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Cancers of the Oral Mucosa

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Updated: Sep 23, 2008

Introduction

Background

Approximately 90% of oral cancers are squamous cell carcinoma (SCC), which is seen in older men, typically on the lip or lateral part of the tongue.

Oral SCC (OSCC) is particularly common in the developing world. The etiology appears to be multifactorial and strongly related to lifestyle, mostly habits and diet (particularly tobacco alone or in betel, and alcohol use), although other factors, such as infective agents, also are implicated. Immune defects, defects of carcinogen metabolism, or defects in DNA-repair enzymes underlie some cases. Sunlight exposure predisposes to lip cancer.

Findings from the history and clinical examination by a trained diagnostician are the primary indicators of OSCC, but the diagnosis must be confirmed histologically.

Pathophysiology

In oral squamous cell carcinoma (OSCC), modern DNA technology, especially allelic imbalance (loss of heterozygosity) studies, have identified chromosomal changes suggestive of the involvement of tumor suppressor genes (TSGs), particularly in chromosomes 3, 9, 11, and 17. Functional TSGs seem to assist growth control, while their mutation can unbridle these control mechanisms.

The regions most commonly identified thus far have included some on the short arm of chromosome 3, a TSG termed *P16* on chromosome 9, and the TSG termed *TP53* on chromosome 17, but multiple other genes are being discovered.

As well as damage to TSGs, cancer may also involve damage to other genes involved in growth control, mainly those involved in cell signaling (oncogenes), especially some on chromosome 11 (*PRAD1* in particular) and chromosome 17 (Harvey ras [*H-ras*]). Changes in these and other oncogenes can disrupt cell growth control, ultimately leading to the uncontrolled growth of cancer. *H-ras* was one of the oncogenes that first caught the attention of molecular biologists interested in cell signaling, cell growth control, and cancer. It and the gene for epidermal growth factor receptor (*EGFR*) are involved in cell signaling.

The genetic aberrations involve, in order of decreasing frequency, chromosomes 9, 3, 17, 13, and 11 in particular, and probably other chromosomes, and involve inactivated TSGs, especially *P16*, and *TP53* and overexpressed oncogenes, especially *PRAD1*.

The molecular changes found in OSCC from Western countries (eg, United Kingdom, United States, Australia), particularly *TP53* mutations, are infrequent in Eastern countries (eg, India, Southeast Asia), where the involvement of *ras* oncogenes is more common, suggesting genetic differences that might be involved in explaining the susceptibility of certain groups to OSCC.

The rare Li-Fraumeni syndrome is associated with defects in *TP53*.

Carcinogen-metabolizing enzymes are implicated in some patients. Alcohol dehydrogenase oxidizes ethanol to acetaldehyde, which is cytotoxic and results in the production of free radicals and DNA hydroxylated bases; alcohol dehydrogenase type 3 genotypes appear predisposed to OSCC. Cytochrome P450 can activate many environmental procarcinogens. Ethanol is also metabolized to some extent by cytochrome P450 IIE1 (CYP2E1) to acetaldehyde. Mutations in some TSGs may be related to cytochrome P450 genotypes and predispose to OSCC. Glutathione S transferase (GST) genotypes may have impaired activity; for example, the null genotype of *GSTM1* has a decreased capacity to detoxify tobacco carcinogens. Some *GSTM1* and *GSTP1* polymorphic genotypes and *GSTM1* and *GSTT1* null genotypes have been shown to predispose to OSCC. *N*-acetyltransferases *NAT1* and *NAT2* acetylate procarcinogens. *N*-acetyl transferase *NAT1*10* genotypes may be a genetic determinant of OSCC, at least in some populations.

Tobacco is a potent risk factor for oral cancer. An interaction ocalvato da Windows Internet Explorer 8> Subject: Cancers of the Oral Mucosa: [Print] - eMedicine Dermatology Date: Fri, 4 Sep 2009 00:59:43 +0200 MIME-Version: 1.0 Content-Type: multipart/related; type="text/html"; boundary="-----_NextPart_000_0301_01CA2CFA.FD5F5550" X-MimeOLE: Produced By Microsoft MimeOLE V6.00.2900.5579 This is a multi-part message in MIME format. -----_NextPart_000_0301_01CA2CFA.FD5F5550 Content-Type: text/html; charset="Windows-1252" Content-Transfer-Encoding: quoted-printable Content-Location: <http://emedicine.medscape.com/article/1075729-print>



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Tobacco is a potent risk factor for oral cancer. An interaction occurs between redox-active metals in saliva and the low reactive free radicals in cigarette smoke. The result may be that saliva loses its antioxidant capacity and instead becomes a potent pro-oxidant milieu.¹

DNA repair genes are clearly involved in the pathogenesis of some rare cancers, such as those that occur in association with xeroderma pigmentosum, but, more recently, evidence of defective DNA repair has also been found to underlie some OSCCs.

Immune defects may predispose to OSCC, especially lip cancer. OSCC is also now being reported with increased frequency in association with diabetes and systemic sclerosis.

Intraoral OSCC primarily affects the posterior lateral part of the tongue. Spread is local, especially through muscle and bone, and metastasis initially is to the anterior cervical lymph nodes and later to the liver and skeleton.

Frequency

International

The oral cavity is 1 of the 10 most frequent sites of cancer internationally, with three quarters of cases affecting people in the developing world, where, overall, oral cancer is the third most common cancer after stomach and cervical cancer. An estimated 378,500 new cases of intraoral cancer are diagnosed annually worldwide.

Unfortunately, the parts of the world where oral cancer is most common are also those where descriptive information (ie, incidence, mortality, prevalence) is least available. In certain countries, such as Sri Lanka, India, Pakistan, and Bangladesh, oral cancer is the most common cancer. In parts of India, oral cancer can represent more than 50% of all cancers.

In developed countries, oral cancer is less common but is the eighth most common form of cancer overall; however, the ranking varies a great deal among countries. For example, in areas of northern France, oral cancer is the most common form of cancer in men. Estimates show that in 1980, more than 32,000 new cases of oral cancer were diagnosed throughout the European community. The prevalence of lip cancer appears to be decreasing, but the prevalence of intraoral cancer appears to be rising in many countries, especially in younger people. This is especially true in Central and Eastern Europe.

Mortality/Morbidity

Mortality rates for oral squamous cell carcinoma (OSCC) have increased, primarily in many eastern European countries.

- In Germany, The Czech Republic, and Hungary, almost a 10-fold increase in mortality from oral cancer in men aged 35-44 years occurred within one generation.
- Systematic analyses of cancer mortality data for 28 European countries showed pronounced upward trends in oral cancer mortality in persons aged 35-64 years from 1955-1989.
- Inspection of age-specific mortality rates reveals substantial increases at younger ages in most European countries, thus indicating the existence of strong cohort effects that will lead to increasing levels of oral cancer among males during future decades.

Race

The prevalence of tongue cancer is consistently found to be higher (by approximately 50%) in blacks compared with whites within the same regions of the United States.² The prevalence of oral cancer is also generally higher in ethnic minorities in other developed countries.³

Sex

Oral cancer affects males more frequently than females, although the ratio is equalizing.

Age

Oral cancer is predominantly found in middle-aged and older persons.

Clinical

History

Some oral squamous cell carcinomas (OSCCs) arise in apparently normal mucosa, but many are preceded by clinically obvious premalignant lesions, especially erythroplakia (red patch), leukoplakia (white patch), a speckled leukoplakia (red and white patch), or verrucous leukoplakia, and many others are associated with such lesions (especially in Southeast Asia).

- Erythroplastic lesions are velvety red plaques, which in at least 85% of cases, show frank malignancy or severe dysplasia. In contrast, most white lesions are not malignant or premalignant. Speckled or verrucous leukoplakias are more likely to be premalignant. Carcinomas are seen 17 times more frequently in erythroplakias than in leukoplakias, but leukoplakias are far more common. The prevalence of malignant transformation in leukoplakias ranges from 3-33% over 10 years; homogeneous leukoplakias are only very occasionally premalignant, but speckled or verrucous leukoplakias are more likely to be premalignant.
- In most cases, a biopsy and a histologic examination are required because dysplasia may precede malignant changes. The rate of malignant changes can be as high as 36% when moderate or severe dysplasia is present.
- Be aware that single ulcers, lumps, red patches, or white patches (particularly if they persist >3 wk) may be manifestations of malignancy.
- OSCC may manifest as the following:
 - A red lesion (erythroplakia)
 - A granular ulcer with fissuring or raised exophytic margins
 - A white or mixed white and red lesion
 - A lump sometimes with abnormal supplying blood vessels
 - An indurated lump/ulcer (ie, a firm infiltration beneath the mucosa)
 - A nonhealing extraction socket
 - A lesion fixed to deeper tissues or to overlying skin or mucosa
 - Cervical lymph node enlargement, especially if hardness is present in a lymph node or fixation: Enlarged nodes in a patient with oral carcinoma may be caused by infection, reactive hyperplasia secondary to the tumor, or metastatic disease. Occasionally, a lymph node is detected in the absence of any obvious primary tumor.
- These potentially malignant lesions and OSCC should be detected at an early stage; however, many oral tumors still are seen only when advanced. Diagnosis is often delayed by up to 6 months, even in developed countries, despite exhortations over the past 25 years to increase the index of suspicion. Early detection and treatment is the short-term goal because this results in considerably better survival rates.
- Early carcinomas may not be painful; however, later, they may cause pain and difficulty with speech and swallowing.

Physical

A systematic and thorough examination of the mouth, fauces, and cervical lymph nodes should be performed by a clinician trained in the diagnosis of oral diseases, and a general physical examination is indicated. Dental practitioners and dental care professionals are trained in the examination of the mouth.

Advanced caries, periodontal disease, or periapical lesions may need early attention, especially if radiotherapy is to be used in management of a tumor. Examine the teeth, periodontium, and entire mucosa in good lighting.

- The most common sites of oral cancer include the lower lip, the lateral margin of the tongue, and the floor of the mouth; however, all areas should be scrutinized. The sump area or "coffin corner" at the posterior tongue/floor of the mouth is a common site for cancer but may be missed by cursory inspection; special care is needed to ensure close examination.
- The clinical appearance of oral cancer is highly variable and includes ulcers, red or white areas, lumps, or fissures.
- Lesions always must be palpated after inspection to detect induration and fixation to deeper tissues.
- Erythroplasia (erythroplakia) is a red and often velvety lesion, which, unlike leukoplakias, does not form a plaque but is level with or depressed below the surrounding mucosa.
 - Of erythroplasia lesions, 75-90% prove to be carcinoma or carcinoma in situ or show severe dysplasia.

- Erythroplasia affects patients of either sex in their sixth and seventh decades and typically involves the floor of the mouth, the ventrum of the tongue, or the soft palate.
- Red oral lesions usually are more dangerous than white oral lesions.
- Oral mucosal white patches usually result from increased keratinization or candidosis.
 - Currently, the term leukoplakia is usually restricted to white patches for which a cause cannot be established; therefore, the term implies a diagnosis by exclusion (eg, lichen planus, candidiasis).
 - The term leukoplakia is also used irrespective of the presence or absence of epithelial dysplasia. Leukoplakia is a clinical term for a persistent adherent white patch with no histologic connotation and no implied premalignant potential; keratosis is the term now commonly used. Oral carcinoma can also appear as a white patch.
- Most lip cancers manifest on the lower lip at the mucocutaneous junction as a chronic small lump, ulcer, or scabbed lesion.
- Most intraoral cancers manifest on the middle third of the lateral margins of the tongue with an erythroplastic component and, sometimes, induration.
- Late tongue cancer may manifest as an exophytic lesion, an ulcer, or an area of superficial ulceration with induration.
- A typical malignant ulcer is hard with heaped-up and often everted or rolled edges and a granular floor.
- The floor of the mouth is the second most common intraoral site for cancer and more commonly is associated with leukoplakia. Most cancer arises in the anterior floor of the mouth as an indurated mass that soon ulcerates, resulting in slurring of speech.
- Carcinomas of the alveolus or gingiva are mostly seen in the mandibular premolar and molar regions, usually as a lump (epulis) or ulcer. The underlying alveolar bone is invaded in 50% of cases, even in the absence of radiographic changes, and adjacent teeth may be loose.
- Carcinomas of the buccal mucosa are mostly seen at the commissure or in the retromolar area. Most are ulcerated lumps, and some arise in candidal leukoplakias.
- Second primary tumors (SPTs) are additional primary carcinomas (synchronous tumors) present in as many as 10-15% of persons with oral carcinoma and are most commonly seen in the mouth in patients with gingival, floor of mouth, lingual, or buccal carcinoma. SPTs may also be present elsewhere in the upper aerodigestive tract.
- Lymph node examination is of paramount importance, and general examination and, possibly, endoscopy, may be indicated to detect metastases or SPTs.
 - From 30-80% of patients with oral cancer have metastases in the cervical lymph nodes at presentation.
 - Oral cancer predominantly metastasizes locally and to regional lymph nodes, primarily in the anterior neck. Later, dissemination to the lungs, liver, or bones may occur.
 - Any chronic oral lesion should be regarded with suspicion, especially when found in an older patient, when lesions appear (see History), with induration, with fixation to underlying tissues, with any recent changes in appearance, with associated lymphadenopathy, or with no obvious explanation for the lesion.
 - Examine the entire mucosa because widespread dysplastic mucosa (field change) or a second neoplasm (see Staging) may be present.
 - Carefully record the location of suspicious lesions, preferably on a standard topographic diagram.

Causes

Tobacco and alcohol use are independent risk factors for mouth cancer and tongue cancer. Heavy tobacco smokers have a 20-fold greater risk; heavy alcohol drinkers a 5-fold greater risk and those who do both have a 50-fold greater risk. Betel-quid chewing and oral snuff are important risk factors in people from specific geographic areas (eg, betel chewing in Southeast Asia). Finally, a diet low in fresh vegetables and fruits has also been implicated in causing oral squamous cell carcinoma (OSCC), and human papillomaviruses have been implicated in oropharyngeal cancers.⁴

- Cigarette smoking: Compared with persons who do not smoke, the risk of oral cancer in persons who smoke low/medium-tar cigarettes and high-tar cigarettes was 8.5- and 16.4-fold greater, respectively. (Note that cigarettes are classified as low/medium if the tar yield is less than 22 mg and high tar if the tar yield is greater than 22 mg). (See the Medscape Smoking Resource Center for additional information.)
- Alcohol
 - Growing evidence is associating increased alcohol consumption with the risk of developing OSCC.⁵

- Alcoholic beverages may contain carcinogens or procarcinogens, including nitrosamine and urethane contaminants and ethanol. Ethanol is metabolized by alcohol dehydrogenase and, to some extent, by cytochrome P450 to acetaldehyde, which may be carcinogenic.
- The combined effects of tobacco use and alcohol consumption are found to be multiplicative. Compared with persons who do not drink and do not smoke, the risk of developing OSCC is increased 80-fold in persons with the highest levels of smoking and alcohol consumption.
- Betel and similar habits⁶
 - The betel quid contains a variety of ingredients, including betel vine leaf, betel (areca) nut, catechu, and, often, slaked lime together with tobacco. Some persons chew the nut only, and others prefer paan, which includes tobacco and sometimes lime and catechu. In 1986, the International Agency for Research on Cancer has deemed betel-quid chewing an important risk factor, and the areca (betel) nut habit with or without tobacco use can cause cytogenetic changes in oral epithelium. Various other chewing habits, usually combinations that contain tobacco, are used in different cultures (eg, Qat, Shammah, Toombak).
 - Tobacco chewing in people from parts of Asia appears to predispose to OSCC, particularly when it is started early in life and is used frequently and for prolonged periods.^{7,8}
 - Studies from India have confirmed the association between paan tobacco chewing and OSCC, particularly cancer of the buccal and labial mucosa.
- Diet: A significant protective effect of diet against oral cancer has generally been shown in persons who consume beta-carotene-rich vegetables and citric fruits.
- Oral health⁹
 - A case-control study (ie, every oral cancer case prior to surgery and every control at the time of interview had a structured oral examination) from China found that wearing dentures, per se, is not a risk factor, although the risk was increased in men who wore dentures made from metal.
 - Poor dentition, as reflected by missing teeth, emerged as a strong risk factor independent of other established risk factors.
- Mouthwash use: The effect of the alcohol in mouthwash appears to be similar to that of alcohol used for drinking, although the contribution of mouthwash use to oral cancer must be small in terms of attributable risk.
- Socioeconomic status: Behaviors that lead to social instability or social instability itself have been linked to an increased risk of oral cancer, but many other explanations may exist (eg, habits, oral health, diet, nutrition).
- Infective agents: *Candida albicans* and viruses, such as herpes viruses and papillomaviruses, may be implicated in some cases. Human papillomaviruses are particularly implicated in oropharyngeal cancers.¹⁰ Also see the
- Other: Associations also are apparent between oral cancer and other various oral conditions (eg, oral submucous fibrosis, oral lichen planus, lupus erythematosus).

Differential Diagnoses

Actinic Keratosis

Candidiasis, Mucosal

Leukoplakia, Oral

Lichen Planus

Workup

Laboratory Studies

- The principles are to confirm the oral squamous cell carcinoma (OSCC) diagnosis histopathologically and to determine whether malignant disease is present elsewhere, including the following:
 - Bone, muscle, or primary tumors: Other primary tumors are typically located in the upper aerodigestive tract (eg, mouth, nares, pharynx, larynx, esophagus). Whether endoscopy is warranted to detect such tumors in all cases remains controversial.

- Metastases: This initially occurs to regional lymph nodes and later to the liver, bones, and brain. Imaging studies may help detect abnormalities missed during the clinical examination.
- Blood tests include the following:
 - Liver function tests: Results may reveal metastases in persons with advanced disease.
 - Complete blood cell count and hemoglobin value
 - Urea and electrolyte measurements
 - Blood group testing and cross-matching
 - Calcium level: As many as 4% of patients with cancer in the head and neck may have elevated serum calcium levels. This is a poor prognostic indicator primarily found in persons with advanced disease.
 - Serum ferritin, alpha-antitrypsin, and alpha-antiglycoprotein levels: Persons with high-stage cancer of the head and neck also have increased levels of serum ferritin, alpha-antitrypsin, and alpha-antiglycoprotein, while those at any stage of disease have increased haptoglobin levels (although not known if this is true specifically for oral cancer). Additionally, prealbumin levels are decreased slightly in persons at any stage. Results from assays of these serum constituents cannot be regarded as sufficiently specific or sensitive to be of reliable clinical value, and this, unfortunately, is also true of the many tissue markers thus far described.

Imaging Studies

- Photography to create a photographic record is especially useful for monitoring the clinical state and site of premalignant lesions.
- Chest radiography and endoscopy are valuable procedures for excluding synchronous SPTs. Chest radiography may be indicated because the lungs are the most common site for metastases and a site for second primary carcinomas.
 - Radiography, sometimes including axial CT scanning or, possibly, other imaging techniques, may be needed to determine the degree of spread of some tumors, particularly to exclude bone invasion and lymph node involvement.
 - Chest radiography is important as a preanesthetic check, especially in patients with known pulmonary or airway disease and to demonstrate metastasis to the lungs or hilar lymph nodes, ribs, or vertebrae.
 - Jaw radiography (often rotating pantomography) may show invasion, although it is inadequate to exclude bone invasion.
- Other imaging investigations include MRI or CT scanning of the primary site, of the head and neck, and of suspected sites of lymph node or distant metastases. Sentinel node biopsy, MRI, 18-fluorodeoxyglucose positron emission tomography (FDG-PET) scanning, or ultrasonography of the neck (or combinations) can be used to delineate the extent of cervical node metastasis.
- Radionuclide scanning occasionally is useful.
 - Bone scanning is of little value in screening because findings are positive only where bone involvement is symptomatic. Bone scanning is primarily used to determine the extent of tumor spread.
 - Liver radionuclide scanning shows abnormal findings in as many as 6% of patients with cancer in the head and neck, but two thirds are false-positive findings; therefore, liver scanning normally is not indicated.
- Routine panendoscopy helps identify simultaneous second primary carcinomas in the esophagus, larynx, or lungs in as many as 14% of patients. Endoscopy is widely recommended, although it is not performed in all centers. More than one third of SPTs are detectable by endoscopy at or within 1 year of diagnosis of the index tumor.

Other Tests

- Electrocardiography

Procedures

- Incisional biopsy, guided when appropriate by vital staining, is essential to confirm the diagnosis. A biopsy must be performed on any oral mucosal lesion suggestive of cancer, including any ulcer that does not heal within 2-3 weeks.
 - An incisional biopsy is always required, usually with the patient under local anesthesia.
 - Always take a biopsy specimen of the red lesions if both red and white lesions are present because red, rather than white, areas are more likely to show dysplasia.

- In vivo staining may help if difficulty arises when deciding which area is most appropriate for the biopsy, particularly if widespread lesions are present.
- Staining with toluidine blue followed by a rinse with 1% acetic acid and then saline may stain the areas most suggestive of findings and indicate which need a biopsy. Oral carcinoma in situ and early invasive carcinoma have an affinity for toluidine blue dye, and although several false-positive results may be encountered, these can be minimized by restaining after 14 days. Toluidine blue clearly is more effective in experienced hands and when used with appropriate clinical judgment.
- Counterstaining with Lugol iodine solution may enhance the usefulness of toluidine blue staining.
- Various light sources are becoming available to help delineate areas for biopsy.
- The biopsy specimen should be sufficiently large to include enough suspect and apparently normal tissue to provide the pathologist an opportunity to make the diagnosis and to not have to request an additional specimen. Most patients tolerate (physically and psychologically) one biopsy session. Most biopsy wounds, whether 0.5 cm (too small) or 1.5 cm long (usually adequate), heal within 7-10 days; therefore, taking at least one ample specimen is better than having to repeat the procedure. Some clinicians always take several biopsy specimens at the first visit to avoid the delay, anxiety, and aggravation resulting from a negative pathology report for a patient in whom cancer is strongly suspected.
- Fix biopsies in 10% normal saline to prevent autolysis.
- Excisional biopsy: Avoid excisional biopsies unless the lesion is small because the procedure is unlikely to have achieved excision of an adequately wide margin of tissue if the lesion is malignant but will have destroyed clinical evidence of the site and character of the lesion for the surgeon or radiotherapist. This can be avoided by tattooing the site.
- Lymph node biopsy: A biopsy is best performed on regional lymph nodes suggestive of cancer using a fine-bore needle to aspirate cells for cytologic examination. Ultrasound-guided fine-needle aspiration cytology is now favored.
 - False-negative results are possible, but the primary danger of incisional biopsy is that it may seed malignant cells.
 - In practical terms, ipsilateral, firm or hard, enlarged regional lymph nodes in a patient with an obvious oral carcinoma are likely to include metastases.

Histologic Findings

The epithelium forms islands resembling normal stratified squamous epithelium, except that the islands are invading the underlying tissues and undergoing aberrant keratinization. Instead of the keratin being formed and shed from the surface, it is formed within the substance of an epithelial island, producing a keratin whorl or epithelial pearl. This is a feature of well-differentiated carcinoma.

Epithelial islands may be discrete and circumscribed, although they are invading the underlying tissues quite extensively or appear more moth eaten with loss of basement membrane; however, loss of basement membrane is not a prerequisite of an invasive tumor. Occasionally, an endogenous foreign body giant cell reaction to the keratin from ruptured pearls occurs.

SCC consists of small islands of squamous cells with a high mitotic index and nuclear hyperchromatism but no obvious keratinization.

Poorly differentiated SCC consists of sheets of cells showing extreme pleomorphism, giant nuclei, and multiple and bizarre mitoses and often is difficult to distinguish from other malignancies, particularly poorly differentiated lymphoma or melanoma. In this instance, immunocytochemical markers such as keratins, common leukocyte antigen, and melanoma-specific antibodies are indicated.

Staging

The 1993 American Joint Committee on Cancer TNM classification and staging of oral cancer is as follows:

- Classification
 - Primary tumor
 - T0 - No primary tumor
 - Tis - Carcinoma in situ

- T1 - Tumor 2 cm or smaller
 - T2 - Tumor 4 cm or smaller
 - T3 - Tumor larger than 4 cm
 - T4 - Tumor larger than 4 cm and deep invasion to muscle, bone, or deep structures (eg, antrum)
 - Lymphatic node involvement
 - N0 - No nodes
 - N1 - Single homolateral node smaller than 3 cm
 - N2 - Nodes(s) homolateral smaller than 6 cm
 - N3 - Nodes(s) larger than 6 cm and/or bilateral
 - Tumor metastasis
 - M0 - No metastasis
 - M1 - Metastasis noted
- Staging
 - Stage I - T1, N0, M0
 - Stage II - T2, N0, M0
 - Stage III
 - T3, N0, M0
 - T1, T2, T3, N1, M0
 - Stage IV
 - T4, N0, M0
 - Any T, N2 or N3, M0
 - Any T, any N, any M

Treatment

Medical Care

Combined clinics that include surgeons, oncologists, and support staff usually have an agreed treatment policy and offer the best outcomes. Oral squamous cell carcinoma (OSCC) currently is treated largely by surgery and/or irradiation, although few unequivocal controlled trials of treatment modalities have been conducted. Photodynamic and chemotherapy have occasional applications.

Important factors to consider are quality of life and patient education. In one study, at least 6 months after the diagnosis of oral cancer, 47% of participants still smoked and 36% drank alcohol to excess. Only one third of the participants were aware that these habits were important in the development of oral cancer.

The prognosis of OSCC is site dependent. For intraoral carcinoma, the 5-year survival rate may be as low as 30% for posterior lesions presenting late, as they often do. For lip carcinoma, the 5-year survival rate often is more than 70%.

Radiotherapy

Advantages of radiotherapy include the facts that (1) normal anatomy and function are maintained, (2) general anesthesia is not needed, and (3) salvage surgery is available if radiotherapy fails.

Disadvantages mainly include the facts that (1) adverse effects are common; (2) cure is uncommon, especially for large tumors; and (3) subsequent surgery is more difficult and hazardous and survival is reduced further.

Radiotherapy can be performed by external beam radiation (teletherapy), which is commonly accompanied by adverse effects, or interstitial therapy (eg, brachytherapy, plesiotherapy). Implants of iridium Ir 192 for a few days are often used, supplying a radiation dose equivalent to teletherapy but one that is confined to the lesion and immediate area. Plesiotherapy causes fewer complications but is suitable only for tumors that are smaller than 2 cm and located in selected sites.

Of short-term complications, the oral mucositis that invariably follows external beam radiotherapy involving the oral tissues or cancer chemotherapy can be the most distressing and may have significant effect on the quality of life. Occasionally, oral mucositis is so severe that cancer therapy needs to be curtailed. As many as 40% of patients can be affected.

Longer-term complications of radiotherapy, such as dry mouth (xerostomia), loss of taste, osteoradionecrosis (ORN) (less commonly), and other problems also may be distressing. Radiotherapy also complicates further surgery, because in particular, the endarteritis impoverishes healing. Prevention and treatment of oral complications whenever possible are important and should be performed by an oncologic team including a dental practitioner and an oral hygienist.

Prevention and treatment planning before cancer therapy

Prevention of oral disease and careful treatment planning are essential to minimize oral disease and the need for, and possible adverse consequences of, operative intervention. Adults with malignant head and neck disease unfortunately often have poor oral hygiene and care and are poorly compliant with oral health care. Most (97%) need oral health care before radiotherapy or chemotherapy for cancer. Almost one third of patients need oral care before bone marrow transplantation.

Extremely important, but often overlooked, is the need for psychosocial counseling; patients must be counseled carefully to ensure they can adjust, at least partially, to the complications of cancer therapy.

Many patients undergoing head and neck cancer surgery, particularly of the neck, can have life-threatening postoperative complications. These can often be predicted by preoperative assessment using a specific activity scale questionnaire, an assessment of alcohol abuse, and a platelet count, because thrombocytosis identifies patients at risk for wound infection.

Fruits and vegetables appear to offer some protective effect. The potential of topical gel formulations for local delivery of chemopreventive plant anthocyanins is being investigated.¹¹

Oral health and disease in cancer therapy

Complications of cancer therapy depend on the type of malignancy and location, the treatment modality used (ie, agents, sequencing, rate of delivery, dosage), and host factors. For example, the severity of oral mucositis following radiation therapy depends on the ionizing radiation used, the rate at which it is delivered, and the total dose given.

Manifestations of cancer therapy may include mucositis and oral ulceration, infections, bleeding, pain, xerostomia, ORN, taste loss, trismus, and caries. These require prevention and management.

- Mucositis
 - Mucositis can be induced either by chemotherapy or by radiotherapy. Mucositis appears from 3-15 days after cancer treatment, earlier with chemotherapy than with radiotherapy.
 - Pain can be so intense that it interferes with eating and quality of life. Occasionally, therapy must be stopped for several days to allow healing.
 - In addition to causing local pain and ulceration, mucositis can provide a portal for microbial entry and thus, can result in local and, sometimes, systemic infection.
 - The acute mucosal reaction to radiotherapy results from mitotic death of cells in the epithelium. The cell cycle time of basal epithelial cells is approximately 4 days, and because this epithelium is 3-4 cells thick, radiation changes begin to appear at approximately 12 days after the start of irradiation, independently of the dose, fractionation, or radiation technique.
 - Initial mucosal erythema is followed after a few days by the appearance of a patchy fibrinous exudate. If a high dose of radiation is given over a short time, ulceration may supervene, with a thick fibrinous membrane covering the denuded surface.

- Surviving epithelial cells respond to radiation damage by dividing more rapidly; therefore, complete healing is the rule. The duration mucositis takes to heal depends on the dose intensity of the radiotherapy, but usually, healing is complete within 3 weeks after the end of treatment. Tobacco smoking delays resolution.
- Cytotoxic drugs, which have a selective action on cells in the mitotic cycle, kill regenerating epithelial cells; therefore, the simultaneous use of chemotherapy and radiotherapy results in more severe and prolonged mucosal toxicity.
- Frank oral ulceration may be a portal for infection and septicemia.
- Preventing or ameliorating mucositis may be possible not only by minimizing exposure to radiation, but also by taking active measures. For example, radiotherapy radically increases oral gram-negative enterobacteria and pseudomonads. The presence of gram-negative bacilli may contribute to the mucositis. In addition, these microorganisms release powerful endotoxins that themselves cause both systemic and local effects on the host.
 - If gram-negative bacilli have a role in the etiology of irradiation mucositis, preventing, treating, or ameliorating mucositis may be possible by abolishing the gram-negative flora.
 - Promising results have been reported in 2 clinical trials using polymyxin E and tobramycin applied locally 4 times daily. This regimen has not been evaluated fully for the treatment of existing irradiation mucositis.
 - Oral hygiene should be maintained with brushing the teeth.
 - Advise the patient to eat a soft, bland diet and avoid irritants such as smoking, spirits, or spicy foods.
 - Topical analgesics (eg, aspirin, benzydamine, lignocaine, dyclonine, diphenhydramine) may provide symptomatic relief.
- Topical chlorhexidine gluconate and sucralfate may reduce the frequency and severity of mucositis.
- Oral infections
 - levels of *Streptococcus mutans*, *Lactobacillus* species, and candidal species significantly increase after radiotherapy. These changes are maximal from 3-6 months after radiotherapy, after which no further change or a partial return towards the baseline flora occurs.
 - The frequency and severity of oral infections with virus, bacteria, and fungi significantly increase after cytotoxic chemotherapy and radiochemotherapy. The primary symptomatic viral infections affecting the mouth in patients with cancer include herpes simplex virus (HSV) and herpes varicella-zoster virus infections. Acyclovir remains the primary treatment, but new agents, such as famciclovir, penciclovir, sorivudine, foscarnet, and other agents, may be needed in cases of acyclovir resistance.
 - Homeostatic microbial communities are protective in health by preventing or interfering with the colonization of exogenous pathogens (colonization resistance). When oral tissues are irradiated, colonization resistance is practically abolished, and alteration of the oral microflora occurs, with increases in yeasts and some gram-negative organisms.
 - The possible role of yeasts in irradiation mucositis has garnered considerable interest because the number of candidal subspecies, in particular, appears to increase.
 - Candidosis is the most common oral fungal infection in patients with cancer and may cause soreness and, occasionally, may be responsible for dissemination of infection. Xerostomia, dental prostheses, alcohol use, and tobacco smoking predispose patients to oral candidosis. A meta-analysis of numerous studies has shown the prophylactic value of clotrimazole or fluconazole.
- Xerostomia
 - Salivary tissue, particularly serous acini, is highly vulnerable to radiation damage, and the parotid glands are damaged most readily. A radiation dose as small as 20 Gy can cause permanent cessation of salivary flow if given as a single dose, and with the conventional treatments for oral carcinoma (60-70 Gy), a rapid decrease in flow occurs during the first week of radiotherapy, with an eventual approximate 95% reduction.
 - Salivary flow begins to diminish. After 5 weeks of radiotherapy, the flow virtually ceases and rarely completely recovers. Both resting and stimulated salivary flow are inhibited. Nevertheless, the sensation of dryness of the mouth tends to diminish after a few months to a year, partly as a result of compensatory hypertrophy of unirradiated salivary glandular tissue. After 1 year, little further improvement occurs.
 - The degree of xerostomia depends on the degree of exposure of the salivary tissue. Xerostomia occurs when the upper border of the radiation field is above the submental area, particularly when the parotid glands are involved. Partially irradiated glands have resultant higher flow rates than fully irradiated glands. Mantle, unilateral, and bilateral fields of radiation can be associated with a reduction in salivary flow of 30-40%, 50-60%, and approximately 80%, respectively.
 - A high initial salivary flow rate is associated with higher flow rates after radiotherapy.

- Radiotherapy to the nasopharynx damages both of the parotid glands and causes severe and permanent xerostomia.
- Radiotherapy to a salivary tumor may avoid the contralateral gland and not cause severe xerostomia.
- Radiotherapy fields used in the treatment of oral cancer normally avoid at least part of the parotid glands; therefore, xerostomia tends not to be as severe as it would be if both glands were irradiated in their entirety.
- Xerostomia leads to discomfort and loss of taste and appetite.
- In addition to minimizing unnecessary glandular irradiation, stimulating the salivary glands prior to radiotherapy has been suggested as valuable for reducing glandular damage. The use of pilocarpine during radiotherapy has shown encouraging results.
- In xerostomia, residual salivary tissue may be stimulated by gustatory or pharmacologic stimuli.
- Sugar-free chewing gum may be a useful stimulus. Drugs that may be effective particularly include various cholinergic agents. Pilocarpine, given as ophthalmic drops placed intraorally or as tablets, is effective in relieving symptoms and in improving salivation when used in doses of up to 5 mg administered 3 times daily.
- Individuals with dry mouth frequently sip water, particularly during eating, and they often need to keep water by their bedsides. Several saliva substitutes or mouth-wetting agents are currently marketed. Most contain carboxymethylcellulose, although some that contain animal mucins and some also contain constituents that may facilitate enamel remineralization. Some patients find these products useful, but clinical experience suggests that they are not always well accepted. Some studies have suggested that mucin-containing preparations are accepted better by patients and may promote the establishment of normal oral flora; however, when cost and convenience are taken into consideration, many patients prefer to simply sip water frequently or to use an aerosol pump of water.
- Advise xerostomia patients to avoid agents such as medications, tobacco, and alcohol that may further impair salivation.
- Dental problems
 - Although periodontal disease is not usually a problem, patients who undergo cancer therapy may be predisposed to caries because of xerostomia, foods with a high sucrose content, and, possibly, a shift to more cariogenic oral microflora. Several types of carious lesions have been identified, most involving the incisal edges and cervical areas. The direct effect of radiation on tooth structure is probably less than the indirect effect (eg, xerostomia).
 - Patients must achieve a good level of oral hygiene before radiotherapy or chemotherapy commences. Dietary control and topical fluoride therapy are essential and must be continued for life. Fluoride is applied best to the entire surface of all teeth to have the maximal protective effect. This is achieved best by providing custom-built carriers for each patient. A gel containing 1% sodium fluoride is put into the carrier and applied to the teeth for 5 min/d. Fluoride mouth rinses are also useful. Sodium fluoride mouth rinses with chlorhexidine diacetate may be particularly effective.
- Loss of taste sensation
 - Patients receiving radiotherapy to the mouth invariably experience some disturbance or loss of taste sensation. The taste receptor cells are relatively radioresistant, and the mechanism of this loss of taste has not been elucidated. Xerostomia probably contributes because disturbance of taste is common after irradiation of the parotid glands.
 - Taste loss can be a distressing symptom and contributes to poor nutrition in patients receiving radiotherapy. Fortunately, taste perception usually recovers slowly within a few months after the end of radiotherapy, although sometimes loss is permanent. Zinc sulphate may help improve taste sensation in some patients.
- Osteoradionecrosis
 - ORN, although uncommon, is potentially the most serious oral complication of radiation therapy. Radiation results in thrombosis of small blood vessels; fibrosis of the periosteum and mucosa; and, damage to osteocytes, osteoblasts, and fibroblasts. The damaged osteoclasts and osteoblasts survive until they attempt to divide, at which time mitotic death occurs. An individual bone cell may not divide for months or years after irradiation, or it may not divide unless stimulated by trauma. Therefore, a slow protracted loss of bone cells occurs after radiotherapy, with a consequent slowing of remodeling, which eventually may result in thinning and reduced bone strength. The mandible consists of more compact bone with a higher density than the maxilla; therefore, it absorbs more radiation than the maxilla.
 - The predisposition to ORN occurs because the blood supply of the mandible in the age group that develops cancer is poor and is almost entirely via the periosteum (which also becomes less vascular). The maxilla, with its lower density and rich vasculature, is rarely the site of ORN.
 - Various factors predispose patients to ORN, but generally, the risk is greatest in the mandible, in higher radiation doses, fraction size, number of fractions, and when teeth are extracted after radiotherapy. Nevertheless, ORN also may

- occur unrelated to trauma. Many patients with oral cancer abuse alcohol and tobacco and are in poor general condition, which together with poor nutritional status and oral hygiene, make them particularly prone to oral ulceration and ORN.
- ORN is most unlikely with radiation doses below 60 Gy; in doses up to 70 Gy, the rate is 1.8%, and in doses higher than 70 Gy, the rate is approximately 9%. In modern series, 5-15% of patients who undergo radiotherapy to the head and neck region develop ORN.
 - Radiation shields decrease the radiation dose received by the bone and minimize the risk of ORN.
 - Because infection or trauma (including surgical intervention) may result in local infection, delayed healing, and ORN, these should be kept to a minimum.
 - The rate of ORN is 3 times higher in dentate than in edentulous patients as a result of infection from periodontal disease and trauma from tooth extraction.
 - Tooth loss after high-dose irradiation is by no means inevitable, and the prevalence of bone necrosis is lowest if extraction can be avoided altogether.
 - The only teeth that need to be extracted before radiotherapy include those that are not vital, need root filling or elaborate restorative techniques, or are associated with active periodontal disease. Extractions of these teeth should be performed atraumatically, the tissues sutured to promote rapid healing, and antimicrobial therapy instituted.
 - All other teeth should be cleaned and restored before radiotherapy begins.
 - If dental extraction is performed shortly after radiotherapy, when devascularization occurs in addition to damage to the osteoblasts, the risk of ORN is particularly high. The risk of ORN is less if dental extraction is performed well before radiotherapy, but, regardless, the risk remains as a consequence of the enhanced remodeling of bone that continues for some months after the extraction.
 - Dental extractions typically are best performed judiciously and a minimum of 2-3 weeks before commencement of irradiation therapy.
 - If surgery later becomes necessary in the management of malignant disease, irradiated tissue should be handled as gently as possible.
 - The highest rate of mandibular ORN occurs in patients who have dental extractions immediately prior to radiotherapy or immediately after. Many authors agree that postradiation extractions should be avoided if possible.
 - A conservative approach to the treatment of ORN is indicated because up to approximately 60% of cases of ORN resolve with conservative therapy. ORN is treated best in a progressive manner, depending on results and the healing of the lesion. Therapeutic approaches include local wound care, topical or systemic antibiotics, ultrasound, hyperbaric oxygen (HBO), and minor-to-extended surgery with reconstruction procedures.
 - Meticulous oral hygiene is essential, including the use of 0.02% aqueous chlorhexidine mouthwashes after meals. Irrigate away debris and allow sequestra to separate spontaneously because any surgical interference only encourages extension of the necrotic process. Any sequestrum that becomes loose should be removed gently along with any sharp edges of spicules of bone.
 - Antimicrobials are not especially effective because the tissues are avascular; therefore, prolonged treatment is necessary. Tetracyclines are useful because of their selective bone uptake, and a regimen of 250 mg of tetracycline 4 times a day for 10 days, followed by 250 mg twice daily continued for several months, is recommended. Add metronidazole at 200 mg 3 times a day in cases of severe infection or when anaerobes are implicated.
 - HBO therapy also has been shown to promote healing. HBO therapy at 2-2.5 atmospheres of pressure for 1.5-2 h/d for up to 84 sessions is recommended.
 - Adverse effects with HBO therapy are uncommon but include transient myopia, seizures, and otic or pulmonary barotrauma; the latter potentially results in air embolism.
 - Concern has been expressed that HBO therapy may exacerbate a variety of autoimmune and immunosuppressive disorders and viremia, although little evidence supports this concern.
 - Relative contraindications to HBO therapy include upper respiratory tract infection, chronic sinusitis, epilepsy, chronic obstructive airways disease, high fever, a history of spontaneous pneumothorax or thoracic or ear surgery, viral infections, congenital spherocytosis, and a history of optic neuritis. Untreated pneumothorax is the only absolute contraindication.

- Risks of HBO therapy may be minimized by a careful pretreatment assessment including chest radiography and electrocardiography. Some advise otolaryngologic and ophthalmologic assessment.
- Therapeutic ultrasound at a frequency of 3 MHz pulsed 1 in 4 at an intensity of 1 W/cm² applied to the mandible for 10 minutes daily for 50 days also may effectively improve ORN.
- Surgical management also has played a role in the treatment of ORN and may include sequestrectomy, alveolectomy with primary closure, closure of oro-cutaneous fistulae, or hemimandibulectomy.

Surgical Care

The goal of surgery for oral squamous cell carcinoma (OSCC) is to remove the primary tumor together with a margin of clinically normal tissue to ensure complete excision of malignant tissue. Surgery thus provides a one-stage definitive procedure, from which the patient normally recovers within 10-14 days. Although modern reconstructive techniques can produce good orofacial aesthetics and function, neither can be totally ensured. Cancer centers receive many patients with advanced disease, and many operations fail to remove the tumor completely, resulting in a poor outcome and recurrence of the tumor.

Ensuring that the patient is as prepared as possible for the major surgery required, particularly in terms of general anesthesia, potential blood loss, and ability to metabolize drugs, is important. In addition, address any potential dental or oral problems preoperatively in order to avoid later complications such as ORN.

Surgery provides complete tumor and lymph node excision. A full histologic examination can then be performed for staging purposes and to help predict prognosis and the need for adjuvant radiotherapy. Surgery also provides another option of treatment for radiotherapy-resistant tumors.

Disadvantages primarily are perioperative mortality and morbidity, but modern techniques have significantly decreased these risks, as well as the aesthetic and functional defects. When OSCC is fatal, it almost always is either because of failure to control the primary tumor or because of nodal metastases. Death resulting from distant metastasis is unusual.

- Ablative surgery ideally excises the cancer with at least a 2-cm margin of clinically normal tissue. If at least 1 node has clinical signs of invasion, a reasonable presumption is that others may be involved and must be removed by traditional radical neck dissection.
- Functional neck dissections (modified to preserve the jugular, sternomastoid, or accessory nerve, while ensuring complete removal of involved nodes) have gained popularity. Moderate-dose radiotherapy occasionally is used to "sterilize" such necks.
- Reconstruction is tailored to the patient's ability to cope with a long operation and the risk of significant morbidity. For soft tissue reconstruction, tissue often must be brought into the region to close the defect using split skin grafts or flaps. Local flaps (eg, nasolabial flaps) provide thin, reliable flaps suitable for repairing small defects. Distant flaps required to repair larger defects include the following:
 - Free flaps: Microvascular surgery facilitates excellent reconstruction in a single operation using, for example, forearm flaps based on radial vessels, which are particularly useful to replace soft tissue, or those based on the fibula when bone is required.
 - Pedicle flaps
 - Myocutaneous or osteomyocutaneous flaps based on a feeding vessel to muscle and perforators to the skin paddle (eg, flaps based on the pectoralis major, latissimus dorsi, or trapezius) may be used in a one-stage operation to replace skin, and because they also contain muscle, they have adequate bulk to repair defects and may be used to import bone (usually rib).
 - Forehead or deltopectoral pedicle flaps, once the mainstay, required a 2-stage operation, replaced only skin, and relied on a tenuous blood supply.
 - Hard tissue
 - Hard tissue reconstruction ideally is performed at the time of tumor resection. Dental implants can be inserted at that point to carry a prosthesis.
 - Bone is traditionally taken as free nonvascularized bone grafts from the iliac crest or rib but may survive poorly if contaminated or if the vascularity is impaired after irradiation. In such cases, or when a large defect is present, an osteomyocutaneous flap greatly improves the graft vascular bed. True free vascularized bone grafts (eg, fibula grafts) have great benefits but are time consuming and require

considerable expertise. The benefits of bone grafting for maxillary defects are less certain, and maxillary reconstruction is usually with an obturator (bung), which has the advantage that the cavity can be readily inspected.

- Specific complications from the surgery of OSCC may include infection and rupture of the carotid artery, salivary fistulae, and thoracic duct leakage (chylorrhea).

Medication

The goals of pharmacotherapy for oral squamous cell carcinoma (OSCC) are to reduce morbidity associated with secondary infection and to prevent complications.

Antiviral agents

Nucleoside analogs are initially phosphorylated by viral thymidine kinase to eventually form a nucleoside triphosphate. These molecules inhibit HSV polymerase with 30- to 50-times the potency of human alpha-DNA polymerase.

Acyclovir (Zovirax)

Inhibits activity of both HSV-1 and HSV-2. Patients experience less pain and faster resolution of cutaneous lesions when used within 48 h of rash onset. May prevent recurrent outbreaks.

Dosing

Adult

HSV-1 or HSV-2: 200 mg PO 5 times/d or 800 mg PO bid

Recurrence: Same regimen for 5 d

Pediatric

250-600 mg/m²/dose PO 4-5 times/d for 7-10 d

Interactions

Concomitant use of probenecid or zidovudine prolongs half-life and increases CNS toxicity

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

Caution in renal failure or when using nephrotoxic drugs; should be administered slowly when given IV because of risk of phlebitis

Famciclovir (Famvir)

Prodrug that when biotransformed into active metabolite penciclovir may inhibit viral DNA synthesis/replication.

Dosing

Adult

Herpes zoster: 500 mg PO q8h for 7 d

HSV-1 or HSV-2: 125 mg PO bid for recurrences or 250 mg PO bid for primary infection

Pediatric

Not established

Interactions

Coadministration of probenecid or cimetidine may increase toxicity; coadministration increases bioavailability of digoxin

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

Caution in renal failure or coadministration of nephrotoxic drugs

Penciclovir (Denavir) topical

Inhibitor of DNA polymerase in HSV-1 and HSV-2 strains, inhibiting viral replication.

Dosing

Adult

Apply q2h while awake for 4 d at first sign of symptom

Pediatric

Administer as in adults

Interactions

None reported

Contraindications

Documented hypersensitivity; previous adverse reaction to famciclovir

Precautions

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

Mild erythema may occur

Foscarnet (Foscavir)

Organic analog of inorganic pyrophosphate that inhibits replication of known herpesviruses, including CMV, HSV-1, and HSV-2. Inhibits viral replication at pyrophosphate-binding site on virus-specific DNA polymerases. Poor clinical response or persistent viral excretion during therapy may result from viral resistance. Patients who can tolerate foscarnet well may benefit from initiation of maintenance treatment at 120 mg/kg/d early in treatment. Individualize dosing based on renal function status.

Dosing

Adult

Induction: 60 mg/kg/dose IV q8h or 100 mg/kg IV q12h for 14-21 d

Maintenance: 90-120 mg/kg/d IV as a single infusion for life

Acyclovir-resistant induction in HSV infections: 40 mg/kg/dose IV q8-12h for 14-21 d

Pediatric

<12 years: Not established

>12 years: Administer as in adults

Interactions

Avoid use in combination with potentially nephrotoxic drugs (eg, aminoglycosides, amphotericin B, IV pentamidine) unless potential benefits outweigh risks; coadministration with IV pentamidine may cause hypocalcemia

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

May cause decline in renal function; for correct dosing, obtain 24-h serum creatinine value at baseline and continue to monitor (discontinue if serum creatinine level >0.4 mL/min/kg); hydration may reduce nephrotoxicity; carefully monitor electrolytes (eg, calcium, magnesium); assess for electrolyte and mineral abnormalities if mild perioral numbness, paresthesias symptoms, or seizures occur; granulocytopenia and anemia may occur (regularly monitor CBC count)

Infuse into veins with adequate blood flow to avoid local irritation; to avoid toxicity, do not administer by rapid or bolus IV injection

Antibiotics

Antimicrobials are not especially effective because the tissues are avascular; therefore, prolonged treatment is necessary.

Tetracycline (Sumycin)

Useful because of selective bone uptake. Treats gram-positive and gram-negative organisms as well as mycoplasmal, chlamydial, and rickettsial infections. Inhibits bacterial protein synthesis by binding with 30S and possibly 50S ribosomal subunit(s).

Add metronidazole in cases of severe infection or when anaerobes are implicated.

Dosing

Adult

250 mg PO qid for 10 d initially, followed by 250 mg PO bid for several months

Pediatric

<8 years: Not recommended

>8 years: Not established

Interactions

Bioavailability decreases with antacids containing aluminum, calcium, magnesium, iron, or bismuth subsalicylate; may decrease effects of oral contraceptives, causing breakthrough bleeding and increased risk of pregnancy; tetracyclines can increase hypoprothrombinemic effects of anticoagulants

Contraindications

Documented hypersensitivity; severe hepatic dysfunction

Precautions

Pregnancy

D - Fetal risk shown in humans; use only if benefits outweigh risk to fetus

Precautions

Photosensitivity may occur with prolonged exposure to sunlight or tanning equipment; reduce dose in renal impairment; consider drug serum level determinations in prolonged therapy; tetracycline use during tooth development (last half of pregnancy through age 8 y) can cause permanent discoloration of teeth; Fanconilike syndrome may occur with outdated tetracyclines

Metronidazole (Flagyl)

Used as adjunct to tetracycline in cases of severe infection or when anaerobes are implicated.

Imidazole ring-based antibiotic active against various anaerobic bacteria and protozoa. Used in combination with other antimicrobial agents (except in *Clostridium difficile* enterocolitis).

Dosing

Adult

250-500 mg PO tid

Pediatric

Not established

Interactions

May increase toxicity of anticoagulants, lithium, and phenytoin; cimetidine may increase toxicity; disulfiramlike reaction may occur with orally ingested ethanol; may increase toxicity of cyclosporine, didanosine, disulfiram, oral contraceptives, tacrolimus, and antiretroviral medications

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

Adjust dose in hepatic disease; monitor for seizures and development of peripheral neuropathy

Antifungal agents

Mechanism of action may involve an alteration of RNA and DNA metabolism or an intracellular accumulation of peroxide that is toxic to the fungal cell.

Clotrimazole (Lotrimin, Mycelex, Femazole, Gyne-Lotrimin)

Broad-spectrum antifungal agent that inhibits yeast growth by altering cell membrane permeability, causing death of fungal cells. Reevaluate diagnosis if no clinical improvement after 4 wk.

Dosing

Adult

10-mg troche dissolved 3 times/d for duration of chemotherapy

Pediatric

<3 years: Not established

>3 years: Administer as in adults

Interactions

None reported

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

Not for treatment of systemic fungal infections

Fluconazole (Diflucan)

Synthetic oral antifungal (broad-spectrum bistriazole) that selectively inhibits fungal cytochrome P450 and sterol C-14 alpha-demethylation.

Dosing

Adult

150 mg PO once or 400 mg PO qd, depending on severity of infection

Pediatric

3-6 mg/kg PO qd for 14-28 d or 6-12 mg/kg qd, depending on severity of infection

Interactions

Levels may increase with hydrochlorothiazides; levels may decrease with long-term coadministration of rifampin; coadministration may decrease phenytoin clearance; may increase concentrations of theophylline, tolbutamide, glyburide, and glipizide; effects of anticoagulants may increase with coadministration; increases in cyclosporine concentrations may occur when administered concurrently

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Monitor closely if rash develops and discontinue if lesions progress; may cause clinical hepatitis, cholestasis, and fulminant hepatic failure (including death) with underlying medical conditions, such as AIDS or malignancy, and while taking multiple concomitant medications; not recommended in breastfeeding

Follow-up

Further Outpatient Care

- Schedule routine follow-up visits for oral squamous cell carcinoma (OSCC) patients.

Deterrence/Prevention

- Instruct patients to minimize habits such as tobacco and alcohol use.

Complications

- Multiple complications are possible (see Medical Care).
- Specific complications from the surgery of OSCC may include infection and rupture of the carotid artery, salivary fistulae, and thoracic duct leakage (chylorrhea).

Prognosis

- Intraoral cancer has a 5-year survival rate of approximately 30%.

Patient Education

- Educate patients regarding lifestyle changes.
- For excellent patient education resources, visit eMedicine's Cancer and Tumors Center and Teeth and Mouth Center. Also, see eMedicine's patient education articles Cancer of the Mouth and Throat and Oral Herpes.

Miscellaneous

Medicolegal Pitfalls

- Failure to diagnose correctly because of inadequate biopsy specimens or inadequate histopathological diagnosis
- Failure to start early treatment
- Failure to exclude complicating factors such as comorbidities, metastases, or second primary neoplasms

Multimedia



Media file 1: Oral squamous cell carcinoma in the most common intraoral site manifesting as a chronic, indurated ulcer.



Media file 2: Early oral squamous cell carcinoma in the buccal mucosa arising from a chronic candidal leukoplakia in a person who smokes heavily. The lesion was a painless, chronic indurated lump.

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