Oral cancer and early detection

Oral cancer is a broad term that includes various malignant diagnoses that present in the oral tissues.

- Even though the management and prognosis may be different between types and stages of oral cancer, it always has a dramatic impact on the patient's life.

- The cancer and cancer therapy are associated with morbidities that may negatively affect the quality of life—from the time of diagnosis, during cancer therapy, in the immediate period after the cancer treatment, and continue throughout the life of the patient.

- Cultural habits, including betel quid chewing, alcohol consumption, and reverse smoking, as well as low socioeconomic status and low consumption of fruits and vegetables contribute to this high prevalence.

- The trend differs between countries in this region (increases in Pakistan and decreases in Philippines and Sri Lanka) and even between provinces of the same country (Thailand).
- The majority of oral cancers are squamous cell cancers.

Other malignant diseases that can occur in the oral cavity include tumors of the salivary glands, lymph nodes, bone, and soft tissue.

- Approximately 95% of oral cancer occur in people older than 40 years, with an average age at diagnosis of approximately 60 years.

- However, OSCC at a young age and even in pediatric may be seen.
- 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.

- Primary squamous cell carcinoma (SCC) of bone is rare; however, a tumor may develop from epithelial rests and from epithelium of odontogenic lesions, including cysts and benign lesions.

- Individuals who have had a previous cancer are at high risk of developing a second primary oral cancer.

Oral cancer nomenclature

➢ Oral cancer nomenclature represents basically the histopathological characteristics of the lesion.

To facilitate communication between health-care providers, a classification system was established by the World Health Organization (WHO); which is updated from time to time based on advances in technology and outcome data.

According to the WHO classification of tumors,
The morphology of the cells
The tissue architecture

As seen in light microscopy is used to define the neoplasm, which may correlate with the biology and behavior of the cancer

WHO Classification of Oral Cancer

Epithelial cancer

Squamous cell carcinoma
Verrucous carcinoma
Basaloid squamous cell carcinoma
Papillary squamous cell carcinoma
Spindle cell carcinoma (sarcomatoid SCC)
Acantholytic squamous cell carcinoma
Adenosquamous carcinoma
Carcinoma cuniculatum
Lymphoepithelial carcinoma

Salivary gland cancer

Salivary gland carcinoma
Acinic cell carcinoma

Mucoepidermoid carcinoma
Adenoid cystic carcinoma
Polymorphous low-grade

adenocarcinoma

Basal cell adenocarcinoma
Epithelial-myoepithelial carcinoma
Clear cell carcinoma, NOS
Cystadenocarcinoma

Hematolymphoid cancer

Diffuse large B-cell lymphoma
Mantle cell lymphoma
Follicular lymphoma
Extranodal marginal zone B-cell lymphoma of MALT type
Burkitt lymphoma
T-cell lymphoma
Extramedullary plasmacytoma
Langerhans cell hystiocytosis
Extramedullary myeloid sarcoma Follicular
dendritic cell sarcoma

Soft tissue cancer

Kaposi sarcoma

Secondary tumors

Mucinous adenocarcinoma
Oncocytic carcinoma
Salivary duct carcinoma
Myoepithelial carcinoma
Carcinoma ex pleomorphic adenoma
Salivary gland adenomasa

Squamous Cell Carcinoma

Etiology and Risk Factors

- 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.
  - In addition, decreased immunologic surveillance over time may be another explanation to the age relation, such as seen in individuals following solid organ and hematopoietic stem cell transplantations, individuals treated with chemotherapy, and HIV-infected individuals.

Tobacco and Alcohol

- Tobacco products and alcohol are acknowledged risk factors for oral cancer.

- Tobacco contains potent carcinogens, including nitrosamines, polycyclic aromatic hydrocarbons, nitrosodiethanolamine, nitrosoproline, and polonium.
- Tobacco smoke contains carbon monoxide, thiocyanate, hydrogen cyanide, nicotine, and metabolites of these constituents.
- Nicotine is a powerful and addicting drug.

- Epidemiologic studies have reported that up to 80% of oral cancer patients were smokers. In addition to the risk of developing primary cancers, the risk of recurrent and second primary oral cancers is related to continuing smoking after cancer treatment.

- The effect of smoking on cancer risk diminishes 5 to 10 years after quitting.
  - Other forms of tobacco use ;smokeless tobacco have been associated with oral cancers.

- Benign hyperkeratosis and epithelial dysplasia have been documented after short-term use of smokeless tobacco products, and it is likely that chronic use is associated with an increasing incidence of malignant lesions.

- The potential risk of oral cancer with cannabis is unclear as data are inconsistent

All forms of **alcohol**, including —hardǁ liquor, wine, and beer, have been implicated in the etiology of oral cancer.

- In some studies, beer and wine are associated with greater risk than hard liquor.
- The combined effects of tobacco and alcohol result in a synergistic effect on the development of oral cancer.

- The mechanisms by which alcohol and tobacco act synergistically may include
  - ✓ **dehydrating effects of alcohol on the mucosa**,
  - ✓ increasing mucosal permeability,
  - ✓ and the effects of potential carcinogens in alcohol or tobacco.

- Various **enzymatic pathways** have been suggested as playing a role in the mechanism of the synergistic effect of smoking and alcohol on the oral mucosa.

- Likewise, it was speculated that smoking and alcohol interaction may **influence central nervous system activity**.

Betel quid (Areca Nut)

- People with a betel quid chewing habit, with or without added tobacco, are at a higher risk to develop oral cancer.

- In parts of Asia where the use of betel nut mixed with lime to form a quid is widespread (e.g., India, Taiwan), the incidence of oral cancer is high and more commonly involves the buccal mucosa.

- It was suggested that similar pattern may exist among immigrants originating from Asia.

- Furthermore, substitutes for betel quid, such as gutkha and pan masala, are potential carcinogenic as well.

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.
- HPV-16 alone is associated with about 85 to 95% of HPV-positive **oropharyngeal (**OPCs).
- The virus penetrates the host cell and integrates into the host cell genome where it can replicate.

- Malignant transformation occurs through the expression of two HPV viral oncogenes, E6 and E7.
- There are many unanswered questions of the biology of HPV infection that include clearance versus persistence of virus, latency and carcinogenesis, site localization, recurrence, and second primary cancers.
- HPV is transmitted by direct contact, primarily by means of vaginal, anal, and oral sex

Risk of developing HPV-positive oropharyngeal carcinoma (OPC) increases with:

- Increasing number of self-reported lifetime sexual partners (oral and vaginal),
- Younger age at first sexual activity,
- And history of having a same-sex partner; in addition, the level of risk can vary according to tumor site.

It is important to note that these findings are related to oropharyngeal carcinoma, whereas HPV is not well defined as risk factor for oral cancer.

Nutritional Factors

- Consumption of fruits and vegetables is associated with a reduced risk for oral cancer.

- This may be due to the antioxidant vitamins C and E and flavonoids. Elevated but inconsistent oral cancer risks have been observed for diets high in eggs and butter and for certain types of meats.
  - Vitamin A may play a protective role in oral cancer

This hypothesis is based on population studies of vitamin A deficiency where an association with the risk of SCC was observed and on studies of reduction in carcinogenesis in cultured head and neck SCC cell lines.

This hypothesis was supported by the fact that vitamin A may cause regression of premalignant leukoplakia.

A decreased risk of head and neck cancer was observed with long-term intake of vitamin C and with term intake of calcium supplement.

In recent years, vitamin D deficiency has also been associated with a plethora of pathologies. However, the association with oral cancer was only based on preliminary studies.

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.

However, the role of **local trauma** in the development of oral cancer remains controversial.

It is possible that chronic trauma, in the presence of other risk factors and carcinogens, may promote the transformation of epithelial cells, as has been demonstrated in animal studies.

- High alcohol content in mouthwashes has been implicated in oral cancer in the past.

More recent studies suggest no significant trend in risk with increasing daily use; Furthermore, the alcohol content of mouthwashes has been reduced, and increased use of non alcohol-based mouthwash has been an ongoing trend.

- **In lip cancer**, sun exposure, fair skin and a tendency to burn, pipe smoking, and alcohol are identified risk factors
- Recurrent Herpes simplex virus of the lip **has not been** associated with increased cancer risk.

- Patients undergoing allogeneic hematologic stem cell transplantation are at an increased risk of developing secondary neoplasms, particularly **leukemias and lymphomas**, which may manifest in the oral tissues.

- Likewise OSCC has been reported up to a 20-fold increase in risk in these patient populations.
- OSCC is documented after an extended period of immunosuppression post transplantation and with similar molecular changes, as seen in nonmedically induced immunosuppression.

Oral cancer may behave more aggressively in patients post hematopoietic stem cell transplantation with chronic graft versus host disease and associated immunosuppression.
Other immunosuppressed patients show increased risk for oral cancer as well, such as patients after liver transplantation

These cancers may be associated with HPV.

- Certain **inherited cancer syndromes** show increased risk for oral cancer. For example, oral cancer is one of the cancers that are typical **for Fanconi anemia patients**.

Fanconi anemia is usually diagnosed in an early age.

Cowden syndrome, xeroderma pigmentosum, and dyskeratosis congenita have also been reported in association with 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.
It is clear that even within the umbrella of potentially malignant disorders, there is a spectrum of risks for the development of oral cancer.
For example, the risk for oral cancer **in erythroleukoplakia** is higher than the risk for oral cancer in **lichen planus**.
Even within a certain oral condition, there may be variable risk for transformation.
For example, under the term —**leukoplakia**,‖ **proliferative verrucous leukoplakia** is more aggressive and has a high risk of progression to SCC.
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.

Function interaction.

Major genes involved in OSCC include oncogenes and tumor suppressor genes (TSGs).
Regulatory genetic molecules may be involved as well.
The genetic changes may be reflected in allelic loss or addition at chromosome regions corresponding to proto-oncogenes and TSGs, or epigenetic changes such as DNA methylation or histone deacetylation.

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

- Oncogenes may encode for growth factors, growth factor receptors, protein kinases, signal transducers, nuclear phosphoproteins, and transcription factors.

- 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.

- Proto-oncogenes associated with head and neck squamous cell carcinoma include ras (rat sarcoma), cyclins, myc (myelocytomatosis),

erb-b (erythroblastosis), bcl (B-cell lymphoma), int-2, CK8, CK19, and epidermal growth factor receptor (EGFR)

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 (the —two-hitll hypothesis).
- Chromosomes are numbered (1–23), and the arms of each chromosome are divided by the centromere into a short arm (designated P) and a long arm (designated Q).
- These TSGs have been associated with sites of chromosome abnormalities where loss of genetic nucleic segments has been reported to commonly involve chromosome arms 3p, 4q, 8p, 9p, 11q, 13q, and 17p.
- TSGs involved in head and neck squamous cell carcinoma are P53, Rb (retinoblastoma), and p16INK4A.
- Other candidates include FHIT (fragile histidine triad),

APC (adenomatous polyposis coli), DOC1 VHL (gene for von Hippel–Lindau syndrome), and TGF-R-II (gene for transforming growth factor type II receptor).

Gene-Regulating Proteins

Part of the oncogenic gene regulation is performed by transcription factors. These transcription factors are proteins binding to DNA sequences to permit or inhibit co-binding to RNA polymerase, which in turn regulates the activation of the DNA segment respective gene.

Loss of Heterozygosity

Loss of heterozygosity (LOH) or allelic loss has been studied in oral premalignant lesions and predicts the malignant risk of low-grade dysplastic oral epithelial lesions.

The importance of allelic loss has been shown in retrospective and crosssectional study and confirmed in a prospective study of patents with dysplasia, where lesions with allelic loss at 3p, 9p, and 17p predict risk of progression to SCC, even in histologically benign or tissue with mild dysplasia.

Hypermethylation

The role of promoter hypermethylation of CpG islands is being investigated in OSCC as methylation of epigenetic DNA has been shown to result in a loss of function in some genes involved in cell cycle regulation and DNA repair that may lead to loss or change in TSGs involved in carcinogenesis

MicroRNA

- MicroRNAs are small segments of non encoding single-stranded RNAs that mediate gene expression at the posttranscriptional level by mRNA degradation or translational repression.
- Aberrant microRNA may disrupt the normal regulation and lead to malignancy. MicroRNAs function either as oncogenes or as tumor suppressors and were suggested to play a role in oral cancer.

Extracellular Enzymes

- ✓ Matrix metalloproteinase (MMP) 2 and tissue inhibitor of metalloproteinase play a role in cancer initiation and development.
- ✓ Others have also supported the prognostic significance of tissue inhibitors of MMP.
- ✓ The development of malignant epithelial neoplasms is associated with disruption of cell-to-cell and cell-to-matrix adhesion.
- ✓ Syndecans are a family of heparin sulfate proteoglycan receptors that are thought to participate in both cell-to-cell and cell-to-matrix adhesion.
- ✓ A reduction of syndecan 1 correlated with histologic grade, tumor size, and mode of invasion.

The initiation or progression of oral cancer may be associated with polymorphism of the vascular endothelial growth factor (VEGF) gene 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.

Other cell surface changes include a loss of cytoplasmic membrane binding of lectins, which has been shown to correlate to the degree of cellular atypia

Immunosuppression

- The development of malignant disease at a higher rate in immunosuppressed patients indicates the importance of an intact immune response.
- Mononuclear cell infiltration correlates with prognosis, and more aggressive disease is associated with limited inflammatory response.
- Total numbers of T cells may be decreased in patients with head and neck cancer, and the mixed lymphocyte reaction is reduced in some patients, and a diminished migration of macrophages has been demonstrated.
- Cluster of differentiation 8 lymphocytes (T suppressor cells) predominate in the infiltrate, suggesting that immunosuppression is associated with progression of disease.

- Langerhans' cells may be altered in neoplastic epithelium

Viruses

- The potential role of viruses in oral cancer is under continuing study.
- The interaction of viruses with other carcinogens and oncogenes may be an important mechanism of disease.
- HPV is a documented risk factor for oropharyngeal cancer OPC.
- It was also identified in oral cancer.
- Current epidemiology show HPV much more commonly associated with OPC. However, as the change in risk factors with HPV continues to evolve, HPV-related lesions are increasingly reported at other head and neck sites including the oral cavity.

Up to 75% of OPC and 26% of oral SCC have been associated with high-risk HPV, showing a continuing trend to increasing HPV in SCC.

The most common HPV subtypes detected in OPC are HPV 16 and 18 (68% and 34%, respectively).

Other types of HPV detected in OSCC are HPV-6,11,31,33,35, and 56.

- **Herpes simplex virus** has been reported to produce a number of mutations in cells.
- A co-carcinogenic effect between Herpes simplex virus and chewing tobacco has been demonstrated in animal studies, but not in human studies.

- Smokers demonstrate higher antibody titers to Herpes simplex virus, suggesting reactivation.
- Neutralizing antibodies to Herpes simplex virus are present in the serum of patients with oral cancer at higher titers in those who have advanced cancer, and antibody response to Herpes simplex virus antigen is greater in patients than in controls.

However, Herpes simplex virus has not been detected in human OSCC

Presenting Signs and Symptoms

- Unfortunately, patients are most often identified after the development of symptoms associated with advanced stages of disease.

- **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 may also 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**, is a red flag that may indicate neural involvement and requires that cancer be ruled out.
- Loss of function involving the tongue can affect speech, swallowing, and diet.

- **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.

- The nodes most commonly involved are those that are on the same side as the primary tumor, although the closer the tumor is to the midline and the more posterior in the oral cavity or oropharynx, the more common are the involvement of the bilateral and contralateral nodes.

- Lymph node involvement may not occur in an orderly fashion.
- Lymph nodes associated with cancer become enlarged and firm to hard in texture, and with progression may become fixed and not mobile.

- The nodes are not tender unless they are associated with secondary infection or an inflammatory response is present, which may occur after a biopsy.

❑ The fixation of nodes to adjacent tissue due to invasion of cells through the capsule is a late occurrence and is evidence of aggressive disease.

❑ The fixation of the primary tumor to adjacent tissue overlying bone suggests the involvement of the periosteum and possible spread to bone.

- Spread of tumor is critical for prognosis and for selection of treatment. The **understaging** of nodes by superficial assessment or the **overstaging** of nodes following a biopsy, when an inflammatory component may be present, impacts the selection of treatment.

- Therefore, accurate node examination is needed before biopsy.

Diagnosis and Histopathology

- The diagnosis is primarily based on histopathology.
- Within the epithelial tumors, SCC is the most prevalent oral malignancy.
- It has several subtypes based on histopathology
- Some of the variants may have unique clinical presentation.

- For the diagnosis of OSCC, dysplasia involves the full thickness of the epithelium and the basement membrane is violated.
- Dysplasia describes a range of cellular abnormalities that includes changes in cell size and morphology, increased mitotic figures, hyperchromatism, nuclear size and

nuclear-cytoplasmic ratio, and alteration in normal cellular orientation and maturation.

Well-differentiated carcinoma **retains** some anatomic features of epithelial cells including the ability to produce keratin, whereas **poorly differentiated carcinoma** **loses** the anatomic pattern and function of epithelium.

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 OSCC 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. Many clinicians combine an imaging-based assessment of the size, lymph nodes, and metastasis with the AJCC clinical staging.

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Table (8-4) Staging of oral cancer and oropharyngeal cancer

Diagnostic Aids

Diagnostic Aids for Early detection

- Early detection of potentially malignant and malignant lesions is a continuing goal.

- Patient history, thorough head and neck and intraoral examinations, is a prerequisite.

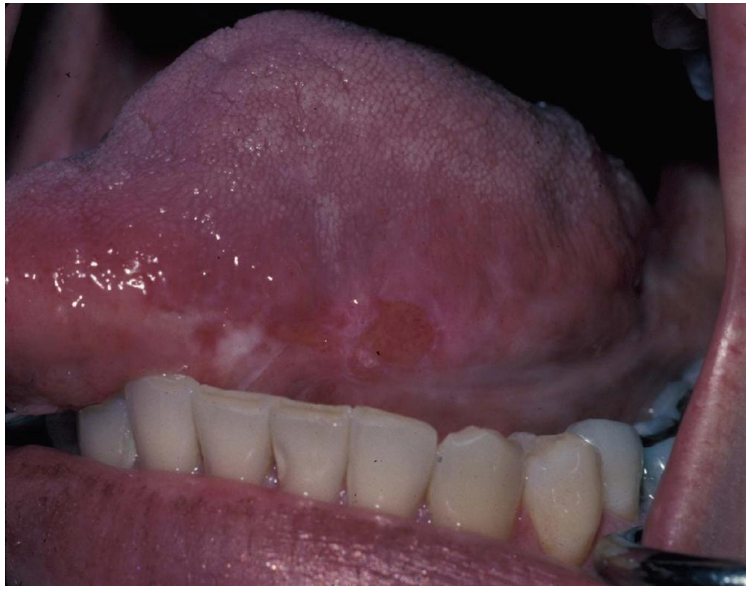
- The definitive test for diagnosis remains tissue biopsy.

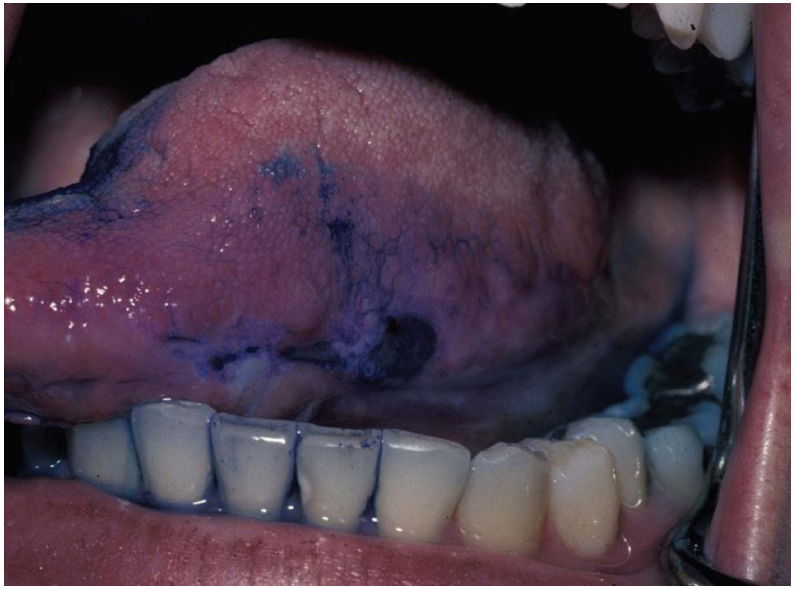
- Several aids to the oral examination have been suggested in the past, including:
  light technologies,
- vital tissue staining using toluidine blue (TB),
- and computer-assisted cytology of oral brush biopsy specimens.
- Additional markers based on blood or saliva samples are also under investigation.

Toluidine Blue

- Vital staining with TB may be used as an adjunctive aid in assessing potentially malignant oral mucosal lesions.

- TB is a metachromatic dye, which has an affinity to bind with DNA.
- TB staining has been correlated with LOH profiles in tissue biopsies.
- TB can be applied directly to suspicious lesions or used as an oral rinse.
- The assessment of dye uptake depends on clinical judgment and experience
- Positive retention of TB (particularly in areas of leukoplakia, erythroplakia, and uptake in a peripheral pattern of an ulcer) may indicate the need for biopsy or assist in identifying the site of 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.

- TB has been suggested as a **diagnostic tool** in potentially malignant oral lesions at risk of progressing to squamous cell cancer, where it may provide guidance for the selection for the biopsy site and accelerates the decision to biopsy.

- In postradiotherapy follow-up, the retention of TB may assist in distinguishing Non-healing ulcers and persistent or recurrent disease.

Visualization Adjunctive Tools

- **Chemiluminescent devices** generate **light based on chemical reactions**. The suspected area of mucosa appears **brighter**.

- Other products **generate fluorescent light using a LED source**, sometimes combined with **optical filtration of a viewfinder**, to enhance natural tissue fluorescence.
- When using the **fluorescence light**, the suspected area shows **loss of fluorescence, which appears dark.**

- **Oral cavity fluorescence**, using **blue light excitation**, is thought to represent the tissue structure, metabolic activity, presence of hemoglobin, vessel dilatation, and possibly inflammation.

- Localized modification in these factors may change the reflective features of the tissue.

- These products are promoted to assist the practitioner in discovering mucosal abnormalities, specifically oral potentially malignant disorders and evaluate margins of resection site.

- There is no consensus regarding the sensitivity and specificity of these devices, and their ability to detect early disease. Nonetheless, fluorescence has been shown to provide evidence on lesion margins in patients with known malignant lesions.
- There is an increasing interest in the use of confocal microscopy and optical coherent tomography systems to provide tissue diagnosis in real time, noninvasively, and in situ.

- Such diagnostic approach is available in dermatology and anticipated to be developed for oral mucosal application in the future.

- Other imaging modalities are being studied due to the need for improved detection and to assist in diagnosis and treatment.

Cytology

- Cytology of the oral mucosa is used to assess cellular morphology. The introduction of a brush designed to sample the entire thickness of the oral epithelium renewed interest in cytology for oral disease.

Originally, the cytobrush was combined with a computer- assisted analysis of the cytologic sample, assessing the cell morphology and keratinization.

- The final diagnosis was made by a pathologist based on the standard histomorphologic criteria.

- Further developments in cytology include molecular evaluation of exfoliated cells for molecular markers of dysplasia or carcinoma to improve the diagnostic and prognostic value.

Molecular Analysis

- Molecular markers obtained from tissue specimens have been suggested to assist with detection and evaluation of cancerous lesions including c-erbB2, Ki67/Mcm2, Cyclin D1, p53, COX-1 and 2, telomerase, loss of 3p or 9p, 8p, 4q, 11q, 13q, 17p.
- Studies have also shown that biomarkers of OSCC are present in saliva

Imaging

- Routine radiology, computed tomography (CT), nuclear scintiscanning, magnetic resonance imaging, and ultrasonography can provide evidence of bone involvement or can indicate the extent of some soft tissue lesions.

- The selection of the appropriate imaging modality is dependent on the type and location of the suspected tumor.

- Positron emission therapy using the radiolabeled glucose analog 18fluorodeoxyglucose offers a functional imaging approach for the entire body.
- Positron emission tomography (PET) is a type of nuclear medicine procedure that measures metabolic activity of the cells of body tissues.

- PET is actually a combination of nuclear medicine and biochemical analysis.

- Used mostly in patients with brain or heart conditions and cancer,
- PET helps to visualize the biochemical changes taking place in the body, such as the metabolism.

- PET differs from other nuclear medicine examinations in that PET detects **metabolism** within body tissues, whereas other types of nuclear medicine examinations detect the amount of a **radioactive substance** collected in body tissue in a certain location to examine the tissue's function.
- PET is most often used by oncologists, neurologists, neurosurgeons, cardiologists
- PET may also be used in conjunction with other diagnostic tests, such as computed tomography (CT) or magnetic resonance imaging (MRI) to provide more definitive information about malignant (cancerous) tumors and other lesions.

Acquisition of a Tissue Specimen

- In addition to standard surgical biopsy techniques, tissue can be acquired for histopathology by using fine-needle aspiration (FNA) or core needle biopsy (CNB).

- Open biopsy of enlarged lymph nodes is not recommended; in such cases, FNA biopsy should be considered.

- FNA/CNB also may aid in the evaluation of suspicious masses in other areas of the head and neck, including masses that involve salivary

glands, tongue, and palate, or when there is contraindication for conventional biopsy (e.g., thrombocytopenia).

- Ultrasound may assist in guiding FNA/CNB.

Treatment

- The principal objective of treatment is to cure the patient of cancer.
- The choice of treatment depends on cell type and 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, and the presence or absence of metastases.
- Treatment decisions are also impacted by appraisal of the ability to preserve oropharyngeal function, including speech, swallowing, and esthetics, as well as the medical and mental status of the patient.

❑Surgery

Surgery is indicated for
(1) early or localized oral cancer,
(2)tumors involving bone, and when the side effects of surgery are expected to be less significant than those associated with radiation,
(3) tumors that lack sensitivity to radiation, and
(4) recurrent tumor in areas that have previously received radiotherapy.

Surgery also may be used in palliative cases to reduce the bulk of the tumor and to promote drainage from a blocked cavity (e.g., antrum).

- Surgical excision of dysplastic and malignant lesions can be accomplished with laser therapy.
- Such therapy for these lesions is generally well tolerated and usually decreases the period of hospitalization and may have similar outcomes as traditional surgical interventions.

- However, laser therapy has the disadvantage of limiting the assessment of the margins for histopathologic confirmation.

- New surgical approaches and new approaches to reconstruction, such as vascularized flaps, microvascular reconstruction, and neurologic anastomoses of free grafts.
- Reconstruction with the use of osseointegrated implants offers the ability to provide stable prostheses and enhanced esthetic and functional results.
- The ability to place implants in irradiated bone has increased options for rehabilitation

Radiation Therapy

- Radiation therapy may be administered with intent to cure, as a single modality, as part of a combined radiation surgery and/or chemotherapy management, or for palliation.
- Radiotherapy with intent to cure causes early and late toxicities.
- In palliative care, radiation may provide symptomatic relief from pain, bleeding, ulceration, and oropharyngeal obstruction.
- Hyperfractionation of radiation (usually twice daily dosing) is one of the strategies to increase intensity of treatment to increase tumoricidal effects, which results in more severe acute effects.

- High-dose re-irradiation is offered in some centers as save treatment and may be considered in case of recurrent or second primary head and neck cancer, particularly when salvage surgery is not feasible.

- Radiation kills cells by interaction with water molecules in the cells, producing charged molecules that interact with biochemical processes in the cells and by causing direct damage to DNA
- The affected cells may die or remain incapable of division.
- Due to a greater potential for cell repair in normal tissue than in malignant cells and a greater susceptibility to radiation due to the higher growth fraction of cancer cells, a differential effect is achieved.

- To achieve therapeutic effects, radiation therapy is delivered in daily fractions for a planned number of days.

The biologic effect of radiation depends on the dose per fraction, the number of fractions per day, the total treatment time, the total dose of radiation, and the radiation used (electron, neutron, proton).

Methods for representing the factors of dose, fraction size, and time of radiation with a single calculation using the time-dose fraction (TDF) and the nominal standard dose (NSD) calculations have been described.

- Radiation therapy has the advantage of treating the disease in situ and avoiding the need for the removal of tissue and may be the treatment of choice for many T1 and T2 tumors, particularly in the base of the tongue and oropharynx.

- Radiation may be administered to a localized lesion by using implant techniques (brachytherapy) or to a region of the head and neck by using external beam radiation.

Cancer Treatment Planning

The radiation treatment plan is determined by the tumor site and size, relation to vital structures, the volume to be radiated, radiation technology available, the number of treatment fractions, the total number of days of treatment, and the tolerance of the patient.

Chemotherapy Cytotoxic Chemotherapy

- Chemotherapy may be used as induction therapy prior to local therapies, concurrent chemoradiotherapy (CCRT), and adjuvant chemotherapy after local treatment.
- The common chemotherapy protocols are listed in Table (8-6).
- The objective of induction chemotherapy is to promote initial tumor reduction and to provide early treatment of micrometastases due to the recognition that local control.

The principal agents that have been studied alone or in combination in head and neck cancer are taxol and derivatives, platinum derivatives (cisplatin and carboplatin), 5-fluorouracil, and hydroxyurea, although hydroxyurea is rarely used in current protocols.

Photodynamic Therapy

- Photodynamic therapy applies light over a tissue that initially absorbed exogenous sensitizer.

- The sensitizing agent may be delivered systemically or topically and then after it selectively accumulates in target tissue.

- The subsequent light delivery to the target tissue results in cellular destruction.

- Due to the focused cellular destruction, the complications and disfigurement associated with this treatment are relatively small.

- Although photodynamic therapy in oral cancer has some encouraging preliminary results, it is not accepted routine treatment.

Gene Therapy

- Gene therapy is being studied with the objective of reversing dysplasia in oral epithelial lesions.

- The modalities evaluated include suicide gene therapy, immunotherapy, oncolytic virus therapy, inhibition of tumor angiogenesis, gene deletion therapy, and antisense RNA.

- Considering the high rate of mutation in p53 in oral cancer, gene therapy focused on p53 gene, mostly with adenoviral vectors, shows promise.

- Additional target genes and vectors are currently being studied.
- None of these approaches have reached conventional clinic care settings

Immunotherapy

- Immunotherapy offers the potential for additional approaches to management, alone or in combination with other therapies.
- Clinical practice guidelines for management of malignant melanoma and other cancers are forthcoming.
- **Keytruda** May be used with the chemotherapy medicines fluorouracil and a platinum as first treatment when head and neck cancer has spread or returned and cannot be removed by surgery.
- Based on an analysis of a gene expression profile in matched tumor and normal fibroblast cell lines, a number of proteins have been detected that might be potential targets for immunotherapy in individuals with head and neck cancer.

- Cell lines studies and animal models support the introduction of immunotherapy for treatment of head and neck cancer.