Oral Cancer

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The incidence of oral cancer is age related, which may reflect time for the accumulation of genetic changes and duration of exposure to initiators and promoters (these include chemical and physical irritants, viruses, and hormonal effects), cellular aging, and decreased immunologic surveillance with aging.

The oral cavity includes the lips, the labial and buccal mucosa, and the anterior two-thirds of the tongue, the retromolar pad, the floor of the mouth, the gingiva, and the hard palate. The oropharynx includes the palatine and lingual tonsils, the posterior one-third (base) of the tongue, the soft palate, and the posterior pharyngeal wall. Approximately 95% of oral cancer occurs in people older than 40 years, with an average age at diagnosis of approximately 60 years.

The majority of oral cancers involve the lateral borders and base of the tongue. The lips, gingiva, dorsal tongue, palate, and salivary glands are less common sites. Individuals who have had a previous cancer are at high risk of developing a second primary oral cancer. The WHO has listed several oral conditions as having the potential to transform into oral cancer, including lichen planus, leukoplakia, erythroplakia, actinic cheilitis, and submucous fibrosis.

Etiology and risk Factors:

***Tobacco and alcohol:** Tobacco and alcohol are risk factors for oral and oropharyngeal cancer. Tobacco contains potent carcinogens, including nitrosamine, nicotine, and metabolites of these constituents.

***Nutritional Factors:**

Vitamin A may play a role in oral cancer. This hypo thesis is based on population studies in which deficiency was associated with the risk of SCC. The consumption of fruits and vegetables which is associated with a reduced risk for oral cancer, this may be due to the antioxidant vitamins C and E and flavonoids.

***Human Papilloma Virus:**

HPVs are DNA viruses that infect various epithelial surfaces. There are more than 120 types of HPVs. HPV-16 and -18 are considered high-risk subtypes due to their association with malignant tumors. The virus penetrates the host cell and integrates into the host cell genome where it can replicate. HPV is transmitted by direct contact, primarily by means of vaginal, anal, and oral sex.

***Other Risk Factors:**

There is no evidence that denture use, denture irritation, irregular teeth or restorations, and chronic cheek-biting habits are related to oral cancer risk. It is possible that chronic trauma, in the presence of other risk factors and carcinogens, may promote the transformation of epithelial cells. In lip cancer, sun exposure, fair skin and a tendency to burn, pipe smoking, and alcohol are identified risk factors.

Patient undergoing allogeneic hematologic stem cell transplantation (HSCT) are at an increased risk of developing secondary neoplasms, particularly leukemia and lymphomas, which may manifest in the oral tissues.

Pathogenesis:

(SQUAMOUS CELL CARCINOMA)

Carcinogenesis is a genetic process that leads to a change in molecular function, cell morphology, and ultimately in cellular behavior. This process is not limited to the epithelium but involves a complex epithelial, connective tissue, and immune function interaction. Major genes involved in OSCC include oncogenes and tumor suppressor genes (TSGs).

The extracellular enzymes, cell surface molecules, and immune function play a role in the development and spread of oral cancer; viruses and carcinogens are involved as well.

Oncogenes:

Although proto-oncogenes increase cell growth and effect differentiation and are likely involved in carcinogenesis, few have been consistently reported in head and neck squamous cell carcinoma.

Tumor Suppressor Genes:

TSGs negatively regulate cell growth and differentiation. Functional loss of TSGs is common in carcinogenesis and in OSCC. Both copies of a TSG must be inactivated or lost for loss of function. TSGs involved in head and neck squamous cell carcinoma are P53, Rb (retinoblastoma).

The development of malignant epithelial neoplasms is associated with disruption of cell-to-cell and cell-to- matrix adhesion.

Cell Surface Changes

Changes in cell surface receptors and major histocompatibility class I and class II antigens have been reported and may indicate that immune surveillance and immune function may be affected in patients with oral cancer.

Presenting Signs and Symptoms:

- Discomfort is the most common symptom that leads a patient to seek care and may be present at the time of diagnosis in up to 85% of patients.
- Individuals present with a mass in the mouth or neck.
- Dysphagia, odynophagia, otalgia, limited movement, oral bleeding, neck masses, and weight loss may occur with advanced disease.
- Loss of sensory function especially when it is unilateral.
- Loss of function involving the tongue can affect speech, swallowing, and diet. Possible tissue changes may include a red, white, or mixed red and white lesion; a change in the surface texture producing a smooth, granular, rough, or crusted lesion; or the presence of a mass or ulceration.

- Lymphatic spread of oral carcinoma most commonly involves the submandibular and digastric nodes, and the upper cervical nodes, but can also involve the remaining nodes of the cervical chain.

Lymph nodes associated with cancer become enlarged and firm to hard in texture, and with progression may become fixed and not mobile.

Staging of Oral Cancer—TNM System:

The American Joint Committee on Cancer (AJCC) has developed Tumor-Nodes-Metastasis (TNM) staging system of cancer, which reflects the prognosis, and is therefore determinants for the treatment strategy. T is the size of the primary tumor, N indicates the presence of regional lymph nodes, and M indicates distant metastasis.

The staging system for OSSC combines the T, N, and M to classify lesions as stages 1 through 4. The AJCC classification is principally a clinical description of the disease.

Stage grouping

Stage 0 Tis N0 M0

Stage I T1 N0 M0

Stage II T2 N0 M0

Stage III. T3 N0 M0

T1 N1 M0

T2 N1 M0

T3 N1 M0

Treatment of OSSC depends on:

- Cell type
- Degree of differentiation.
- The site and size of the primary lesion.
- Lymph node status.
- The presence of local bone involvement.
- The ability to achieve adequate surgical margins
- The presence or absence of metastases.

Surgery and radiation are used in the treatment of oral cancer; chemotherapy and targeted therapy are used together with principle therapeutic modalities of radiation and surgery; however, combined radiation and chemotherapy with or without surgery is usually employed for more advanced disease.

Diagnostic Aids:

The definitive test for diagnosis remains tissue biopsy. Several aids to the oral examination have been suggested in the past, including light technologies, vital tissue staining using toluidine blue (TB), and computer-assisted cytology of oral brush biopsy specimens. Additional markers based on blood of saliva samples are also under investigation.

Adjunctive clinical techniques such as:

1. **Toluidine blue (vital tissue staining).**
2. **Exfoliative cytology (computer-assisted cytology).**
3. **Brush biopsy.**
4. **Chemiluminescence.**
5. **Tissue auto fluorescence.**
6. **For bone involvement** can be used the Routine radiology, computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography (also can indicate the extent of some soft tissue lesions).

All these have been suggested to increase our ability to identify areas of dysplasia/early OSSC that are not visible to naked eye.

1. **Toluidine blue staining** (vital tissue staining): is a vital dye (tolonium chloride) that is believed to stain nucleic acids. It has been used to identify mucosal abnormalities and as a useful way for demarcating the extent of a potentially malignant lesion prior to excision.

- Positive retention of toluidine blue (particularly in areas of leukoplakia, erythroplakia, and uptake in a peripheral pattern of an ulcer) may indicate the need for biopsy. False-positive dye retention may occur in inflammatory and ulcerative lesions, but false- negative retention is uncommon. A return appointment in 14 days, providing time for inflammatory lesions to improve, may lead to a decrease in false-positive results.
- If the lesion is stained, the test is positive, biopsy immediately.

2. **Exfoliative cytology:** microscopic examination of cells desquamated from a tissue surface or lesion as a means of detecting malignancy and microbiological changes.

   Indications for oral cytology:

   - Diffused lesions
   - Premalignant or malignant lesions.
   - Patient not indicated for biopsy.

3. **Brush biopsy:** the use of a specially designed circular brush (Oral CDx Brush), which is used to sample cells of the suspected epithelial lesion.

   Clinically:

   - The brush may be moistened with water or the patient's saliva and applied to the surface of the lesion.
   - Contact between the brush and the mucosal surface with moderate pressure applied.
   - The brush is then rotated until pinpoint bleeding is noted, signaling entry into the lamina propria and obtaining epithelial cells.
   - Removed cells are transferred to a glass slide.
   - A fixation step follows immediately by flooding the slide with fixative solution (alcohol/propylene glycol).

- Allowing it to air dry the stained with pap stain (modified Papanicolaou test).
- Analyzed microscopically via a computer-based imaging system.

4. **Chemiluminescence:** clinical inspection of oral mucosa with the aid of chemiluminescent blue/white light (Vizilite system) was recently suggested to improve the identification of mucosal abnormalities.
5. **Tissue auto fluorescence:** the use of optical spectroscopy systems to provide tissue diagnosis (is a non-invasive technique used in detection of the soft tissue lesions). Oral cavity fluorescence using blue light excitation was reported due to interaction with collagen and modified by epithelial cellular and related to collagen breakdown and increased hemoglobin absorption of light.

- **Normal cell emit green light.**
- **Dysplastic cells emit red light.**
  This phenomenon is utilized in the detection of cancer using fluorescence spectroscopy.

Surgical biopsy: classified as

1. Exisional biopsy: involve total removal of the lesion with slight peripheral and in depth safety margins, such biopsies have a diagnostic and therapeutic.

2. Incisional biopsy: involves the removal of a representative portion of the target lesion and the part of healthy tissue.
3. Aspiration biopsy is only useful for deep lesions.

Malignant tumors of the salivary glands:

Most salivary gland tumors spread by local infiltration, by perineural or hematogenous spread and, less commonly, via lymphatics.

Non-Hodgkin's lymphoma:

Non-Hodgkin's lymphoma (NHL) may primarily be localized in the oral soft tissues (e.g. the gingiva, palate, and tongue). Oral NHL may be one of the manifestations of human immunodeficiency virus (HIV) infection. Hodgkin's lymphoma rarely occurs in the mouth, in contrast to NHL. The clinical presentation of oral NHL is a sub-mucosal swelling, sometimes bilaterally, especially at the junction of the hard and soft palate and the gingiva. NHL may also be located within the jaw bones, particularly in the mandible and symptoms may consist of unilateral anesthesia of the lower lip and sometimes swelling of the involved part of the bone.

Diagnosis:

-FNA (fine needle aspiration) biopsy.

-Incisional biopsy in conjunction with immunocytochemistry is a useful aid in diagnosing malignant lymphoma.

-In most cases, a biopsy is required.

Complications of Cancer treatment:

- Acute complication include ulcerative mucositis occur during the course of radiotherapy and combined radio-chemotherapy because of direct tissue toxicity and possibly secondary bacterial irritation, these reactions resolve over weeks to months following the completion of therapy.
- Chronic complications or late radiation reactions occur due to change in the vascular supply, epithelial atrophy, fibrosis in connective tissue and muscle, and change in the cellularity of tissues. These complications develop slowly over months to years. The connective tissue and musculature may demonstrate increased fibrosis, which may result in limited movement and altered function like in bone.

1. Mucositis:

Ulcerative oral mucositis is a painful and debilitating condition that is a dose- and rate-limiting toxicity of cancer therapy. It's characterized by severe pain, increased risk of local and systemic infection, compromised oral and pharyngeal function and oral bleeding that affect quality of life; may lead to hospitalization. . Increased risk of mucositis has been associated with poor oral hygiene, tobacco use, hypo salivation at baseline, and older age.

Clinical manifestation:

The first signs of mucositis may be a white appearance to the mucosa, caused by epithelial hyperplasia/hypertrophy and intraepithelial edema, or a red appearance due to hyperemia and epithelial thinning. Pseudomembrance formation represents ulceration with a fibrous exudate with oral debris and microbial components.

2. Tissue Necrosis:

Soft tissue and osteonecrosis:

Soft tissue necrosis may involve any oral site, including the cheeks, tongue and involvement of tissue overlying bone that has received high-dose radiation may predispose patients to necrosis of bone. The Post radiation osteonecrosis (PRON) may be chronic or progressive. Radiation therapy causes endarteritis that affects vascularity, resulting in hypo vascular, hypo cellular, and hypoxic tissue that is unable to repair or remodel itself effectively when a challenge occurs, the challenge may take the form of trauma (such as from surgical procedures), active periodontal disease or denture trauma.

Symptoms and signs are discomfort or tenderness at the site, bad taste, paraesthesia and anesthesia, extra oral and oroantral fistulae, secondary infection causing secondary osteomyelitis, and pathologic fracture.

3. Speech and mastication:

Abnormal speech may follow surgery or radiation due to removal of structure and because of hypo salivation and fibrosis that affects tongue mobility, mandibular movement, and soft palate function.

4. Nutrition: taste and smell impairment:

Radiation therapy produces changes in the patient's taste, the taste may be affected directly, due to an effect on the taste buds, or indirectly, due to hypo salivation and secondary infection. Taste often will recover slowly over several months, but permanent alteration may result.

Zinc supplementation (zinc sulfate, 220 mg twice daily) may be useful for some patients who experience taste disturbances.

5. Mandibular dysfunction

Musculoskeletal syndromes may arise due to fibrosis of muscles, which may follow radiation and surgery. Limited opening has been related to radiation exposure of the upper head of the lateral pterygoid muscle.

6. Chronic and post-therapy pain.

Pain Management in Head and Neck Cancer:

- Topical anesthetic (give topical anesthesia)
- Analgesic (Elevate pain threshold)
- Anti-inflammatory (Reduce inflammation; mild to moderate)
- Antimicrobial (Modify pathologic process)
- Anticonvulsant (Modify pathologic process)
- Anxiolytic (Antianxiety)
- Antidepressant (Reduce depression; analgesic effect; promote sound sleep)
- Muscle relaxant (Reduce muscle tension or spasm).