Cancer and Oral Care of the Patient

Falace, chapter 26
Burket, chapter 7
Cancer is a condition that is characterized by uncontrolled growth of aberrant neoplastic cells. Cancerous cells kill by destructive invasion of tissues, that is, by direct extension and spread to distant sites by metastasis through blood, lymph, or serosal surfaces.

Malignant cells arise from genetic and acquired mutations, chromosomal translocations, and overexpression or underexpression of factors (oncogenes, growth factor receptors, signal transducers, transcription factors) that cause cells to lose their ability to regulate deoxyribonucleic acid (DNA) synthesis and the cell cycle.

Cellular abnormalities of malignancy result in three common features: uncontrolled proliferation, ability to recruit blood vessels (i.e., neovascularization), and ability to spread.
• At least three to six somatic mutations are needed for a normal cell to be transformed into a malignant cell.
• Acquired mutations may result from exposure to hazardous chemicals and pathogens that leads to activation of oncogenes, inactivation of tumor suppressor genes (pRb and p53), and chromosomal abnormalities.
• Accumulation of these abnormalities results in a cell that becomes functionally independent and aggressive.
• Natural killer cells provide surveillance for cancerous cells.
• Reduced numbers or functions of natural killer cells, which occur during immunosuppression, increase the risk for cancer.
• Loss of regulatory control in a cell destined to become a cancer cell results in a series of pathologic changes that include hyperproliferative epithelium, dysplasia, and, finally, carcinoma.

• Dysplastic tissue is characterized by atypical cell proliferation, nuclear enlargement, failure of maturation, and differentiation short of malignancy.

• Cancer often presents as a palpable mass that increases in size over time.

• Initial features may include a change in surface color, a lump, enlarged lymph nodes, or altered organ function.

• Symptoms include pain and paresthesia. Tumors permitted to increase in size often result in a reddened epithelial surface (caused by increased blood vessels) that ulcerates.

• Generically speaking, Stage I is localized and is confined to the organ of origin. Stage II is regional in nearby structures. Stage III is extensive beyond the regional site, crossing several tissue planes, and Stage IV is widely disseminated.

• The TNM system is frequently employed, whereby $T$ stands for tumor size, $N$ represents nodal involvement, and $M$ indicates metastases.
• The diagnosis of cancer is based on microscopic examination of an adequate sample of tissue taken from the lesion. Tissue can be obtained by cytologic smear, needle biopsy, or incisional or excisional biopsy.

• Therapeutic modalities include surgery; radiation (external beam or implants); cytotoxic, chemotherapeutic, and endocrine drugs; and possibly, stem cell or bone marrow transplantation.

• Breast cancer is the most common type of cancer in the United States; 98% of cases occur in women.

• The incidence of breast cancer increases with age. Risk factors include early menarche, late menopause, and nulliparity (women who do not bear children).

• The most important risk factor for breast cancer is family history of the disease.
• Breast cancer often is detected as a lump in the breast with or without nipple discharge, breast skin changes, and breast pain.
• In a small percentage of patients, the first sign is an axillary mass.
• Treatment selected for breast cancer depends on the histologic type and stage of cancer.
• Lumpectomy (when the tumor is smaller than 5 cm) or lumpectomy plus radiotherapy is preferred to radical mastectomy. Axillary node dissection is performed if the regional sentinel node is positive.
• Accordingly, the American Cancer Society recommends a mammogram and a professional clinical examination every year for women 40 years of age and older.
• Women 20 to 29 years of age should have a professional breast examination at least every 3 years.
• Women 20 years of age and older should perform a breast self-examination every month.
Mammogram showing a radiodense area in the breast, suggestive of a malignancy.
• Cervical cancer is relatively uncommon in developed countries because of intensive screening programs that are in place.
• Human papillomaviruses (HPVs), which are epitheliotropic sexually transmitted DNA viruses, are the major causative factor in cervical carcinogenesis.
• Certain HPV strains (HPV 16, 18, 45, 56) are classified as high-risk types.
• Cervical cancer typically involves a long asymptomatic period before the disease becomes clinically evident. This cancer classically presents in women who are between 40 and 60 years of age.
• Metastases often affect renal tissues, resulting in ureteral obstruction and azotemia.
• Treatment is based on disease stage and involves hysterectomy in the early stages and radiation therapy for disease that extends to or invades local organs.
• The American Cancer Society recommends that a Pap smear and a professional pelvic examination be performed in women at the onset of sexual activity or at 18 years of age.
• Cancer of the large bowel (colon and rectum) is the most common malignancy of the gastrointestinal tract.

• This risk increases with a high-fat diet (40% of total calories), low dietary fiber intake, and cigarette smoking for 20 years or longer. By contrast, the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and folate reduces the risk for colorectal cancer.

• Colonic adenomas (polyps) have malignant potential; however, less than 5% develop into carcinoma. The exception to this rule is seen in Gardner’s syndrome, through which virtually all affected patients develop malignant polyposis by age 40 unless treated.

• Colorectal cancer is not often seen until age 40, and it increases in incidence after age 50.

• Major signs and symptoms of colorectal cancer include rectal bleeding, abdominal pain, and change in bowel habits (constipation).

• Surgical excision is the treatment of choice for lesions encroaching on the distal 5 cm of the colon; this results in colostomy. Radiation therapy is used for rectal and anal cancer. Chemotherapy is used when metastatic spread occurs.
• Lung cancer is the cause of 14% of cancer cases and is the leading cause of cancer deaths.
• Lung cancer is more prevalent in industrialized countries, but increased incidence in nonindustrialized countries has resulted from the introduction of cigarettes into these regions.
• Lung cancer is a clinically silent disease until late in its course. Tumors that grow locally can produce a cough or change the nature of a chronic cough. Cancers that invade adjacent structures can produce chest pain and dyspnea or hemoptysis or may cause syndromes from disruption of nerves in the chest and neck, or endocrine, cutaneous, or neurologic manifestations.
• Metastases to the brain, bone, adrenal gland, and liver produce features associated with mal-function of these organs and lymphadenopathy.
• During advanced disease, patients present with anorexia, weight loss, weakness, and profound fatigue.
• The diagnosis of lung cancer is made via imaging studies, bronchoscopy, bronchial washings, brush and tissue biopsies, and histologic examination of cells and tissue.
• Stages I and II non–small cell lung cancers are treated by surgical resection.
• Radiotherapy is used for more advanced non–small cell lung cancers and for patients with Stage I or II disease who refuse to undergo or are medically unfit for surgery.
• Chemotherapy comprising two or three agents is employed in combination with radiotherapy for Stage III and IV non–small cell lung cancers and is the mainstay of treatment for small cell lung cancer.
Prostate cancer is the second most common cancer. At present, causes of prostate cancer remain unknown. High dietary fat intake and mutations in chromosome 1 appear to increase risk for prostate cancer.

Cancer of the prostate produces few signs and symptoms other than problems in urination (hesitancy, decreased force of urination) that, if present, occur late in the course of the disease.

Methods used to screen for prostate cancer include digital rectal examination (DRE) in combination with blood tests for prostate-specific antigen (PSA) and endorectal ultrasound.

Metastasis occurs by lymphatic or hematogenous dissemination. Lymphatic spread usually occurs to thoracic and pelvic regions, and hematogenous spread is usually to bone. Bony metastasis is often identified in the pelvis, spine, and femur.

Treatment options include radical prostatectomy, external beam radiation, interstitial seed radiation, and cryosurgery.
Of the three primary types of skin cancer, basal cell carcinoma is the most common type, followed by SCC and melanoma.

Basal cell carcinomas are more common in older persons with lighter skin and blond and red hair. However, diagnosis during the second and third decades is becoming more common. About 85% of lesions appear on sun-exposed surfaces of the head and neck (including the lip).

Four types of basal cell carcinomas are recognized: nodular, superficial, sclerosing (morpheaform), and pigmented forms.

Classically, the nodular basal cell carcinoma is a pearly papule with telangiectasias, a rolled waxy border, and a central ulceration (“rodent ulcer”).

A history of intermittent encrustation and bleeding is common. Less common types appear reddish, pigmented, or scarlike.

Basal cell carcinomas are readily removed through cryotherapy and surgical excision.
• Melanoma is a malignant neoplasm that arises from melanocytes. This cancer occurs primarily in skin but can occur at any site where melanocytes are found, including the oral cavity.

• Ultraviolet light sun exposure is the major causative factor. Increased risk also is associated with light skin type, severe sunburns as a child, overall nevus count greater than 50, light and red hair color, and extensive freckling. Men are more commonly affected, as are persons over the age of 50.

• Approximately 30% of melanomas arise from previously existing pigmented lesions, particularly those associated with a history of trauma.

• Early diagnosis and complete resection are critical to long-term survival.

• Prevention of skin cancer is attained through the use of sun protection measures (sunscreens and clothing) and periodic screening.
• More than 90% of oral cancer are attributed to SCC. About 9% are carcinomas that arise from salivary gland tissue and other tissue types such as sarcoma and lymphoma.
• The vast majority of oral cancers occur in patients older than 45 years of age; incidence increases with each decade after age 40 for men and women until age 65.
• At least 80% of cases are associated with multiple cellular abnormalities that result from chronic and excessive exposure to carcinogens found in smoking tobacco, alcohol (including mouthwashes with high alcohol content), smokeless tobacco, and betel leaf that contains areca nut.
• Ultraviolet light exposure and immunodeficiency (e.g., HIV infection, solid organ transplant recipients) are associated with approximately 10% of cases, particularly those involving the lip.
• HPV (high-risk types) infection can be detected in about 30% of cases.
• Plummer-Vinson syndrome and vitamin A deficiency also increase the risk of cancer of the oral cavity and oropharynx.
• Other factors suggested to play a minor role in the cause of oral cancer include arsenic compounds used in the treatment of syphilis, nutritional deficiencies, heavy exposure to materials such as wood and metal dusts, and Candida infection.
• Oral SCC has a variable appearance. It may occur as a white or red patch, an exophytic mass, an ulceration, a granular raised lesion, or combinations of these.
• White lesions that cannot be scraped off and are clinically nonspecific, called leukoplakia, are potential precursors lesions.
• About 19% of leukoplakias are dysplastic, and about 4% are considered SCC at initial biopsy. Leukoplakias that are not cancerous when they are first biopsied have about a 6% chance of developing into cancer over time. Thus, the overall incidence of SCC in oral leukoplakia is approximately 10%.
Malignant transformation rates for homogeneous and mixed leukoplakias are higher (as high as 17.5%).

Leukoplakias with areas of erythema have a 3 to 5 times greater chance of being cancerous at initial biopsy or developing into cancer than do homogeneous leukoplakias.

Nonspecific red lesions involving the oral mucosa (erythroplakia), although less common than white lesions, are malignant at initial biopsy in more than 60% of cases.

Most early carcinomas are asymptomatic and have an erythroplastic component. Advanced lesions are more often ulcerated, with raised margins and induration. Pain is often absent until late in the course of the disease.

High-risk sites include the floor of the mouth, lateral (posterior) and ventral (anterior) surfaces of the tongue, the soft palate, and surrounding tissues.
• These areas are less keratinized and are more susceptible to carcinogens. The buccal mucosa and gingivae also are common sites, especially in regions where social oral habits result in placement of carcinogens in close proximity to these tissues. Carcinomas of the upper lip and the dorsum of the tongue are rare.

• Oral SCC spreads by local infiltration into surrounding tissues or by metastasis to regional lymph nodes. through lymphatic channels. Spread to local structures results in induration, fixation, and lymphadenopathy.

• Distant metastasis is rare but occurs more commonly to the lung, liver, and bone. Lesions of the floor of the mouth, tongue, and posterior sites tend to metastasize earlier than carcinomas located in anterior oral sites such as the lip.

• Lesions in the maxillary region have a greater tendency to metastasize than do those in the mandibular region.
• Oral cancer can lead to death caused by the following:
  • Local obstruction of the pathway for food and air
  • Infiltration into major vessels of the head and neck (resulting in significant blood loss)
  • Secondary infection
  • Impaired function of other organs caused by distant metastases
  • General wasting
  • Complications of therapy
    ▪ In advanced cases of oral carcinoma, the patient may report weight loss and difficulty in breathing, or nerve involvement that may cause local musculature to become atrophic or that may result in unilateral paralysis (e.g., loss of the gag reflex when the soft palate is involved).
    ▪ Other symptoms include hoarseness, dysphagia, intractable ulcers, bleeding, numbness, loosening of teeth, difficulty opening, and a change in the fit of a denture.
• The diagnosis of oral cancer is made on the basis of microscopic examination of tissues or cells taken from the lesion. Vital staining with toluidine blue can aid in identification of the location from which to obtain a biopsy specimen.

• Most early oral SCCs are amenable to surgery, whereas Stage III or IV cancers (and those involving bone, vascular structures, and multiple lymph nodes) are usually treated by mean of combination therapy (irradiation and surgery).

• “Prophylactic” neck dissection is performed to minimize the development of metastases after the primary tumor has been treated.
Recently, a new oral complication of cancer treatment was identified—bisphosphonate-associated osteonecrosis (BON).

Bisphosphonates, synthetic analogs of inorganic pyrophosphate that have a high affinity for calcium, are also potent inhibitors of osteoclastic activity.

Bisphosphonates are used to treat osteoporosis, Paget’s disease of bone, and hypercalcemia of malignancy.

In patients with osteoporosis, it is expected that bisphosphonates will arrest bone loss and increase bone density, decreasing the risk of pathologic fracture caused by progressive bone loss.

Bisphosphonates are given to patients with cancer to help control bone loss caused by metastatic skeletal lesions. They reduce skeletal events associated with multiple myeloma (such as fractures) and metastatic solid tumor (such as breast, lung, and prostate cancers) in the bone.
- BON can occur with the oral administration of bisphosphonates but is rare. In contrast, BON is a much more common complication of injected bisphosphonates.
- The exact mechanism that leads to the induction of BON remains unknown. However, risk factors have been recognized and may be classified as systemic or local.
- These involve use of intravenous bisphosphonates, diabetes mellitus, overall cancer stage and tumor burden, overall systemic and immune health, immunosuppressive drug use, any periodontal or other oral infection, and history of radiation to the jaws.
- During bone remodeling, the drug is taken up by osteoclasts and inhibits osteoclastic function and induces apoptotic cell death. It also inhibits osteoblast-mediated osteoclastic resorption and has antiangiogenic properties.
- As a result, bone turnover becomes profoundly suppressed and, over time, the bone shows little physiologic remodeling. The bone becomes brittle and unable to repair physiologic microfractures that occur in the human skeleton as the result of daily activity.
- In the oral cavity, the maxilla and the mandible are subjected to constant stress from masticatory forces.
• It is theorized that in a patient who is taking a bisphosphonate, resultant microdamage is not repaired, thus setting the stage for oral osteonecrosis to occur. Therefore, BON results from a complex interplay of bone metabolism, local trauma, increased demand for bone repair, infection, and hypovascularity.

• In the early stages of oral BON, no radiographic manifestations may be seen. Patients usually are asymptomatic but may develop severe pain because of the fact that necrotic bone becomes infected secondarily after it has been exposed to the oral environment.

• Osteonecrosis often is progressive and may lead to extensive areas of bony exposure and dehiscence. When tissues are acutely infected, patients may report severe pain and lack of sensory sensation (paresthesia). This may be an indication of peripheral nerve compression.

• In patients who develop BON spontaneously, the most common initial complaint is the sudden presence of intraoral discomfort and roughness that may progress to traumatization of the oral soft tissues surrounding the area of necrotic bone.
Treatment strategies have included local surgical debridement, bone curettage, local irrigation with antibiotics, and hyperbaric oxygen therapy.

The dentist should manage patients who are taking oral bisphosphonates in the following ways:

1. Medical consultation should be obtained to determine medical diagnoses and types of drugs taken.
2. Protocol for prevention of complications from cancer chemotherapy or radiation therapy:
   a. Comprehensive examination
   b. Excellent periodontal health (eradicate infection or inflammation)
   c. Immediate extraction of all nonrestorable or questionable teeth
   d. Elimination of dental caries
   e. Excellent oral hygiene and oral health maintenance
3. Routine dental care can and should be provided, with the use of routine local anesthetics.
4. All procedures should be performed as atraumatically as possible with little tissue trauma, bleeding, and risk for postoperative infection.
5. Should BON occur, only sharp edges of exposed bone should be removed; minimal surgery should be performed. No definitive treatment for BON is available at this time.

6. In case of any infection, aggressive use of systemic antibiotics is indicated.
• Dental treatment planning for the patient with cancer begins with establishment of the diagnosis. Planning involves the following:
  • Pretreatment evaluation and preparation of the patient
  • Oral health care during cancer therapy, which includes hospital and outpatient care
  • Posttreatment management of the patient, including long-term considerations
• Cancers that are amenable to surgery and that do not affect the oral cavity require few treatment plan modifications. However, some cancers affect oral health directly because of surgery or indirectly through chemotherapy or immunosuppression.
• **Pretreatment Evaluation and Considerations:**

  A patient who is to receive palliative therapy may not want replacement of missing teeth; however, this patient must be free of active dental disease that could worsen during cancer therapy.

  By contrast, a patient who has cancer in Stage I or II and no evidence of regional spread can be managed for future dental care as a normal patient, except that the dentist should consider recalling this patient for more frequent examinations for evidence of metastases, recurrence of the lesion, or presence of a new cancer.

  This is particularly important for patients with oral cancer who are at increased risk for a second primary cancer in the respiratory system, upper digestive tract, or oral cavity.

  The risk for a second oral cancer in smokers whose habits remain unchanged is about 30%, as compared with 13% for those who quit.
A pretreatment oral evaluation is recommended for all patients with cancer before cancer therapy is initiated to attain the following:

- Rule out oral disease that may worsen during cancer therapy.
- Provide a baseline for comparison and monitoring of sequelae of radiation and chemotherapy damage.
- Detect metastatic lesions.
- Minimize oral discomfort during cancer therapy.

This evaluation should include a thorough clinical and radiographic examination and review of blood laboratory findings. Edentulous regions should be surveyed so that impacted teeth, retained root tips, and latent osseous disease that may worsen during immunosuppressive cancer therapy can be ruled out.

Pretreatment care should include oral hygiene instructions, encouragement of a noncariogenic diet, calculus removal, prophylaxis and fluoride treatment, and elimination of all sources of irritation and infection.
In children undergoing chemotherapy, mobile primary teeth and those expected to be lost during chemotherapy should be extracted, and gingival opercula should be evaluated for surgical removal to prevent entrapment of food debris. Orthodontic bands should be removed before chemotherapy is begun.

If head and neck radiation and immunosuppressive chemotherapy are scheduled, the following recommendations should be considered:

- Reduction in radiation exposure to noncancerous tissues (salivary glands) with lead-lined stents, beam-sparing procedures, or the use of anticholinergic (biperiden) or parasympathomimetic (pilocarpine HCl [Salagen]) drugs during and after radiotherapy should be discussed with the radiation oncologist and the patient.

- Nonrestorable teeth with poor or hopeless prognosis, acute infection, or severe periodontal disease that may predispose the patient to complications (e.g., sepsis, osteoradionecrosis) should be extracted; sharp, bony edges trimmed and smoothed; and primary closure obtained. Chronic inflammatory lesions in the jaws and potential sources of infection should be examined and treated or eradicated before radiation or chemotherapy.
• Symptomatic nonvital teeth should be endodontically treated at least 1 week before initiation of head and neck radiation or chemotherapy. However, dental treatment of asymptomatic teeth even with periapical involvement may be delayed.

• To optimize oral health and reduce the risk of oral complications such as mucositis and infection, tooth scaling and prophylaxis should be provided before cancer therapy is initiated. Removable prosthodontic appliances should be removed during therapy.

• Patients who will be retaining their teeth and undergoing head and neck radiation therapy must be informed about problems associated with decreased salivary function, which include xerostomia, the increased risk of oral infection, including radiation caries, and the risk for osteoradionecrosis.

• Dental preparation of the patient with cancer who is about to undergo surgical treatment is not as critical as for the patient about to undergo head and neck radiation and chemotherapy.
• Guidelines for Tooth Extraction in Patients Scheduled to Receive Radiation Treatment to the Head and Neck (Including the Mouth) or Chemotherapy:

• INDICATORS OF EXTRACTION:
  • Pocket depths are 6 mm or greater, mobility is excessive, purulence is seen on probing
  • Periapical inflammation is noted
  • Tooth is broken down, nonrestorable, nonfunctional, or partially erupted; patient is noncompliant with oral hygiene measures
  • Patient has no interest in saving tooth/teeth
  • Tooth is associated with an inflammatory (e.g., pericoronitis), infectious, or malignant osseous disease

• EXTRACTION GUIDELINES:
  • Perform extraction with minimal trauma
  • At least 2 weeks before initiation of radiation therapy
  • Ideally 3 weeks before initiation of radiation therapy
  • At least 5 days (in maxilla) before initiation of chemotherapy
  • At least 7 days (in mandible) before initiation of chemotherapy
• Trim bone at wound margins to eliminate sharp edges
• Obtain primary closure
• Avoid intra-alveolar hemostatic packing agents that can serve as a nidus of microbial growth
• Transfuse if the platelet count is less than 50,000/mm³
• Delay if the white blood count is less than 2000/mm³ or the absolute neutrophil is less than 1000/mm³ or is expected to be this level within 10 days; alternatively, prophylactic antibiotics (cephalosporin) may be used with extractions that are mandatory.
Complications of Head and Neck Radiotherapy and Myelosuppressive Chemotherapy:

- Nausea and vomiting (acute onset)
- Mucositis—Starts about second week
- Ulceration (C)
- Taste alteration—Starts about second week
- Xerostomia (R)—Starts about second week
- Secondary infection (fungal, bacterial, viral)
- Bleeding (C)
- Radiation caries (R) (delayed onset)
- Hypersensitive teeth (acute and delayed onset)
- Muscular dysfunction (R) (delayed onset)
- Osteoradionecrosis (R) (delayed onset [more common in mandible, less common in maxilla])
- Pulpal pain and necrosis (delayed onset [R]—Orthovoltage, not found with cobalt-60)
Oral Care During Cancer Therapy:

Oral infections and potential problems should be eliminated before cancer therapy is provided to patients who are undergoing head and neck radiation and inpatient chemotherapy; routine dental care should be delayed until after cancer therapy has been completed. Patients given outpatient chemotherapy require provision of dental treatment at appropriate times between cycles.

Most chemotherapeutic agents cause alopecia, breakdown of the mucous membranes (mucositis), depression of the bone marrow (infection, bleeding, anemia), gastrointestinal changes (diarrhea, malabsorption), and altered nutritional status;

They may also induce cardiac and pulmonary dysfunction.

Bone marrow suppression and mucositis associated with chemotherapy are predictable, dose dependent, and usually manageable. Patients receiving chemotherapy may manifest erythema and ulceration of the oral mucosa, infection of the surrounding tissues, excessive bleeding with minor trauma, xerostomia, anemia, and neurotoxicity.
• Mucositis, inflammation of the oral mucosa, results from the direct cytotoxic effects of radiation or antineoplastic agents on rapidly dividing oral epithelium and the upregulation of proinflammatory cytokine expression.

• Mucositis occurs in up to 40% of patients who are undergoing chemotherapy and is often a dose-limiting factor for chemotherapy and a cause of dose interruption in radiation therapy.

• It develops more often in nonkeratinized mucosa (buccal and labial mucosa, ventral tongue) and adjacent to metallic restorations by the end of the second week of radiation therapy (if the dose is 200 cGy per week).

• It generally subsides 1 to 2 weeks after completion of treatment.

• Young patients with cancer who have higher division rates have a greater prevalence of chemotherapy-induced mucositis than do older patients with cancer.
Mucositis produces red, raw, and tender oral mucosa with epithelial sloughing similar to that seen in a severe oral burn. Oral ulcerations may result from breakdown of the epithelial barrier and from infection by viral, bacterial or fungal organisms. Patients typically report ulceration, pain, dysphagia, loss of taste, and difficulty in eating, which increases the risks for oral and systemic infection.

If the major salivary glands have been irradiated, xerostomia may occur after the onset of mucositis.

Complications of mucositis and xerostomia make the patient extremely uncomfortable and increase the difficulty associated with maintaining proper nutritional intake.

Dentures should not be worn until the acute phase of mucositis has resolved. Dentures should be cleaned and soaked with an antimicrobial solution daily for the prevention of infection.
• **MUCOSITIS:**
  • Eliminate infection and irritation; establish good oral hygiene.
  • Use mouth rinse.
  • Recommend a salt and sodium bicarbonate mouthwash (1 tsp of each in 1 pint of water).
  • Provide elixir of diphenhydramine (Benadryl) or viscous lidocaine 0.5% in Milk of Magnesia, Kaopectate, or sucralfate.
  • Use chlorhexidine 0.12%
  • Prescribe antiinflammatory agents (e.g., topical steroids, kamillosan liquidim).
  • Use protectants (e.g., Orabase).
  • Avoid tobacco, alcohol, and carbonated drinks.
  • Follow a soft diet; maintain hydration.
  • Use a humidifier or vaporizer.
  • Consider topical and systemic antimicrobials, if severe.

• **XEROSTOMIA:**
  • Recommend sugarless lemon drops, sorbitol-based chewing gum, buffered solution of glycerine and water, or salivary substitutes.
Severe xerostomia that developed from the effects of radiation on the oral mucosa.

Classic “curdled milk” appearance of the oral lesions of pseudomembranous candidiasis.
During radiation and chemotherapy, patients are prone to secondary infection. Because of the quantitative decrease that occurs in actual salivary flow, and because of compositional alterations in saliva, several organisms (bacterial, fungal, and viral) may opportunistically infect the oral cavity.

Moreover, if the patient is immunosuppressed as the result of chemotherapy, and if the WBC count falls to below 2000 cells/mm³, the immune system is less able to manage these infections. Opportunistic infections are also common in patients who receive chemotherapy and broad-spectrum antibiotics.

The organism that most frequently opportunistically infects the oral cavity in individuals undergoing cancer therapy is Candida albicans.

Cytologic study, potassium hydroxide (KOH) staining, microscopic examination, and Candida-specific cultures are often performed to establish a definitive diagnosis.

Candidal infections may produce pain, burning, taste alterations, and intolerance to certain foods, especially acidic citrus fruits or spicy foods. They present clinically in four different forms, ranging from denuded epithelium to hyperplastic lesions.
During cancer therapy, the most common type is pseudomembranous candidiasis, which produces white plaques that are easily scraped off, leaving behind tiny petechial hemorrhages.

Slightly less prevalent is the erythematous, atrophic form, which manifests as a red patch accompanied by a burning sensation.

Other forms of candidiasis (i.e., angular cheilosis and the less common hypertrophic form, which presents as a thick, white plaque that cannot be scraped off) are more commonly detected in patients with chronic hyposalivation.

Candidiasis is best managed with the use of topical oral antifungal agents. These include nystatin (oral suspension 100,000 international units [IU]/mL 4 to 5 times daily), clotrimazole (Mycex lozenges 10 mg 5 times day), and other preparations (e.g., vaginal topical antifungal agents).

Prophylactic use of antifungal agents may be required in patients undergoing chemotherapy who have frequent recurrent infections. Ketoconazole, fluconazole, or itraconazole may be used if systemic therapy is warranted, or if patients develop unusual oral fungal infections (Torulopsis, aspergillosis, mucormycosis) or fungal septicemia (possibly from the oral cavity).
• Oral bacterial infections may appear with typical signs of swelling, erythema, and fever. Alternatively, these features may be masked in patients with low WBC counts due to chemotherapy.

• The most common presentation is an oral ulceration.

• If a bacterial infection is suspected, appropriate antibacterial therapy should be initiated. Antimicrobial sensitivity data are important for the selection of an effective antibiotic when the clinical course shows little or no improvement over several days.
• Recurrent herpes simplex virus (HSV) eruptions occur often during chemotherapy if antiviral agents are not prophylactically prescribed. They are infrequent during radiation therapy. Herpes recurrences in patients with cancer who are undergoing chemotherapy tend to be larger and to take longer to heal than herpetic lesions found in nonimmunocompromised patients.

• Antiviral agents (e.g., acyclovir, famciclovir, valacyclovir) are recommended prophylactically for HSV antibody–positive patients who are undergoing chemotherapy, to prevent recurrence. A daily dose of at least 1 g acyclovir/equivalent is needed to suppress HSV recurrences. Because these ulcers mimic the appearance of aphthous and may occur on nonkeratinized mucosa in immunocompromised patients with cancer, culture or use of an enzyme-linked immunoassay is important for accurate diagnosis.
Patients with cancer who undergo total body irradiation or high-dose chemotherapy, or who have bone marrow involvement due to disease, are also susceptible to thrombocytopenia.

Gingival bleeding and submucosal hemorrhage as a result of minor trauma (e.g., tongue biting, tooth brushing) can occur when the platelet count drops to below 50,000 cells/mm³.

Palatal petechiae, purpura on the lateral margin of the tongue, and gingival bleeding/oozing are common features.

Gingival hemorrhage is aggravated by poor oral hygiene. When gingival tissues bleed easily and the platelet count is severely reduced, the patient should avoid vigorous brushing of the teeth and should begin using softer devices such as gauze wrapped around a finger and dampened in warm water or an antimicrobial solution.

During this stage, patients should be instructed not to use toothpicks, water-irrigating appliances, or dental floss. To control gingival bleeding, local measures, such as pressure applied with a gelatin sponge along with thrombin or microfibrillar collagen placed over the area or an oral antifibrinolytic rinse (aminocaproic acid [Amicar] syrup, 250 mg/mL) placed in a soft vinyl mouth-guard, can be used to control bleeding. If local measures fail, medical help should be obtained and platelet transfusion considered.
Many patients who are receiving radiation therapy experience a diminished sense of taste, probably as a result of damage to the microvilli of the taste cells.

Patients who are given chemotherapeutic agents complain of bitter tastes, unpleasant odors, and conditioned aversions to foods.

To minimize sensory stimulation, the dentist should avoid wearing cologne or perfume when in contact with patients who are undergoing radiation/chemotherapy.

In most patients, the ability to taste is restored within 3 to 4 months after completion of radiotherapy. In cases of chronic loss of taste, zinc supplementation has been reported to improve taste perception (220 mg of zinc 2 times per day for patients with severe chronic loss of taste).
Neurotoxicity is an adverse effect of chemotherapeutic agents, particularly vincristine and vinblastine. Although this complication commonly arises in the peripheral nerves, patients may experience odontogenic pain that mimics irreversible pulpitis caused by these agents. Pain is more common in the molar region and can be bilateral.

Recommendations for Invasive Oral Procedures in the Cancer Patient Undergoing Chemotherapy in an Outpatient Setting:

- Provide routine care when:
  - The patient feels best—generally, 17 to 20 days after chemotherapy
  - Granulocyte count >2000 cells/mm³
  - Platelet count >50,000 cells/mm³
• Prosthetic implants (breast, penile, oral) that have been placed to restore esthetics or function lost as the result of cancerous tissue or cancer treatment are not considered at risk for bacterial seeding from oral invasive procedures and do not require antibiotic coverage.

• If urgent dental care is needed and the granulocyte count is less than 2000 cells/mm$^3$, consultation with the physician is recommended and antibiotic prophylaxis should be provided.

• Penicillin V 500 mg every 6 hours, starting at least 1 hour before any invasive procedure that involves bone, pulp, or periodontium and continuing for at least 3 days, is a reasonable regimen.
Post–Cancer Treatment Management:

Usually, the patient is seen once every 1 to 3 months during the first 2 years and at least every 3 to 6 months thereafter. After 5 years, the patient should be examined at least once per year.

This recall program is important for the following reasons:

• A patient with cancer tends to develop additional lesions
• Latent metastases may occur
• Initial lesions may recur
• Complications related to therapy can be detected and managed
• The usual long-term complications associated with cancer and its therapy include chronic xerostomia, loss of taste, altered bone, and related problems.
• Recall appointments are also important to ensure that the dentate patient continues to maintain good oral hygiene (including daily brushing, flossing, and continued use of daily fluoride gel applications); detection of oral soft tissue and hard tissue disease can occur early, before inflammation and infection involve the underlying bone, leading to necrosis.
• Salivary gland tissue is moderately sensitive to radiation damage. Because of this, acinar tissue that is within the field of radiation can be permanently damaged during head and neck radiation therapy, resulting in hyposalivation.

• The degree of hyposalivation that occurs is directly related to the radiation field and dose and to baseline salivary function. Dosages in excess of 3000 cGy are the most damaging, especially if shielding or medication is not provided to the patient during radiation.

• Irradiated salivary glands become dysfunctional owing to acinar atrophy, vascular alterations, chronic inflammation, and loss of salivary parenchymal tissue.

• Usually, a 50% to 60% reduction in salivary flow occurs during the first week after irradiation therapy is provided. After radiation therapy has been given, saliva is reduced in volume and altered in consistency, pH, and immunoglobulin concentration. It becomes mucinous, thick, sticky, and ropy because serous acini are more sensitive than mucous acini to radiation.
• Clearly, saliva is an important host defense mechanism against oral disease, and it serves a variety of important functions in the oral cavity.

• In a healthy mouth, copious saliva containing essential electrolytes, glycoproteins, immunoglobulins, hydrolytic enzymes (amylase), antimicrobial enzymes, and a number of other important factors continually lubricates and protects the oral mucosa.

• Saliva in normal quantities and composition serves to cleanse the mouth, clear potentially toxic substances, regulate acidity, buffer decalcifying acids, neutralize bacterial toxins and enzymes, destroy microorganisms, and remineralize enamel with inorganic elements (e.g., calcium, phosphorus), thus maintaining the integrity of the teeth and soft tissues.

• Dry, atrophic, and fissured oral mucosa and soft tissues usually result from the hyposalivary condition, along with accompanying ulcers and desquamation, opportunistic bacterial and fungal infections, inflamed and edematous tongue, caries, and periodontal disease.
• Extreme difficulty in lubricating and masticating food (sticking to the tongue or hard palate) and in swallowing food (dysphagia) is common; Additionally, lack of or altered taste perception (i.e., hypogeusia or dysgeusia) and tolerance for certain acidic foods (e.g., citrus fruits, acetic acid, vinegar) are substantially altered in these individuals. As a result, nutritional intake may be impaired.

• Manifestations of salivary hypofunction in patients who have undergone irradiation therapy for head and neck cancer include severe xerostomia (less than 0.2 mL/min unstimulated salivary flow), mucositis, cheilitis, glossitis, fissured tongue, glossodynia, dysgeusia, dyseusia, and a severe form of caries called radiation caries.

• A prescription for concentrated fluoride toothpaste (5000 ppm) should be provided to these patients for use in custom trays or brush-on application, and salivary flow should be assessed.
Management of Salivary Dysfunction:

1. MOISTURE/LUBRICATION

General

a. Drink—Sip water, other liquids (that lack fermentable carbohydrate and carbonic acid).
b. Avoid ethanol, tobacco, coffee, tea, and hot spicy foods.
c. Use sugarless candy/gum

Over-the-Counter (OTC) products

Oral balance: Apply 1/2 tsp 5 to 6 times daily.

Prescription (Rx) products

• Pilocarpine HCl 2% (Salagen) 5 mg 3 or 4 times daily
• Anethole trithione (Sialor) 25 mg 3 times daily
• Bethanechol chloride (Urecholine) 25 mg 3 times daily
• Cevimeline (Evoxac) 30-mg caps 3 times daily
• Artificial salivas: Glandosane Spray, Moi-Stir, Mouthkote, Optimoist, Roxane Saliva Substitute, Salivart Spray, Salix Lozenges, or generic (sodium carboxymethylcellulose 0.5% aqueous solution)
2. SOFT TISSUE LESIONS/SORENESS

**OTC**
- Oral balance
- Biotene mouthwash

**Rx**
- Diphenhydramine (Benadryl) + Maalox nystatin elixir (±sucralfate) (±0.5% viscous lidocaine)
- Dexamethasone (Decadron Elixir) 0.5 mg/5 mL
- Triamcinolone 0.1% (in hydrocortisone acetate [Orabase], Orabase-HCA)
- Clotrimazole (Mycelex) 60-mg troches
- Nystatin and triamcinolone ointment (Mycolog II, Tristatin II, Mytrex)

3. PREVENTION OF CARIES/PERIODONTAL DISEASE

**General**
- Practice meticulous personal oral hygiene.
- Avoid acidic drinks.
- Use toothpaste (Biotene).
- Attend regular hygiene recalls, and comply with dental prophylaxis.
- Use mechanical brushes (Waterpik) and sodium bicarbonate (NaHCO₄) rinses.
- **Rx products:**
  - Neutral NaF 1.0%, trays (Prevident 5000)
  - Chlorhexidine gluconate (Peridex, Periguard)

Extensive cervical caries in a patient who received radiotherapy.
• During and after radiotherapy, the teeth may become hypersensitive; this event may be related to decreased secretion of saliva and the lowered pH of secreted saliva. Topical application of a fluoride gel should be of benefit in reducing these symptoms.

• Radiation therapy of the head and neck can cause damage to the vasculature of muscles (obliterative endoarteritis) and thus trismus of the masticatory muscles and joint capsule.

• To minimize the effects of radiation on muscles around the face and muscles of mastication, a mouth block should be placed when the patient is receiving external beam irradiation.

• The patient also should perform daily stretching exercises to improve trismus and should apply warm, moist heat. One exercise requires the patient to place a given number of tongue blades inside the mouth at least 3 times a day for 10-minute intervals. With a slow increase in the number of tongue blades, muscle stretching occurs and improved function ensues.
- Patients should avoid wearing their dentures during the first 6 months after completion of radiotherapy because mild trauma to the altered mucosa can result in ulceration and possible necrosis of underlying bone.
- In severe cases of chronic xerostomia, a small amount of petrolatum can be applied to the mucosal surface of the denture to enhance adhesion.
- Implants may be placed 12 to 18 months after radiation therapy has been provided.
- Osteoradionecrosis (ORN) is a condition that is characterized by exposed bone that fails to heal (present for 6 months) after high-dose radiation to the jaws.
- Most cases result from damage to tissues overlying the bone rather than from direct damage to the bone. Accordingly, soft tissue necrosis usually precedes ORN and is variably present at the time of diagnosis.
• Risk is greatest in posterior mandibular sites for patients whose jaws have been treated with in excess of 6500 cGy, who continue to smoke, and who have undergone a traumatic (e.g., extraction) procedure.

• Risk is greater for dentate patients than for edentulous patients, and periodontal disease enhances risk.

• Nonsurgical procedures that are traumatic (e.g., curettage) or that cause a reduction in blood supply to the region (e.g., use of vasoconstrictors) can result in ORN.

• Spontaneous ORN also occurs. This risk continues throughout a patient’s lifetime.

• Clinicians should be aware that risk of ORN increases with increasing dose to the jaws (e.g., 7500 cGy presents a greater risk than 6500 cGy).
Recommendations for Preventing Osteoradionecrosis in the Head and Neck–Irradiated Patient:

1. Extract teeth with questionable and hopeless prognosis at least 2 weeks before radiotherapy.
2. Avoid extractions during radiotherapy.
   • The mandible is at greater risk than the maxilla.
   • Posterior sites are at greater risk than anterior sites.
3. Minimize infection.
   • Use prophylactic antibiotics.
   • Give 2 g penicillin VK orally 1 hour before the surgical procedure.
   • After surgery, continue with penicillin VK 500 mg 4 times daily for 1 week.
4. Minimize hypovascularity after radiotherapy.
   • Use nonlidocaine local anesthetic (e.g., Prilocaine plain or forte) for dental procedures.
   • Minimize or avoid vasoconstrictor use if necessary, consider low-concentration epinephrine (1 : 200,000 or less).
   • Consider hyperbaric oxygen.
5. Minimize trauma.
• Endodontic therapy is preferred over extraction (assuming the tooth is restorable).
• Follow atraumatic surgical technique.
• Avoid periosteal elevations.
• Limit extractions to two teeth per quadrant per appointment.
• Irrigate with saline, obtain primary closure, and eliminate bony edges or spicules.

6. Maintain good oral hygiene.
• Use oral irrigators.
• Use antimicrobial rinses (chlorhexidine).
• Use daily fluoride gels.
• Eliminate smoking.
• Attend frequent postoperative recall appointments.
• Bisphosphonate-associated osteonecrosis (BON) is potentially a very serious oral complication of cancer therapy. In patients who develop BON spontaneously, the most common initial complaints are the sudden presence of intraoral discomfort and the presence of roughness that may progress to traumatization of oral soft tissues surrounding the area of necrotic bone.

• Treatment strategies have included local surgical debridement, bone curettage, local irrigation with antibiotics, and hyperbaric oxygen therapy.

• Patients who have received neck irradiation (more than or equivalent to 45 Gy) are more likely to develop carotid artery atheroma (calcified atherosclerotic plaque) after treatment than are risk-matched control patients who have not been irradiated. These lesions may be detected by panoramic radiography and represent a risk factor for stroke that warrants referral of the patient to a physician for evaluation.
Squamous Cell Carcinoma

- If oral cancers and cancers of the nasopharynx, pharynx, larynx, sinus, and salivary glands are combined, these sites represent more than 5% of total body cancers.
- In males, oral cancer represents 4% of total body cancers; in females, 2% of all cancers are oral.
- Oral cancer accounts for 2% of cancer deaths in males and 1% of cancer deaths in females.
- The majority of oral cancers are squamous cell cancers.
- Other malignant diseases that can occur in the head and neck include tumors of the salivary glands, thyroid gland, lymph nodes, bone, and soft tissue.
• Approximately 95% of oral squamous cell carcinoma (OSCC) occur in people older than 40 years, with an average age at diagnosis of approximately 60 years.
• Oral tongue and base of the tongue and tonsilar malignancies have increased in 20- to 44-year-old adults.
• The majority of oral cancers involve the tongue, oropharynx, and floor of the mouth. The lips, gingiva, dorsal tongue, and palate 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 ameloblastoma.
• Individuals who have had a previous cancer are at high risk of developing a second oropharyngeal cancer.
• 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, hormonal effects), cellular aging, and decreased immunologic surveillance with aging.

• Tobacco and alcohol are acknowledged risk factors for oral and oropharyngeal cancer.

• In addition to the risk of 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.

• It has been observed that the tongue is a common site in the nonsmoking group in contrast to the smoking group in which the floor of the mouth is a common location.
The combined effects of tobacco and alcohol result in a synergistic effect on the development of oral cancer. The mechanism(s) 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.

Secondary liver dysfunction and nutritional status also may play a role.

Vitamin A may play a role in oral cancer. Vitamin A may cause regression of premalignant leukoplakia.

Factors for which no evidence for a role in oral cancer has been documented include denture use, denture irritation, irregular teeth or restorations, chronic cheek-biting habits, HSV-1 and HSV-2, HPV and high-alcohol mouthwash.

In lip cancer, sun exposure, fair skin and a tendency to burn, pipe smoking, and alcohol are identified risk factors.
The suggested association between sideropenic anemia (Plummer-Vinson disease) and head and neck cancers appears to be more of limited significance in lesions arising in the postcricoid region of the hypopharynx.

Patients undergoing allogenic stem cell transplantation are at high risk of developing secondary neoplasms, particularly leukemias and lymphomas.

Carcinogenesis is a genetic process that leads to a change in morphology and in cellular behavior.

Major genes involved in head and neck squamous cell carcinoma (HNSCC) include proto-oncogenes and tumor suppressor genes (TSGs).

The current model of carcinogenesis is a multistage process, with loss occurring on chromosome arms 3p and 9p early in the lesion’s progress from benign to dysplastic, with additional losses later in the disease, often involving 8p, 13q, and 17p.

Putative TSGs at these sites of loss are P16 loss at 9p and P53 gene loss at 17p.
• LOH on 3p and/or 9p is seen in virtually all progressing cases.
• This is of importance as the majority of oral premalignant lesions (hyperplasia, mild and moderate dysplasia) do not progress to cancer.
• Oropharyngeal SCC, particularly involving the tonsil, base of the tongue, and larynx, has a higher prevalence of high-risk HPV-16 than oral SCC. Nonkeratinizing cancer of the base of the tongue and the tonsil associated with HPV appear to have an improved response to radiation sensitivity.
• SCC primarily spreads by direct local extension and by regional extension via the lymphatics. Regional spread in the oral mucosa may occur by direct extension and sometimes by submucosal spread and result in wide areas of involvement.
• Discomfort is the most common symptom that leads a patient to seek care.
• Dysphagia, odynophagia, otalgia, limited movement, oral bleeding, neck masses, and weight loss may occur with advanced disease.
• Examination of the oral cavity should not neglect any area, but the high-risk sites for oral carcinoma, including the lower lip, the anterior floor of the mouth, and the lateral borders of the tongue, must be carefully examined.
• The patient should be assessed for tissue changes that 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.
• The lesion may be flat or elevated and ulcerated or nonulcerated and may be minimally palpable or indurated.
• Lymphatic spread of oral carcinoma usually involves the submandibular and digastric nodes, the upper cervical nodes, and, finally, 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 is the involvement of the bilateral and contralateral nodes.

• Lymph nodes associated with cancer become enlarged and firm to hard in texture. 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 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. It is critical that the status of the lymph nodes be carefully assessed before a biopsy is performed.

**diagnostic aids:**
- Toluidine blue can be applied directly to suspicious lesions or used as an oral rinse.
- 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.
- The definitive test remains a biopsy, and any suspicious lesion should not remain undiagnosed.
- Toluidine blue predicts oral premalignant lesions at risk of progressing to squamous cell cancer, provides guidance for the selection for the biopsy site, and accelerates the decision to biopsy.
- In postradiotherapy follow-up, the retention of toluidine blue may assist in distinguishing nonhealing ulcers and persistent or recurrent disease.
- Routine radiology, computed tomography (CT), nuclear scintiscanning, magnetic resonance imaging (MRI), and ultrasonography can provide evidence of bone involvement and can indicate the extent of some soft tissue lesions.
- Soft tissue involvement of the antrum and nasopharynx can be assessed with CT and MRI. Panoramic radiography of patients with antral carcinoma may document the lesion in a large number of such cases.
- Each MRI image should include T1-weighted images, which demonstrate normal anatomy with detail and soft tissue definition, and T2-weighted images, which demonstrate the tumor in comparison with adjacent muscle and other soft tissues.
- MRI will allow more accurate distinctions between tumor and benign inflammatory disease than CT.
- CT and MRI aid in determining the status of the cervical lymph nodes.
• Small-part ultrasonography may also be of value for imaging salivary gland masses and for the assessment of lymph nodes; however, differentiation between benign and malignant nodes may not be possible.

• The ultrasonographically guided needle biopsy technique may be useful in the assessment of head and neck masses, including lymph nodes.

• In addition to the standard biopsy techniques, tissue can be acquired for histopathology by using fine-needle aspiration (FNA) and exfoliative cytology.

• Open biopsy of enlarged lymph nodes is not recommended; in such cases, FNA biopsy should be considered. FNA also may aid the evaluation of suspicious masses in other areas of the head and neck, including masses that involve the salivary glands, tongue, and palate.
- Dysplasia or atypia describes a range of cellular abnormalities that includes changes in cell size and morphology, increased mitotic figures, hyperchromatism, and alteration in normal cellular orientation and maturation.
- The descriptions of mild, moderate, and severe dysplasia refer to epithelial abnormality of varying severity. When the abnormality involves the full thickness of the epithelium, the diagnosis is carcinoma in situ. When the basement membrane is violated, carcinoma is diagnosed.
- Well-differentiated carcinoma may retain some anatomic features of epithelial cells and may retain the ability to produce keratin, whereas poorly differentiated carcinoma loses the anatomic pattern and function of epithelium.
- Recognition of tumor invasion may be assisted by a study of type IV collagen (basement membrane collagen) by immunocytochemistry.
• Verrucous carcinoma is a subtype of SCC with characteristic clinical findings.
• Verrucous carcinoma can be described clinically as papillary, verrucoid, fungating, or cauliflower-like.
• Verrucous carcinoma may develop from progression of proliferative verrucous leukoplakia and progress to carcinoma.
• Histologically, the first change is a piling up of keratin on the surface, with downgrowth of club-shaped fingers of hyperplastic epithelium pushing rather than infiltrating into the tissue. Only mild dysplasia may be present.
• Verrucous carcinoma rarely spreads to lymph nodes and remains locally destructive.
• The treatment is surgical excision as verrucous carcinoma is relatively resistant to radiotherapy.
Variants of SCC other than verrucous carcinoma:

- Basaloid squamous carcinoma (BSC), Spindle cell carcinoma, adenoid SCCs, Papillary squamous carcinoma, carcinoma cuniculatum and Intraoral sebaceous carcinoma.

The choice of treatment depends upon cell type and degree of differentiation; the site and size of the primary lesion; lymph node status; the presence of bone involvement; the ability to achieve adequate surgical margins; the presence or absence of metastases, the ability to preserve oropharyngeal function, including speech, swallowing, and esthetics; the medical and mental status of the patient; available support throughout therapy; a thorough assessment of the potential complications of each therapy; the experience of the surgeon and radiotherapist; and the personal preferences and cooperation of the patient.
• Surgery and radiation are used with curative intent in the treatment of oral cancer. Chemotherapy is an adjunct to the principal therapeutic modalities of radiation and surgery and is now standard combined therapy in management of advanced disease.

• Technical advances such as intensity-modulated radiotherapy (IMRT) reduce the size of the high-dose field of irradiation and limit the exposure of adjacent vital structures, including the salivary glands.

• Due to poor cure rates in head and neck cancer, particularly at advanced stages of disease, more intensive treatment including hyperfractionation, combined chemoradiotherapy, and reirradiation for recurrence of second primary cancers are provided.

• Surgery is indicated (1) for tumors involving bone, (2) when the side effects of surgery are expected to be less significant than those associated with radiation, (3) for tumors that lack sensitivity to radiation, and (4) for 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).

• Surgery may fail due to incomplete excision, tumor seeding in the wound, unrecognized lymphatic or hematogenous spread, neural invasion, or perineural spread.

• Adequate surgical margins are required but may not be attainable due to the size and location of the tumor and limited information on the molecular status of the margins.

• In some cases with minimal bone involvement of the alveolar crest, a partial mandibulectomy may allow the continuity of the mandible to be maintained. However, in many cases, mandibulectomy and resection in continuity with the involved nodes are required.

• Surgical management of clinically positive cervical nodes is the treatment of choice. Surgery is needed when bone is involved, and radiotherapy alone cannot be considered adequate to produce a cure.
Radiation therapy may be administered with intent to cure, as part of a combined radiation-surgery and/or chemotherapy management, or for palliation.

Radical radiotherapy is intended to cure, the total dose is high, the course of therapy is prolonged, and early and late radiation effects are common.

In palliative care, radiation may provide symptomatic relief from pain, bleeding, ulceration, and oropharyngeal obstruction.

Hyperfractionation of radiation (usually twice-daily dosing) is being used more extensively as chronic complications appear to be reduced although acute complications are more severe.

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 relatively hypoxic central tumor cells are less susceptible to radiotherapy but may become better oxygenated as peripheral cells are affected by radiation and thus become more susceptible to subsequent fractions of radiation.
• SCC are usually radiosensitive, and early lesions are highly curable. In general, the more differentiated the tumor, the less rapid will be the response to radiotherapy.
• Exophytic and well-oxygenated tumors are more radiosensitive, whereas large invasive tumors with small growth fractions are less responsive.
• SCC that is limited to the mucosa is highly curable with radiotherapy; however, tumor spread to bone reduces the probability of cure with radiation alone.
• Small cervical metastases may be controlled with radiation therapy alone, although advanced cervical node involvement is better managed with combined therapy.
• The biologic effect of radiation depends on the dose per fraction, the number of fractions per day, the total treatment time, and the total dose of radiation.
Late effects are related to the number of fractions, fraction size, total dose, tissue type, and volume of tissue irradiated.

An increase in fraction size or a reduction in the number of fractions with the same total dose results in increased late complications, including tissue fibrosis and soft tissue and bone necrosis.

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.

Concurrent Chemotherapy and Radiotherapy (CCRT) and IMRT are becoming a standard modalities of treatment of head and neck SCC.

CCRT has increased cure rates but is associated with a concomitant increase in toxicity.

Primary tumors of the posterior third of the tongue, oropharynx, and tonsillar pillar are best treated by external beam radiotherapy, with or without chemotherapy and surgery is reserved for the treatment of tumors with node involvement.
• Electrons are useful in providing radiation to skin lesions, parotid tumors, and cervical nodes.
• Deep-seated tumors may be treated with heavy-particle irradiation, such as neutron beam radiation, which is considered for salivary gland tumors and central nervous system malignancies.
• Brachytherapy (Interstitial and intracavitary implants) may be the primary treatment modality for localized tumors in the anterior two-thirds of the oral cavity, for boosted doses of radiation to a specific site, or for treatment following recurrence.
• Chemotherapy is used as induction therapy prior to local therapies, simultaneous chemoradiotherapy (concurrent CCRT), and adjuvant chemotherapy after local treatment.
• The potential toxic effects of chemotherapy include mucositis, nausea, vomiting, and bone marrow suppression.
• The initial tumor response to chemotherapy prior to radiotherapy may predict tumor responsiveness to radiation.
Concurrent chemotherapy and radiotherapy protocols are now the standard of care for stage 3 and 4 as primary therapy and following surgery for disease with poor prognostic findings following surgery including close margin, and vascular invasion by tumor.

Surgery more readily manages tumor masses that may possess relatively radiation-resistant hypoxic cells and tumor that involves bone.

Thus, combined therapy (RT and surgery) can result in improved survival in cases of advanced tumors and tumors that show aggressive biologic behavior.

Radiation can be used preoperatively, postoperatively, or with a planned split-course approach.

The advantages of preoperative radiation are the destruction of peripheral tumor cells, the potential control of subclinical disease, and the possibility of converting inoperable lesions into operable lesions.

The disadvantages include delayed surgery and delayed postsurgical healing. Postoperative chemoradiotherapy can be used to treat cells that remain at the margin of resection and to control subclinical disease.
• Local or regional spread of oral SCC is common and affects the choice of therapy and prognosis. Metastases to cervical lymph nodes are common, but distant metastases below the clavicle are rare.

• Oral cancer occurring in the posterior aspect of the oral cavity and oropharynx and inferior in the mouth tends to be associated with a poorer prognosis, which may be explained by diagnosis occurring with advanced disease and a higher incidence of spread to lymph nodes at the time of diagnosis.

• Ipsilateral lymph node metastases are frequent; however, spread to contralateral nodes also occurs and is more common with midline and posterior lesions.

• The most important factor in survival is the stage of disease at diagnosis.
• Tumors of the salivary glands, the majority of which involve the parotid glands, represent less than 5% of all head and neck tumors.
• Approximately two-thirds of these tumors are benign mixed tumors (pleomorphic adenomas).
• When tumors involve the submandibular or sublingual glands, there is a high probability that they are malignant.
• In order of decreasing frequency, the malignant salivary gland tumors are mucoepidermoid carcinoma, adenoid cystic carcinoma, adenocarcinoma, SCC, malignant pleomorphic adenoma, undifferentiated carcinoma, lymphoma, melanoma, and a mixed group of sarcomas.
• Most salivary gland tumors spread by local infiltration, by perineural or hematogenous spread and, less commonly, via lymphatics.
• Rarely, metastases from other malignancies may involve the parotid glands.
• Malignant salivary gland tumors most commonly present as a mass that may be ulcerated.
• Neurologic involvement may lead to discomfort and numbness, and with parotid gland tumors, involvement of the facial nerve may cause facial paralysis.
• The majority of minor salivary gland tumors are malignant.
• The most common site is the posterior hard palate, but other sites in the oral cavity or upper respiratory tract may be involved. The presentation is usually a painless mass.
• Necrotizing sialometaplasia is a self-limiting non-neoplastic inflammatory condition of unknown etiology that affects the palatal salivary glands.
• The painful lesion occurs in sites of mucus-secreting glands and results in an ulceration with rolled borders.
• Necrotizing sialometaplasia will resolve spontaneously, usually within 1 to 2 months.
Biopsy of masses in the major glands may be accomplished by FNA, and diagnosis may be made without open biopsy.

Surgery is the principal treatment of the primary tumor.

Radiotherapy at a high dose is effective in malignant salivary gland tumors.

Postoperative radiation can contribute to cure and to improved local control and is indicated for patients with residual disease following surgery, extensive perineural involvement, lymph node involvement, high-grade malignant disease, tumors with more than one local recurrence after surgery, inoperable tumors, or malignant lymphoma and for those who refuse surgery.

The prognosis of salivary gland tumors is related to tumor type, tumor size, lymph node involvement, and extension of disease.

Small tumors, acinic cell tumor, low-grade mucoepidermoid carcinoma, and mixed tumors have a high probability of cure.

Tumors with a poor prognosis include large tumors, adenocarcinoma, adenoid cystic carcinoma, high-grade mucoepidermoid carcinoma, poorly differentiated carcinoma, and SCC.
• **Osteosarcoma** is a malignant tumor, characterized by the direct formation of bone or osteoid by the tumor cells. Osteosarcomas are more common in patients between 10 and 25 years of age and occur more often in men than in women.

• The most common presenting finding of osteosarcomas of the jaws is mass (85–95.5%). Pain accompanies the swelling in approximately half of cases, and trigeminal sensory disturbances occur in 21.2% of cases.

• The etiology is unknown, although trauma has been suggested as a possible trigger. Osteosarcomas may also develop in a patient affected by Paget’s disease or in a patient who has been irradiated either for a benign bone lesion or for adjacent soft tissue disease.

• Approximately 6% of all osteosarcomas are located in the jaws.

• Osteosarcomas occur slightly more often in the mandible than in the maxilla.
Most osteosarcomas of the jaws are centrally located in the bone.

Juxtacortical or parosteal location, a location adjacent to the outer surface of the cortical bone, is unusual.

Associated symptoms consist of swelling, mobile teeth, anesthesia or paresthesia, toothache, and nasal obstruction.

In the osteoblastic type, the radiograph may show an opaque lesion, with bony trabeculae directed perpendicularly to the outer surface resulting in a “sunray” appearance. Over time, there is expansion and perforation of the cortical bone.

The osteolytic type is far less characteristic and appears as an ill-defined lucency that causes expansion and destruction of the cortical bone. In the presence of teeth, a widening of the periodontal ligament may be observed even before changes can be noticed elsewhere in the bone. Loss of follicular cortices of unerupted teeth is highly suggestive of malignancy. Widening of the mandibular canal is another ominous sign.
• Bone scintigraphy will show a positive picture but is not diagnostic.
• Treatment requires aggressive local surgery.
• Metastasis is usually via the bloodstream and often occurs within 1 to 2 years.
• Primary SCC of the jaw is a rare disease and may arise from epithelial rests in the jaw or from the epithelium of odontogenic lesions.
• Tumors metastatic to the jaw most often involve the posterior mandible. Metastases are rare, representing approximately 1% of all oral malignant tumors.
• Common tumors that metastasize to the jaw are adenocarcinomas (of the breast, prostate, and gastrointestinal tract) and renal carcinoma.
• Symptoms associated with metastasis to the jaw may include pain, paresthesia, anesthesia, mobility of teeth, and swelling.
Multiple myeloma may cause radiolucent lesions and pain in multiple bones, including the jaw. Multiple myeloma frequently presents with pain and presents a clinical and radiologic diagnostic challenge when associated with the teeth.

Nasopharyngeal cancer (NPC) presents a number of concerns to dental providers because patients may present with complaints that may mimic temporomandibular disorders (TMDs).

Symptoms associated with NPC include pain, limited jaw opening, earache, and other ear complaints.

Symptoms that aid in differentiation of TMD and NPC may occur late or concurrently and include nasal stuffiness, nosebleed, and neck mass.

Risk factors for NPC include Epstein-Barr virus infection, smoking, childhood consumption of salted fish.

FNA can provide tissue diagnosis, and the sensitivity can be enhanced by DNA amplification (polymerase chain reaction) of the Epstein-Barr virus genome, which is commonly associated with NPC but is rare in other head and neck cancers.
Treatment requires radiation therapy, which is increasingly combined with chemotherapy and IMRT or a three field set-up for conventional radiotherapy.

Surgery may play a role in involved neck nodes but not in the treatment of the primary tumor.

Treatment is primarily surgical, although radiotherapy may be required for lesions not amenable to excision or to incompletely excised or recurrent tumors.

**Basal cell carcinoma (BCC)** is a locally destructive cancer that may occur in the head and neck.

Sun exposure is considered the principal etiologic factor.

BCC presents as persistent keratotic lesions (indurated papules) of the skin that may develop rolled borders and ulcerate. If advanced, they may lead to locoregional tissue necrosis and ulceration.

Although BCC rarely metastasizes, recurrence or second primary lesions are common.

Treatment is primarily surgical, although radiotherapy may be required for lesions not amenable to excision or to incompletely excised or recurrent tumors.
Melanoma may present as an area of altered pigmentation involving the skin. Oral malignant melanoma is extremely rare (2% of all melanomas).

The oral lesions may present as tissue masses or ulceration that may be pigmented, but nonpigmented lesions also are reported.

Most intraoral cases occur in the maxillary mucosa, presenting as a mass or flat lesions that may ulcerate and may be associated with bleeding.

Melanoma is an aggressive malignant disease; metastasis is through lymphatic and hematogenous routes, and the prognosis is poor.

Aggressive therapy of the primary tumor is needed with hypofractionated radiotherapy and CT and careful investigation for metastases.
Non-Hodgkin’s lymphoma (NHL) may primarily be localized in the oral soft tissues (eg, the gingiva, palate, and tongue).

Primary NHL of salivary glands is usually of the mucosa-associated lymphatic tissue (MALT) lymphoma type.

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 usual clinical presentation of oral NHL is a submucosal 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. Symptoms may consist of unilateral anesthesia of the lower lip and sometimes swelling of the involved part of the bone.

The radiograph may mimic the picture of osteomyelitis.

FNA biopsy or incisional biopsy in conjunction with immunocytochemistry is a useful aid in diagnosing malignant lymphoma, but in most cases, a confirmatory biopsy is required.
• The oral NHLs usually involve the B-cell system, less often T cells and infrequently the histiocytic-monocytic system.
• Treatment usually consists of a combination of chemotherapy and radiotherapy and hematopoietic stem cell transplantation.
• **Soft tissue sarcomas** of the oral cavity are rare and account for approximately 1% of all malignancies.
• Subtypes include fibrosarcoma, malignant fibrous histiocytoma, liposarcoma, rhabdomyosarcoma, leiyomyosarcoma, angiosarcoma and alveolar soft part sarcoma.
• Soft tissue sarcomas usually presents as a slow- or rapid-growing swelling of the mucosa involving any part of the oral cavity.
• Treatment usually consists of surgery with adjuvant radiotherapy for those with high-grade tumors and/or positive margins.
Neuropathies are commonly reported in patients with malignancy, comprising direct effects of the tumor, paraneoplasia, and treatment-related toxicity.

Of paraneoplastic syndromes, neuropathy is the most common and has been reported in as many as 5% of all cancer patients.

Paraneoplastic sensory neuropathy is most frequently associated with small cell lung cancer and less often with stomach, colon, breast, and ovarian cancer.

Paraneoplastic pemphigoid presents in a similar manner as benign mucous membrane pemphigoid and may present with gingival and mucosal involvement with erythema and ulceration.

In patients with paraneoplastic syndromes, the most common clinical picture is that of numbness, paresthesias, and burning pain, which are often accompanied by detectable autoantibodies.
- HIV infection that leads to immunosuppression increases the risk of the development of neoplastic disease.
- Improved management of HIV disease using highly active antiretroviral therapy (HAART) and newer agents has led to a dramatic decrease in the prevalence of oral manifestations, including Kaposi’s sarcoma (KS), although lymphoma remains a common malignancy.
- KS is the most common neoplastic disease of acquired immune deficiency syndrome (AIDS).
- Lymphoma is the most rapidly increasing malignant disease of AIDS. NHL, most commonly of B-cell origin, may present with central nervous system involvement but also may present with head, neck, or oral lesions.
- The lymphomas are aggressive and carry a poor prognosis.
- Oropharyngeal SCC has been reported in patients with HIV disease.
- KS (HHV-8) is a multicentric neoplastic proliferation of endothelial cells.
• KS can involve any oral site but most frequently involves the attached mucosa of the palate, gingiva, and dorsum of the tongue. Lesions begin as blue purple or red purple flat discolorations that can progress to tissue masses that may ulcerate. The lesions do not blanch with pressure.

• Initial lesions are asymptomatic but can cause discomfort and interfere with speech, denture use, and eating when lesions progress.

• The differential diagnosis includes ecchymosis, vascular lesions, and salivary gland tumors.

• Definitive diagnosis requires biopsy.

• Because KS is a multicentric neoplastic disease, multiple sites of involvement can occur, including skin, lymph nodes, gastrointestinal tract, and other organ systems.

• Intralesional chemotherapy for treatment of oral KS has shown effective palliation.

• KS is radiosensitive, and radiation can be palliative for regional disease.
▲ Pretreatment oral and dental assessment:

- (1) identify oral involvement by cancer, (2) reduce the risk or severity of complications, (3) reduce the risk of infection involving the dentition and mucosa, and (4) minimize and manage the complications of hyposalivation.

- The assessment must be comprehensive and include head and neck examination (with attention to the presence of lymphadenopathy), intraoral mucosal examination, and periodontal and dental examination.

- The periodontal examination must include full periodontal probing. Periodontal attachment loss is greater in radiated fields, and this future attachment loss should be considered in preradiotherapy treatment planning.

- Radiographic examination should allow detailed evaluation of the teeth and periapical regions and should include imaging of any bone pathosis.

- Saliva production should be measured prior to therapy to document any change in flow rate, which may predict a risk of oral complications.
Prior to radiation therapy, teeth to be maintained should be scaled and root planed. Sites of potential mechanical irritation should be eliminated.

The prevention of osteonecrosis requires the extraction of nonrestorable or questionable teeth, root tips, and periodontally involved teeth in the planned radiation field.

If time permits, asymptomatic periapical radiolucent lesions can be managed; however, endodontics can be performed following radiation if expert management is accomplished.

Detailed review of oral hygiene, oral care during radiation therapy, and oral care following radiotherapy is an important part of long-term care.
Complications of Cancer treatment:

- Acute reactions occur during the course of radiotherapy and combined radiochemotherapy because of direct tissue toxicity and possibly secondary bacterial irritation resulting in ulcerative mucositis; 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, fibrosis in connective tissue and muscle, and change in the cellularity of tissues. These complications develop slowly over months to years following treatment.

- Chronic effects in the mucosa include epithelial atrophy, altered vascular supply, and fibrosis in connective tissue, resulting in an atrophic and friable and sensitive mucosa.

- The connective tissue and musculature may demonstrate increased fibrosis, which may result in limited movement and altered function.
• In salivary glands, loss of acinar cells, alteration in duct epithelium, fibrosis, and fatty degeneration occur.
• In bone, hypovascularity and hypocellularularity lead to the risk of osteoradionecrosis.
• Surgical treatment of the malignant disease results in acute pain and may result in chronic complications due to structural change, fibrosis, and neurologic changes.
• Hyperfractionation of radiation therapy may reduce the late complications but increases the severity of the acute reactions.
• Ulcerative oral mucositis is a painful and debilitating condition that is a dose- and rate-limiting toxicity of cancer therapy.
• The potential sequelae of mucositis consist of severe pain, increased risk of local and systemic infection, compromised oral and pharyngeal function, and oral bleeding.
- Mucositis is the most common cause of pain during the treatment of cancer and the most distressing side effect of head and neck radiation therapy and myelosuppressive chemotherapy and stem cell transplantation.
- Pain due to oropharyngeal mucositis frequently requires the use of opioid analgesics, which is associated with increased costs and side effects.
- The increasing use of more aggressive therapy to improve cancer cure rates has increased the frequency and severity of oral complications.
- In neutropenic patients, the risk of systemic infection due to oral opportunistic and acquired flora is increased with mucosal ulceration.
- Increased risk of mucositis has been associated with poor oral hygiene, tobacco use, hyposalivation at baseline, and older age.
• Cytotoxic chemotherapy and radiation therapy have direct effects on connective tissue and vascular elements and mucosal epithelial cells, resulting in thinning of the epithelium and ultimately to loss of the barrier.

• Mucositis begins with an initial inflammatory/vascular and epithelial phase that is followed by an ulcerative/bacteriologic phase and, ultimately, a healing phase.

• The oral microflora appear to play a role following the development of the ulcerative phase. Shifts in the oral microflora include the development of a flora high in *Streptococcus mutans*, lactobacilli, *Candida*, and gram-negative bacilli, which may result in oral infections and may aggravate mucositis.

• Resolution of mucositis is dependent on epithelial cell regeneration and angiogenesis and may also be dependent on white blood cell function and the production of growth factors.
• Pain associated with mucositis is dependent on the degree of tissue damage, the sensitization of pain receptors, and the elaboration of inflammatory and pain mediators.

• Oral defenses compromised due to irradiation include altered mucosal cell turnover, increased permeability and loss of the mucosal barrier, changes in saliva production, reduced levels of antimicrobial factors in saliva, loss of protective mucins, and diluting effects.

• Impairment of the mobility of oral structures may lead to reduced clearing of local irritants and food products.

• 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.

• Pseudomembrane formation represents ulceration with a fibrinous exudate with oral debris and microbial components.
• Radiation has more marked effects on nonkeratinized mucosa. Late changes in the mucosa reflect endarteritis and vascular changes associated with hypovascularity and with hyalinization of collagen.

• With common fractions of 180 to 220 cGy per day, mucositis with erythema is noted in 1 to 2 weeks and increases throughout the course of therapy (often to a maximum in 4 to 5 weeks), with persistence until healing occurs 2 or more weeks after the completion of therapy.

• Metal dental restorations, implants, and appliances may block radiation, affecting tumor dose, reflect the beam, and produce secondary radiation, altering the impact of irradiation on adjacent tissue, resulting in increased mucositis and risk of late effects. Thus, removable dental appliances should be removed during radiation.
Bilateral exposure of the major salivary glands to radiation therapy will predictably result in hyposalivation. In patients who receive radiotherapy for treatment of Hodgkin’s disease, saliva production is affected when the upper limit of the field is at the chin to the mastoid.

Irreversible effects occur at a total dose of greater than 5,000 Gy. Radiation results in acinar cell atrophy and necrosis, changes in the vascular connective tissue, and altered neurologic function.

During radiation, the serous acini are affected earlier than the mucinous acini, resulting in a thick viscous secretion that can be upsetting to the patient. Saliva production rapidly decreases and can be reduced by 50% after 1 week of standard fractionated radiation.

Depending on the volume of salivary tissue in the field, hyposalivation may improve within 6 months, but in many cases, the loss of function is permanent.

Changes in the composition of saliva also occur. Decreases in secretory immunoglobulin A, buffering capacity, and acidity are seen. These changes affect the microbial flora and the remineralizing potential of teeth.
Radiotherapy-related mucositis is the most frequent complication in patients receiving irradiation for head and neck cancers. Chronic oral sensitivity frequently continues after treatment, due to mucosal atrophy (33%) and neurologic syndromes (16%).

Oral colonization by *Candida* species and candidiasis is common during and following radiotherapy and is related to hyposalivation and to denture and tobacco use.

Amifostine (Ethyol) is a sulfhydryl compound that acts by scavenging free radicals generated in tissues exposed to radiation and that promotes repair of damaged DNA.

Amifostine has been shown to protect a variety of tissues, including mucosa, cardiac tissue, renal tissue, bone marrow, and neuro and ototoxicity when administered prior to irradiation and chemotherapy.
• Maintaining good oral hygiene has been shown to reduce the severity of oral mucositis and does not increase the risk of septicemia in neutropenic patients.
• Mucositis is not reduced with the use of chlorhexidine rinses during radiation therapy. This may be due to the inactivation of chlorhexidine by saliva, the lack of an etiologic role for gram-positive bacteria in mucositis, and a limited effect of chlorhexidine on gram-negative organisms that may be important in the development of ulcerative mucositis.
• Palliation of symptoms of mucositis may be achieved by the use of bland oral rinses and topical anesthetic and coating agents.
• Saline, bicarbonate, dilute hydrogen peroxide, and water also have been suggested for hydrating and diluting by rinsing.
• Lip applications with water-based lubricants or preparations that contain lanolin have been suggested rather than the use of oil-based products because the chronic use of oil-based products (eg, Vaseline) results in the atrophy of epithelium and the risk of infection under occlusion of the application.
• Lidocaine may cause local symptoms that include burning and that eliminate taste and affect the gag reflex.
Potent topical anesthetic agents should be used with caution due to their potential for decreasing the gag reflex, causing central nervous system depression or excitation and causing cardiovascular effects that may follow excessive absorption.

Local applications of topical anesthetic creams or gels may be useful for local painful mucosal ulcerations.

Benzydamine hydrochloride is a nonsteroidal agent that possesses analgesic anti-inflammatory properties and is mildly anesthetic.
Management of mucositis:

- **Diluting agents**
  Saline, bicarbonate rinses, frequent water rinses, ice chips

- **Coating agents**
  Kaolin-pectin, aluminum chloride, aluminum hydroxide, magnesium hydroxide, hydroxypropyl cellulose, sucralfate

- **Lip lubricants**
  Wax, water based lubricants, lanolin

- **Topical anesthetics**
  Dyclonine HCl, xylocaine HCl, benzocaine HCl, diphenhydramine HCl

- **Topical anesthetics**
  Benzydamine HCl; doxepin HCl

- **Maintain nutrition and hydration**

- **Maintain oral hygiene**

- **Systemic analgesics**
• For patients with residual gland function, high fluid intake and the use of sugarless gum or candies also may assist the stimulation of residual gland function.

• Systemic sialagogues offer the advantage of stimulating saliva secretion that includes all normal components and protective functions of saliva.

• Measurement of saliva flow rates to determine the amount of residual function should be conducted before prescribing a sialagogue. If no saliva is collected under resting or stimulated conditions, it is unlikely that a systemic agent will be effective.

• Pilocarpine is a parasympathomimetic agent and has its major effects at the muscarinic cholinergic receptor of salivary gland acinar cells. In doses of 5 to 10 mg tid, increased secretion of saliva occurs, and few cardiovascular side effects have been noted.

• Other agents have been studied, including Bethanechol (75–200 mg/d in divided doses), and cevimeline (25 mg tid).
• Mouth-wetting agents or saliva substitutes may be used when it is not possible to stimulate salivary function. Frequent sipping of water and a moist diet are mandatory.
• The majority of products currently available are based on carboxymethylcellulose.
• In irradiated patients, the most common clinical infection of the oropharynx is candidiasis.
• Patients who receive radiation therapy can be managed with topical antifungals because oral candidiasis produces oral discomfort but does not lead to systemic infection unless the patient is immunocompromised.
• Systemic azoles are used for infection that occurs while using topicals and if compliance with topical oral therapy is poor.
• When prescribing topical antifungal drugs, the presence of sucrose in the product must be known because frequent use of sucrose-sweetened products may promote caries, particularly in patients with dry mouth.
Caries associated with hyposalivation typically affect the gingival third and the incisal cusp tips of the teeth. The etiology is related to a lack of production of saliva, loss of remineralizing potential, loss of buffering capacity, reduced pH, and change in the bacterial flora. Treatment of each component of the caries process must be addressed to prevent demineralization and rampant caries.

The tooth structure may be hardened by the use of fluorides, and remineralization may be enhanced by the use of fluorides and remineralizing products. The effects of topical products may be enhanced by increased contact time on the teeth, which can be achieved by applying them with occlusive vacuform splints or gel carriers, which should extend over the gingival margins of the teeth. Custom vinyl trays are useful for the application of fluoride to prevent and control caries in high-risk patients.
Soft tissue necrosis may involve any oral site, including the cheeks and tongue. Involvement of tissue overlying bone that has received high-dose radiation may predispose patients to necrosis of bone. Postradiation osteonecrosis (PRON) may be chronic or progressive.

Radiation therapy causes endarteritis that affects vascularity, resulting in hypovascular, hypocellular, 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, and idiopathic or spontaneous necrosis for which no known cause is identified.

Although PRON may be secondarily infected, the infection is not etiologic.

Symptoms and signs may include discomfort or tenderness at the site, bad taste, paresthesia and anesthesia, extraoral and oronasal fistulae, secondary infection causing secondary osteomyelitis, and pathologic fracture.
The primary risk factor for the development of PRON is radiation therapy, in which dose, fraction, and numbers of fractions result in the biologic effect.

The volume of bone included in the field of irradiation increases the risk. The presence of teeth in a high-dose radiation field represents a risk factor for PRON, probably in relation to dental or periodontal disease or irritation. The risk of necrosis is lifelong and may occur many years after irradiation.

Osteonecrosis and osteomyelitis of the jaws may develop in patients using bisphosphonate. The clinical presentation is of bone exposure with or without pain, swelling, and fistula formation.

The prevention of osteonecrosis begins with the preradiation dental examination and radiotherapy treatment planning.

Teeth in the high-dose fraction with questionable prognosis (particularly when due to periodontal disease and when excellent compliance with regular oral care is unlikely) should be extracted prior to radiotherapy.
• For bisphosphonate-associated osteonecrosis (BON), pretreatment examination is encouraged and teeth with infection or that may require surgery for future care should be extracted.

• Dental treatment may be without additional risk in the first several months of use of bisphosphonates. If extractions are planned, it is desirable to allow as much healing time as possible; 7 to 14 days and up to 21 days prior to radiotherapy have been suggested. The time required may depend on the nature of the extraction, and expert atraumatic extraction will require less healing time.

• Therapy is not defined for BON; however, for BON and PRON, management recommendations include avoiding mucosal trauma and irritants, discontinuing the use of dental appliances if they contact the area of the lesion, maintaining nutritional status, stopping smoking, and eliminating alcohol consumption.

• Topical antibiotic (ie, tetracycline) or antiseptic (chlorhexidine) rinses may reduce the potential secondary local irritation from the microbial flora.
When secondary infection occurs, topical and systemic antimicrobials are needed.

For chronic persisting PRON (stage II), this therapy and regular follow-up may be the best approach to treatment.

Hyperbaric oxygen (HBO) therapy increases the oxygenation of tissue, increases angiogenesis, and promotes osteoblast and fibroblast function.

In PRON cases associated with symptoms of pain and progression (stage III), HBO is a part of therapy.

HBO therapy and surgical guidelines have been established for PRON but not for BON.

Sequestra may be managed with limited resection or may require mandibulectomy. If surgery is required, postsurgical HBO therapy of is recommended. The mandible can be reconstructed to provide continuity for esthetics and function for PRON because the field of bony change is known; however, in BON, the entire bone is affected.

In PRON, vascularized grafts and microvascular surgery has improved outcomes in cases in which affected bone and soft tissue can be replaced with vascularized tissue and good blood supply established.
Abnormal speech may follow surgery or radiation due to removal of structure and because of hyposalivation and fibrosis that affects tongue mobility, mandibular movement, and soft palate function.

Maxillectomy that produces a palatal defect must be managed with prostheses to allow function in speech, mastication, and deglutition.

Radiation therapy produces changes in the patient’s perceptions of taste and smell. Taste may be affected directly, due to an effect on the taste buds, or indirectly, due to hyposalivation and secondary infection.

A total fractionated dose of >3,000 Gy reduces the acuity of all tastes (ie, sweet, sour, bitter, and salty). 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.
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.

Mandibular stretching exercises and prosthetic aids (Therabite device or tongue blades) and use of microcurrent electrotherapy and pentoxifylline may increase mouth opening and may reduce the severity of fibrosis and limited mandibular movement when conducted before severe limitation has developed, but few benefits are seen after such limitation has developed.

Mandibular discontinuity following surgery and the emotional stress associated with malignant disease and its treatment may influence musculoskeletal syndromes, causing pain.

Therapy may include occlusal stabilization appliances, physiotherapy, exercises, trigger point injections and analgesics, muscle relaxants, tricyclic medications, and other chronic pain management strategies.
When children receive radiotherapy to the facial skeleton, future growth and development may be affected.

Agenesis of teeth, cessation of root formation, abnormal root forms, or abnormal calcification may occur. Despite these dental abnormalities, teeth will erupt even without root formation and may be retained for years.

Growth of the facial skeleton in the radiated field may be affected, which can result in micrognathia, retrognathia, altered growth of the maxilla, and asymmetric growth. Altered growth and development may occur if treatment affects the pituitary gland. Trismus may occur in patients secondary to fibrosis of muscles.

Head and neck and oral pain may be due to a number of causes and is particularly challenging as oral function including speech, swallowing, and other motor functions of the head and neck and oropharynx are constant triggers of pain and compound the affective and cognitive impact of the pain experience.
- **Pain due to tumor:**
  - Loss of epithelial barrier; ulceration
  - Exposure of nerves; tumor necrosis; secondary infection
  - Chemosensitization of nerves; pressure on nerves
  - Tumor infiltration of bone, muscle, nerve, blood vessels
  - Exacerbation of dental or periodontal disease
  - Pain due to cancer therapy
  - Pain following surgery
  - Acute surgical injury
  - Secondary infection
  - Myofascial or musculoskeletal syndromes
  - Neuroma; deafferentation pain
  - Pain due to radiotherapy Mucositis
  - Necrosis of soft tissue or bone
  - Myofascial or musculoskeletal syndromes
  - Exacerbation of dental or periodontal disease
  - Pain due to chemotherapy Mucositis
  - Peripheral neuropathy
  - Infection
  - Exacerbation of dental or periodontal disease
  - Pain unrelated to cancer or cancer therapy
In cancer patients, the post-treatment pain experience is characterized by acute pain lasting 1 to 2 months with a gradual time-related improvement.

Neurologic pain states, including neuropathic pain and neuralgia-like pain, may require the use of centrally acting medications, including antidepressants and anticonvulsants.

Chronic pain management approaches, including counseling, relaxation therapy, imagery, biofeedback, hypnosis, and transcutaneous nerve stimulation, may be needed.

Topical anesthetics are used for mucositis pain, producing a short period of mucosal anesthesia (up to half an hour), but may sting with application on damaged mucosa and affect taste and gag reflex.

Topical anesthetics are often mixed with coating and antimicrobial agents such as milk of magnesia, diphenhydramine, or nystatin;
Topical doxepin, a tricyclic antidepressant, produces analgesia for 4 hours or longer following a single application in cancer patients.

Topical coating agents have been promoted for use in patients with mucositis.

Other approaches that may improve pain control include opioid substitution and opioid rotation and adjuvant medications.

Adjuvant medications, such as tricyclic antidepressants and other centrally acting pain medications, such as neurontin, should be considered.

Gabapentin is a voltage-sensitive sodium and calcium channel blocker that may be used for adjuvant pain management.

If sleep is nonrestorative, adequate pain control should include the additional use of medications to promote sound sleep.

Tricyclic antidepressants, some of the anxiolytic/hypnotics, and some of the benzodiazepines can be considered.

Analgesics, when required, should be provided on a regularly scheduled or time-contingent basis, not on an as-needed basis, as improved pain control can be achieved using lower total doses of analgesics.
Molecular model with early and late changes that accumulate over time, leading to cancer.
Nonpainful, irregular indurated exophytic and ulcerated buccal mass histopathology revealed squamous cell carcinoma.
Irregular erthroleukoplakia, following application by toluidine blue. Inferior of lesion and superior stained site, were biopsy proven squamous cell carcinoma.
Eroded, erythroluekoplakic, indurated lesion in the R posterior third of the lateral border of tongue diagnosed as squamous cell carcinoma.
indurated and ulcerated lesion of the R anterior tongue in a 15 year old girl, persisting after removal of orthodontic appliances, proven to be squamous cell carcinoma on biopsy.
Asymptomatic erythroplakia in the floor of the mouth in a patient presenting due to toothache, diagnosed on biopsy as squamous cell carcinoma.
Previously treated squamous cell carcinoma, are at risk of recurrent squamous cell carcinoma. This case was treated with surgery and post-operative radiation therapy, and presented with an area of leukoerythroplakia that was diagnosed as recurrent squamous cell carcinoma.
Periapical radiograph demonstrating bone destruction in the furcation of the first molar tooth and associated resorption of the root. A subsequent biopsy specimen demonstrated squamous cell carcinoma, which was diagnosed as a primary intra-alveolar lesion.
Periapical radiograph demonstrating an irregular radiolucency involving the bone of the apical region of the mandibular anterior teeth, without a change in root anatomy. The teeth tested vital. The radiographic finding was the first indication of involvement of the bony adenocarcinoma.
Panoramic radiograph taken at the time of diagnosis of adenocarcinoma.
Panoramic radiograph showing bony destruction of the molar region of the right mandible due to invasion of contiguous tumor. Paresthesia of the right lip was present at the time of diagnosis.
Massive bone destruction of the mandible, shown after 5 years of follow-up in a case of adenocarcinoma extending to the molar regions bilaterally. The anterior teeth had been lost due to progressive destruction of the anterior mandible and floor of the mouth.
Panoramic radiograph demonstrating a destructive lesion of the right mandible overlying the mandibular canal. Anesthesia of the mandibular nerve and jaw pain were present. The bone biopsy specimen was consistent with metastatic colon carcinoma, which was subsequently diagnosed.
Computed tomographic scan demonstrating destruction of the medial wall of the antrum and opacification of the antrum. Additional views suggested that the opacification represented a tissue mass that was consistent with tumor.
Bilateral involvement of the anterior and posterior hard palate with purple discolorations consistent with Kaposi sarcoma.
Palatal and gingival involvement by Kaposi sarcoma, with discoloration and enlargement and soft tissue mass on the maxillary tuberosity.
Radiation mucositis with erythema and developing ulceration in the floor of the mouth and ventral tongue; angular cheilitis representing a clinical manifestation of candidiasis.
Extensive ulceration and pseudomembrane formation of the labial mucosa, compromising oral hygiene which may further aggravate oral mucositis.
Erythema and ulceration increasing in the floor of the mouth in the fourth week of radiation therapy.
Panoramic radiograph of postradiation osteonecrosis, demonstrating bone destruction approaching the inferior border of the mandible.