or xerostomia. Mucosal lesions can be severe enough to necessitate interruption of therapy and/or hospitalization with nutritional support, but typically heal without scarring 1B2 weeks after completion of treatment (Fig. 4).

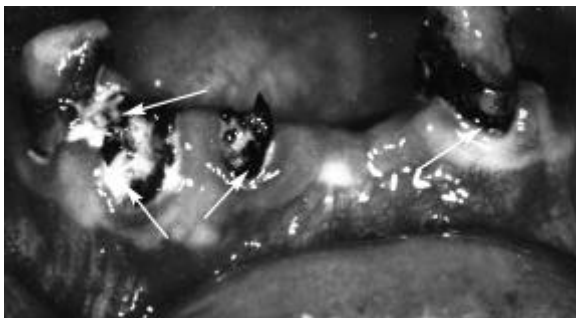


Fig. 4. Radiation-induced oral mucositis after 40 Gy of external beam radiation for floor of the mouth cancer

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To date, attempts to prevent or reduce duration and severity of radiation-induced mucositis have produced little success. Thus, standard care for this painful condition consists of palliation of symptoms and prevention of infectious complications (34). Preliminary studies of benzydamine (an anti-inflammatory medication), antimicrobial lozenges, and low-power laser therapy have shown some promise, with further investigation possibly establishing these modalities as efficacious prevention/therapy for this side effect (35, 36). Late effects of ionizing radiation typically appear weeks to months after completion of therapy and persist for the patient's lifetime. These effects result from tissue injury and fibrosis, with subsequent loss of function that is proportional to the amount of injury sustained by that tissue. In particular, salivary glands and intraosseous blood vessels can be affected irreversibly by this process, resulting in salivary hypofunction and risk for osteoradionecrosis, respectively (37).

Decrease in salivary production is not always correlated with the degree of xerostomia. However, salivary hypofunction does result in a proportionally increased risk for mucosal and dental infections, and patients are typically plagued by fungal overgrowth and dental caries (Fig. 5).

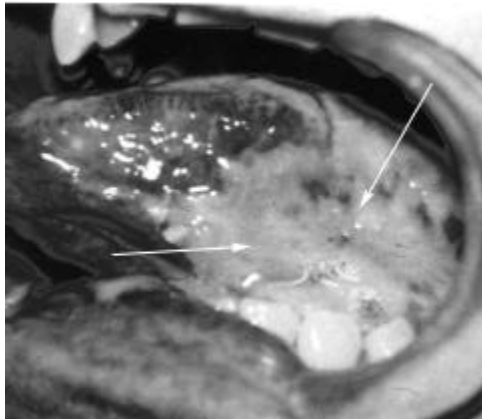


Fig. 5. Rampant caries 7 months status post 70 Gy radiation therapy.

Meticulous oral hygiene, augmented by chlorhexidine gluconate oral rinses and topically applied 1B2% fluoride gel, is mandatory for these patients (topical antifungal medications such as nystatin suspension and clotrimazole troches have a high sucrose concentration and are not recommended for dentate patients). Additionally, it is possible to increase salivary output in patients with residual gland function by using oral pilocarpine hydrochloride (Salagen⁷, MGI Pharma), at 5B10 mg three to four times daily (38, 39). Recent pilot studies suggested an advantage in salivary function preservation and patient comfort when pilocarpine is started during, rather than after, radiation therapy (40, 41). This advantage must be confirmed by larger, independent studies that will also assess effects of the regimen on tumor response and recurrence rate.

The definition of osteoradionecrosis (ORN) is still debated in the literature. Most experts in the field agree, however, that loss of bone vitality, with or without sequestration in the field of previous high dose ionizing radiation, is necessary to diagnose this condition (42). The pathogenesis of ORN consists of gradual fibrosis and narrowing of feeding intraosseous vessels, followed by infarction and tissue death (42, 43). The necrotic bone may be exposed to the oral environment

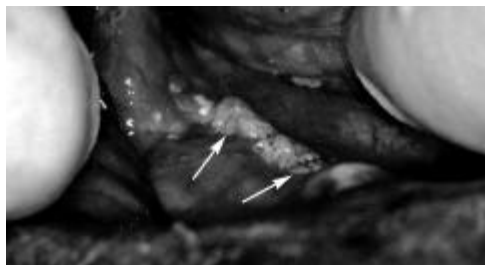


Fig. 6. Osteoradionecrosis of the mandible at 14 months status post 72 Gy radiation therapy. A tooth was extracted in that area one month prior to the photograph.

spontaneously or by trauma to overlying mucosal tissues, and superinfection may follow with oral microorganisms (Fig. 6). This process correlates directly with the amount of radiation the bone has received and inversely with the supply of collateral circulation (44). The gradual deterioration of the local circulation is irreversible and reaches its peak approximately 6 months to a year after completing radiotherapy. Thus, all necessary oral surgical procedures should be completed either before or within 6 months after radiation (45). Patients requiring surgery after this period and those who develop spontaneous ORN can benefit from hyperbaric oxygen therapy (46, 47). Studies have shown this treatment to enhance wound healing and stimulate angiogenesis in irradiated tissues. The inconveniences of this treatment are its long duration (20B30 dives are recommended), its expense, and the paucity of available hyperbaric chambers. Recent case series reports have shown that successful surgical treatment in irradiated jaws as well as management of cases of ORN are possible even without the benefit of hyperbaric therapy (48, 49). It is still unclear, however, which cases can be managed conservatively and which stand to benefit most from the expensive hyperbaric chamber.

Use of cytotoxic medications alone for oral squamous cell carcinoma has shown no success in improving life expectancy in these patients. Despite a high percentage of initial partial and complete tumor response, a majority of these cancers recur within months unless another therapeutic method is implemented (50). Neither adjuvant nor neoadjuvant protocols containing various drug combinations have demonstrated increased survival. Nevertheless, chemotherapy is the only systemic therapeutic approach available and thus represents the single current option for fighting metastatic disease. The high tumor response rate makes it plausible that cytotoxic drugs actually do eradicate microscopic disease (51), and this modality should be included in all cases where distant spread is suspected.

The standard of care for advanced oral and pharyngeal cancer consists of combined surgical and radiation therapy, most commonly in this chronological order. When surgery up-front is not feasible, radiation therapy may be followed by salvage surgery for elimination of residual disease. Recent attention has focused on treatment of advanced oral cancer with concomitant or alternating combination chemo-radiotherapy, and results have been encouraging thus far (52B54). These protocols have generally been applied to patients with stage III and IV disease. Most studies have shown the combination therapies to be superior in both survival and disease-free survival rates at the expense of more severe side effects during treatment. Finally, a recent study has resurrected the idea of neoadjuvant chemotherapy by reporting excellent results with a protocol of two rapid cycles of cytotoxic medications followed immediately by irradiation (55). Dose-limiting side effects of combination regimens are mainly local, with severe mucositis reported in more than 90% of the

patients. This finding adds urgency to the quest for an effective mucositis-preventive protocol which may provide patient comfort and allow for more aggressive treatment, with better disease control and survival.

Cancer Chemoprevention

When discussing this topic, we must mention from the start that oral cancer chemoprevention research has been hampered by lack of a clear precancerous lesion and absence of biomarkers to measure intermediate outcomes. Thus, results published must be interpreted cautiously. The problem has two aspects: prevention of malignant transformation in committed premalignant tissues, and return to normal growth control patterns; and prevention of multiple primary tumors in tissues adjacent to a successfully treated carcinoma. The basic idea is that the carcinogenic process may be inhibited or reversed by administration of various exogenous compounds. Based on earlier evidence that malignant transformation favors patients deficient in certain nutrients, attention has focused on antioxidant substances from the retinoid (vitamin A) and tocopherol (vitamin E) families (56). Consistent and encouraging results were obtained *in vitro* and in animal studies. Several human trials, however, reported either no significant activity or unacceptable severity of side effects and recurrence of premalignant lesions after cessation of therapy (56, 57). Additionally, the Beta-Carotene and Retinol Efficacy Trial (CARET) has found that patients randomized to vitamin A and beta-carotene had an increased overall mortality and lung-cancer-related deaths (58). These studies are hard to reconcile with data showing increased risk for cancer in patients deficient in retinoids and other antioxidant substances. Once again, a better understanding of the malignant molecular process may elucidate these issues.

Conclusion

Cancer of the oral cavity and pharynx is still taking a high toll in those populations at risk. These lesions are easily visualized, and early detection could dramatically contribute to decreasing morbidity and mortality from this disease. Recent research has identified changes in epidemiological patterns and etiologic agents related to various oral subsites of oropharyngeal squamous cell carcinoma. Treatment of advanced stages of the disease is also changing to include the addition of chemotherapy to surgical and/or radiation protocols. Finally, contrary to expectations, chemopreventive regimens have been disappointing in their ability to control or reverse the malignant process. New clinical trials must incorporate the effects of various substances on oral mucosal tissues, if further progress is to be made in our understanding of carcinogenesis.

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