

Radiation Therapy Toxicity in Head and Neck Cancer

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- Radiation therapy (RT) can cure patients with head and neck cancer.
- However, this cure can Supportive management is essential during radiation treatment.
- Patient education and specialist utilization, as needed,
- Validated common scoring systems to track toxicity

Category

- Acute effects
- Late Effects

Grade and score system

- Radiation Therapy Oncology Group (**RTOG**)
- European Organisation for Research and Treatment of Cancer (**EORTC**)—
- Common Terminology Criteria for Adverse Events (**CTCAE**)—grades only acute effects
- Grading scales that incorporate patient-reported outcomes (**PROs**)
- Radiation-Induced Skin Reaction Assessment Scale (**RISRAS**)

- Catterall Skin Scoring Profile
- Skindex-16
- Skin Cancer Index
- Dermatology Life Quality Index
- Grading scales incorporating PROs when using targeted therapies:
- Functional Assessment of Cancer Therapy Epidermal Growth Factor Receptor Inhibitor (FACT-EGFRI-18)

ACUTE TOXICITY

- Dermatitis
- Xerostomia
- Mucositis
- Dysgeusia
- Oral Infection
- Nausea
- Fatigue
- Depression
- Alopecia

LATE TOXICITY

- External Lymphedema/Fibrosis
- Pharynx: Dysphagia
- Dental Issues and Osteoradionecrosis (ORN) of the Jaw
- Hearing Loss
- Voice Dysfunction
- Peripheral Neuropathy
- Psychosocial/Economic Effects

Dermatitis

- Acute radiation dermatitis results from injury to the rapidly dividing cells of the dermis, epidermis, and feeding vasculature.
- erythema, edema, dry and wet desquamation, blistering and bleeding, and erosion and ulceration of the skin. .

Timing

Prodromal changes within 24 hours

- Visible reaction 10 to 14 days
- Dry desquamation expected at dosages over 30 Gy
- Wet desquamation expected at dosages over 40 Gy.

Prevention

- Should observe three basic principles at all times:
- Lubrication and restoration of moisture to the skin;
- Protection of the skin from environmental stress or exposure.
- Unscented, lanolin-free, water-based moisturizing lotion

Treatment

- Avoid contact of irritant product
- Avoid alcohol- or menthol-containing products
- Avoid perfumes, aftershave, or chlorine exposure;
- Use a mild, nonalkaline, unscented soap;
- Use an electric razor to avoid cuts to the skin;
- Wear loose-fitting clothing and avoid scratching or rubbing the skin.
- Good hygiene and cleanliness is needed; washing the skin with lukewarm water or saline soaks is encouraged
- Avoidance of sun exposure or sunscreen when necessary
- Topical low-dose steroids are commonly used to soothe local irritation and itching

- Avoid bolus effect of tape or bandages.
- Dry slough should be manually or enzymatically debrided.
- Friction may be reduced with nonstick barrier films or specialized nonadherent dressings.
- Infection should be addressed promptly with topically applied antibiotic medications or dressings.
- Specialized topical dressings should be applied to any areas of friction or open wound.
- Frequent use of moisturizing lotions or creams

SCREENING

Physician should be aware of patient-related factors:

- Anatomic site;
- Body mass index;
- Age;
- Ethnicity;
- Sun-reactive skin type;
- Medical comorbidities such as collagen vascular disease and HIV; Smoking;
- Possible genetic mutations.

- Treatment-related factors may pose increased risk:
- Volume of skin within the high-dose treatment area
- Beam energy;
- Total dose and fractionation;
- Use of bolus and its frequency;
- Use of tangential beams or intensity-modulated radiation;
- Concurrent or recent use of radiosensitizers, chemotherapy, and targeted therapy

Xerostomia

- A feeling of oral dryness
- decreased function or of the salivary glands;
- Results in altered taste, reduced intraoral lubrication, halitosis, dental 42
- infections, caries, and speech and eating difficulties.

Timing

Typically peaks in severity in the last two weeks of a radiation treatment course;

- May be perceived by patients as early as the first week of treatment

Prevention

- Radiation dosage to the parotid and submandibular glands is critical.
- The effects are proportional to the amount of radiation dosage delivered.
- Standard known tolerance levels, if exceeded, will result in very severe effects

Screening

- Patients should be inspected at least weekly for signs of worsening xerostomia.
- All patients receiving more than 2 to 3 weeks of RT to the oral cavity or pharyngeal regions are at risk for severe xerostomia.
- Validated common scoring systems to track toxicity:

Treatment

- **Salivary substitutes**

that temporarily hydrate the mucosa: such as hyetellose, hyprolose, or caramellose.

- **Gustatory stimulants:**

Acidic, bitter, or sweet substances such as citrus flavors or cough drops. Xylitol, a sugar substitute used in gum and lozenges, may have positive effects on dentition.

- **Pharmacologic stimulants**

- parasympathomimetic agents: Bethanechol, pilocarpine, and cevimeline comprise this class of medications . (Common side effects include sweating, dizziness, headache, nausea, flushing, and increased urge to urinate)`.

- Acupuncture:
- Found to be effective in some single-institution experiences and uncontrolled trials, but a systematic review failed to identify compelling evidence of efficacy
- A prospective randomized phase II trial of standardized electronic acupuncture found some evidence of similar efficacy to pilocarpine with fewer side effects

Dysgeusia

Radiation may cause alterations in taste perception

- dysgeusia
- ageusia
- hypogeusia
- Alteration of taste may occur in up to 75% of head and neck cancer patients
- Dysgeusia results in anorexia, weight loss, malnutrition, and poor quality of life (QOL)

- **Timing**

- • RT causes a dose-related cytotoxic effect on taste buds which reduces their density, which is linked to taste perception and sensitivity . Dysgeusia correlates with the extent of oral cavity radiated to high doses (50 Gy), with peak incidence of symptoms at 1 month after RT followed by improvement until at least 12 months .

Prevention

- • Avoidance of a high mean dose to the oral cavity may be the best form of prevention.
- • Studies of zinc supplementation to prevent radiation-induced taste effects have yielded highly conflicting results

Treatment

Reducing effects of xerostomia may help to mitigate some taste alteration.

Mucositis

Definition

- Acute mucositis results from progressive vasocongestion and edema of the mucosa accompanied by erosion and denudation of the surface epithelium. ● It may affect the mouth, pharynx, esophagus, or other gastrointestinal organs.
 - Severe cases progress to ulceration with pseudomembrane formation and constant pain.
- Mucositis increases the risk of infection due to disruption of the mucosal barrier.
- The resultant pain and dysphagia affect oral intake and nutrition

World Health Organization's Oral Toxicity Scale

Severe Mucositis

Grade 1

Soreness
± erythema

Grade 2

Erythema,
ulcers;
patient can
swallow
solid food

Grade 3

Ulcers with
extensive
erythema;
patient
cannot
swallow
food

Grade 4

Mucositis
to the extent
that
alimentionation
is not
possible



Timing

Typically begins at 2 to 3 weeks after start of RT and plateaus at the 4th week

May persist for weeks to months after discontinuation of an extended radiation treatment course.

Prevention

Patient risk factors include

- Radiated subsite of the oral cavity or oropharynx;
- Age;
- Smoking;
- Alcoholism;
- Poor oral health;
- Poor nutritional status;
- HIV status;
- Concurrent or recent exposure to radiosensitizers, chemotherapy, and targeted therapies.

Treatment-related factors include

- The volume of mucosa included in the high-dose areas of radiation; Total dosage prescribed;
- Higher dose per fraction;
- Use of altered fractionation or hyperfractionation;
- Use of conventional versus intensity-modulated RT (IMRT).

Treatment

- Oral cavity should be kept very clean and free of residue:
- Rinse thoroughly after meals.
- Frequent oral cleansing and disinfection with a weak solution of salt and baking soda several times daily.
- Commercially available supersaturated calcium phosphate solutions (Caphosol, NeutraSal, SalivaMAX) have shown some advantage in head to-head trials against the standard baking soda and salt solution.
- Injury and irritation to the mucosal surfaces should be avoided:

Recommend a soft bland diet that requires minimal chewing. Patients should avoid spicy or acidic foods.

- Caffeine and alcohol result in irritating or drying the mucosa. Extra-soft toothbrush minimizes trauma.
- Soothing and lubricating the mucosal surfaces of the mouth and throat
- help to prevent and heal mucositis:
- Oratect gel and Gelclair are mucosal adhesive, water-soluble films that provide a protective barrier (38).
- Sucralfate is a mucosal coating agent designed to protect the mucosa, but there may be no difference when compared to saline rinses (39). Small pilot studies using glutamine have demonstrated a reduction in severity and length of mucositis and pain (40,41).
- Randomized trials and a meta-analysis of honey have shown promising results (42–44).

- Results of clinical trials for amifostine, a radioprotectant, are conflicting
- Side effects include hypotension and potentially severe nausea.
- Granulocyte macrophage colony stimulating factor (GM-CSF) given either subcutaneously or orally showed promising results in some in pilot
- Palifermin is a novel keratinocyte growth factor and has demonstrated efficacy in the acceleration of epithelial restoration in stem cell transplant patients although the benefit in a head and neck cancer trial was not significant
- Topical short-acting pain control is important to maintain oral intake and relieve pain:

- Topical analgesic solutions such as benzylamine or phenol are frequently used, although these only treat the symptoms and not the underlying condition.
- Viscous lidocaine is frequently combined with an antihistamine (diphenhydramine, eg, Benadryl) and antacid (magnesium hydroxide/aluminum hydroxide, eg, Maalox) +/- antifungal medication (nystatin) and does show efficacy against pain, but systemic absorption and lack of true efficacy against the underlying condition is a concern (49–51).
- In a small study, morphine mouthwash appeared to provide

- reduction in mucositis and superior patient satisfaction to lidocaine-based solution
- Doxepin mouthrinse was shown to produce overall benefits superior to placebo and equivalent to lidocaine-based preparations and may be longer acting (49,53).
- Low-energy helium-neon laser treatment was associated with a reduction in the frequency of grade 3 mucositis and pain compared to placebo, but this is not widely available (54).
- If pain is continuous and refractory to topical approaches, blocking pain responses centrally is important for patient well-being:
 - Opioid analgesics
 - Gabapentin has shown to produce improved analgesia and reduce opioid requirements

Oral Infection

Definition

- Bacterial, fungal, or viral infections can occur, especially in areas of injury within the oral or pharyngeal regions

Prevention

- Excellent oral hygiene promotes control over microbial flora. Frequent rinsing and gargling of the mouth and throat will reduce the overall pathogenic load.
- Use of a water-pik, extra-soft toothbrush, or oral swab may be useful in removing debris and residue that adheres to mucosal surfaces

Screening

- • Patients should be examined at least weekly to check for signs of mucosal injury and infection.
- • Fungal infection is extremely common and should be anticipated in the majority of patients receiving radiation to the mouth or throat

Treatment

- • The majority of oral infections in patients with mucositis are due to *Candida albicans* but other *Candida* species are often present (59):
- Typically whitish, cottony appearance.
- May be easily confused with early mucositis or pseudomembrane formation.
- Commonly treated either topically or systemically:
- Nystatin rinse;
- Clotrimazole troche;
- Fluconazole is an effective drug of choice in many cases
- One small study showed a reduction in severe mucositis with fluconazole prophylaxis (62).

- In the less than 10% of cases of infection refractory to fluconazole,
- lesions should be cultured to ascertain species and sensitivity; alternative azoles may be required (63).
- Herpes simplex virus (HSV) accounts for most other severe infections, especially in transplant patients.
- May occur in over one-fourth of patients with ulcerative radiation mucositis
- Treated effectively with acyclovir or valacyclovir.
- For intraoral bacterial infections, minocycline or tetracycline have shown efficacy when added to dental rinse solutions

Nausea

Definition

- Nausea consists of gastrointestinal discomfort and a sensation of wanting to vomit which may precede actual vomiting.

Timing

- May occur in patients who have received more than 3 weeks of radiation treatment;
- Often related to timing of radiation and/or chemotherapy administration.

Prevention

- The best treatment of nausea is prevention.
- Fifty percent to 80% of patients undergoing radiation and all patients undergoing systemic therapy treatments should be considered at some level of risk (68).
- Preventive medications should be prescribed in advance of the anticipated symptoms, to a level concordant with the risk associated with the specific regimen (69).

Screening

- Patient factors that increase the risk of nausea:
- Prior nausea reactions;
- Younger patient age;
- Female gender
- Recent or current exposure to emetogenic systemic therapy agents . The characteristics of the RT strongly influence the likelihood of experiencing nausea or vomiting:

- Large-scale mucosal irradiation increases the risk of inflammatory secretions and tissue edema which worsen the sensation of nausea. Brain and skull base irradiation may affect the physiologic vomiting center in the medulla or the chemoreceptor trigger zone in the base of the fourth ventricle.
- Patients receiving concurrent radiosensitizing chemotherapy that is
- emetogenic experience combined effects
- Cisplatin is the most emetogenic chemotherapy agent in common use.
- Any patient receiving any form of systemic therapy is considered at increased risk for nausea.

Treatment

Major classes of anti-nausea agents

- Antihistamines (diphenhydramine, meclizine);
- Anticholinergics (scopolamine);
- Benzodiazepines (lorazepam);
- Steroids (dexamethasone, methylprednisolone);
- Dopamine antagonists (metoclopramide, prochlorperazine, promethazine); 5-HT receptor (serotonin) antagonists (ondansetron, granisetron, palonosetron);

- Substance P antagonists (aprepitant, fosaprepitant);
- Evolving treatment paradigms:
- An antipsychotic medication, olanzapine, was recently found to be more effective than metoclopramide, and as effective as aprepitant in combination with 5-HT antagonists
- Dronabinol, a synthetic form of the active ingredient in cannabis, is approved for refractory chemotherapy-induced nausea and vomiting
- The efficacy of ginger is supported by only limited data
- Patients at high risk for nausea should take a 5-HT antagonist with consideration of around-the-clock scheduled use and may also require short preparatory or pulsed courses of dexamethasone.

- • Substance P antagonists are not yet clearly indicated for RT-induced nausea,
- but are highly effective in patients who take chemotherapy.
- • Patients experiencing nausea may find it difficult to ingest oral medications, and effective management may require intravenous or transdermal administration of anti-nausea medications.

Fatigue

Definition

- Fatigue is a “distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning”
- Causes are very uncertain, with theories related to
- Inflammatory mediators released during treatment;
- Stress of transportation to daily radiation treatment;
- The emotional stress of cancer;
- Effects due to circulating cancer cells or the malignant cancer mass itself;
- Sleep disturbance related to treatments;
- The very common usage of steroids during cancer therapy; A combination of all of these factors.

Timing

- The onset may occur after as little as a week of exposure to RT.
- Effects may linger for a few to several months or even years

● Prevention

- Avoid excessive use of steroids at night if possible.
- ● Encourage excellent sleep hygiene:
- Avoidance of alcohol or late meals in the evening;
- Reduced emotional and physical stimulation prior to sleep time; Removal of light sources and noise from the room.
- ● Address any potential medical causes of fatigue such as:
- Medication effects;
- Uncontrolled pain;

Screening

- Almost all patients undergoing large-scale RT complain of some level of fatigue.
- The National Comprehensive Cancer Network (NCCN) guidelines recommend assessing fatigue with the question, “How would you rate your fatigue on a scale of 0 to 10 over the past 7 days?”

Anemia;

Malnutrition;

Psychological or psychiatric disorder;

Physiologic reasons for sleep disturbance such as obesity or altered airway;

Renal, cardiac, or pulmonary dysfunction;

Endocrine dysfunction such as hypothyroidism or hypogonadism

Treatment

- **Short-acting benzodiazepines are not recommended for addressing sleep disturbance in elderly adults due to side effects:**
 - Tolerance and addiction;
 - Rebound insomnia;
 - Reduced deep sleep;
 - Daytime fatigue and cognitive impairment;
 - Increased risk for vehicular accidents and falls.
- **Nonbenzodiazepine hypnotics (zolpidem, eszopiclone):**
 - May produce less tolerance and rebound effect than benzodiazepines;
 - Use for more than a few weeks is discouraged due to similar long-term effects.

Nonpharmacological intervention

- Increased exercise;
- Strict sleep hygiene and better regulation of the sleep-wake cycle; Psychosocial or cognitive-behavioral interventions (83);
- Nutritional counseling;
- Meditation, yoga, and mindfulness-based stress reduction methods • Stimulants (methylphenidate, modafinil) (86,87):
- Have been used to combat daytime fatigue;
- In randomized trials, showed no improved effect over placebo

Depression

Definition

- Depression is a mood disorder characterized by:
 - Persistent feelings of sadness and/or anxiety;
 - Loss of interest or pleasure in hobbies and activities;
 - Decreased energy;
 - Feelings of hopelessness, helplessness, and irritability.
 - ● Patients may have difficulty concentrating, remembering things, or making decisions.
 - ● Patients may have sleep disturbances, such as oversleeping, not wanting to wake up, or waking up in the middle of the night.
 - ● Patients may have appetite or weight changes.

Timing

- It may be coincident with cancer diagnosis or may be of longstanding nature that preceded the cancer diagnosis and is exacerbated by it.
- Exacerbation of underlying mood disorder may become acutely apparent during any phase of the process of cancer workup and treatment. ● Among patients with head and neck cancer, the incidence of major depressive disorder is 15% to 50%

Prevention

- While prevention of depression is not possible, its detrimental effects on the quality of care can be prevented with screening, identification, and prompt referral to a qualified mental health specialist.

Screening

- Screening for depression is recommended for head and neck cancer
- patients in the NCCN guidelines; practitioners are referred to the NCCN guidelines in “distress management.”
- Specific details of screening tools or recommendations for action when depression is identified are limited, due to a wide variety in the availability of mental health services and approaches to management of depression.
- Suicidality, with a specific plan to harm oneself, or psychosis, is an indication for urgent hospitalization.
- A 24-hour, toll-free National Suicide Prevention Lifeline is accessible at 1- 800-273-TALK (8255) or

Treatment

- Management of pain and other physical symptoms should be instituted before or with initiation of antidepressant treatment.
- Pharmacologic intervention
- Should be considered for moderate to severe major depression; Should be combined with psychosocial interventions.
- Major classes of antidepressant medications include: Selective serotonin reuptake inhibitors (SSRI); Serotonin and norepinephrine reuptake inhibitors (SNRI); Tricyclic antidepressants (TCA); Monoamine oxidase inhibitors (MAOI); Unique medications such as mirtazapine and bupropion. All antidepressants carry a U.S. Food and Drug Administration (FDA)- mandated black box warning:
 - In some cases, children, teenagers, and young adults under age 25 years may experience an increase in suicidal thoughts or behavior when taking antidepressants.
 - This is especially in the first few weeks of starting a new antidepressant or changing a dose of medication.
 - Patients of all ages taking antidepressants should be watched closely. Prompt referral to a qualified mental health specialist is mandatory.

Alopecia

Definition

- Alopecia, or epilation of the hair-bearing skin, is due to the high susceptibility of the growing hair follicles to ionizing radiation.

Timing

- Hair loss is related to the radiation dose received to the hair follicles in the hair-bearing regions of the skin.

- At 3 Gy, there is early reversible alopecia, while some degree of permanent

- alopecia begins to occur at doses above 7 Gy to 8 Gy

- Complete hair regrowth will occur by 2 to 4 months after the occurrence of reversible radiation-induced alopecia.

Prevention

- • Exiting radiation beams can be assessed to predict where the greatest areas of hair loss will occur
- • Dosimetric protection of hair-bearing areas (such as used in the “scalp sparing technique”) is effective at reducing hair loss
- • Preventives under study include nitroxides (Tempol), vitamin D₃, or

● *Treatment*

- Avoid sun exposure to the scalp.
 - Treat the hair gently using a soft brush and gentle shampoo.
 - Avoid use of heat on the hair, such as hair dryer, hot rollers, or curling irons.
 - Avoid use of bleach or hair dyes or permanent curling solutions. Use a wig or hat.
 - Reconstructive surgical procedures such as scalp tissue expansion and hair transplantation can address permanent alopecia
- Avoid sun exposure to the scalp

Pain

Timing

- In head and neck oncology, pain is often a tumor-revealing problem—approximately 50% of cancer patients have pain at diagnosis (100). ● A majority of patients will develop pain during treatment.
- Approximately one-third of patients will note posttreatment pain months after completion of therapy.
- The presentation of worsening pain in the head and neck cancer survivor is a strong indicator of tumor recurrence. A diagnosis of chronic pain is made only after tumor recurrence has been ruled out with physical examination, imaging, and/or biopsy.

Prevention

- Posttreatment chronic pain is a complex, multifactorial problem. ● Chronic pain may result from permanent damage to the oral soft tissues, including epithelial atrophy, submucosal fibrosis, and/or neuropathy. ● Avoidance of mouth irritants can help minimize/prevent posttreatment pain: tobacco smoke, harsh mouthwash, alcohol
- Prior to the initiation of radiation, patients should have a comprehensive oral assessment with extraction of nonrestorable teeth.

Screening

- All evaluations in the follow-up setting should record pain on a 1 to 10 scale.

Treatment

- Physical therapy/massage therapy
- Although frequently prescribed, investigations into the efficacy of posttreatment physical therapy are incomplete.
- Progressive resistance exercise training (PRET) significantly reduced shoulder pain when compared to standard therapeutic exercises for patients managed with a head and neck operation (102).

- Acupuncture
- A randomized trial of acupuncture once a week for 4 weeks versus usual care demonstrated a significant amelioration of symptoms related to shoulder pain from a neck dissection among head and neck cancer survivors (103).
- • Topical and nonnarcotic agents
- In the setting of radiation mucositis during treatment, patients may develop protracted mucosal sensitivity.
- Topical rinses (magic mouthwash and mucosal lidocaine) can provide temporary mucosal relief.
- Anti-inflammatory medications are often prescribed, although little data is available to ascertain the degree of relief that these medications provide.
- • Narcotic pain medications
- If nonnarcotic attempts to ameliorate pain are unsuccessful, narcotic pain medications can be employed

LATE TOXICITY

External Lymphedema/Fibrosis

Definition

- External lymphedema describes symptoms pertaining to the skin and subcutaneous/deep soft tissues of the face, neck, and shoulders. It may result in swelling, tightness, and decreased range of motion with associated limited range of motion and discomfort.
- **Timing**
- Can be appreciated as early as 3 months after completion of head and neck therapy
- Severity can increase with time, as lymphedema results when the lymphatic load exceeds the transport capacity of the lymphatic system secondary to tumor and/or surgery and/or radiation

Prevention

- For many patients secondary lymphedema may be unavoidable.
- Avoidance of bilateral neck dissections (106) if an oncologically safe alternative is available.

Screening

- External lymphedema/fibrosis occurs in approximately 50% of head and neck cancer patients.

- Patients note many symptoms consistent with fibrosis on routine follow-up (“stiffness,” “tightness,” “pain”).

- Tape measurement, useful in other areas of lymphedema (eg, extremity) is not useful secondary to no consistent and reproducible reference points.

- • There is no validated, reliable, clinically useful tool for clinicians to monitor external lymphedema in the head and neck cancer patients.
- • Major discrepancies exist between physician-based and patient based assessments of fibrosis

Treatment

- • Complete decongestive therapy (CDT) has four components: Manual lymph drainage (MLD);
- Use of compression garments and pads;
- Skin care;
- Basic face, neck, and oral cavity exercises.
- • CDT improves head and neck lymphedema in 60% of patients (109). • Outpatient CDT seems to be more successful than patient-directed CDT at home.

- ● Pentoxifylline + vitamin E can be effective in the management of radiation induced fibrosis (110): Pentoxifylline dose is 800 mg/day; Vitamin E dose is 1000 IU/day;
- Duration of therapy can be long (at least 6 months).
- ● Early physical therapy after neck dissection is associated with increased range of motion of the shoulder
- **Evidence**
- Mucosal head and neck squamous cancer has a proclivity to metastasize to lymph nodes, and is frequently regionally advanced at diagnosis (often requiring multimodality therapy to the neck)—therefore, secondary lymphedema/fibrosis is often unavoidable. It is therefore not surprising that an estimated 50% of patients treated for head and neck cancer develop this symptom.
- Postradiation bilateral neck dissections should be avoided as the practice is associated with higher rates of posttreatment complications than unilateral neck dissections

Pharynx: Dysphagia

Definition

- Difficulty swallowing, often described as food hanging up or getting stuck, 56
- increased choking. Posttreatment dysphagia is a recognized but incompletely understood complication of head and neck cancer therapy.

● *Timing*

- Most patients will be swallowing worse than baseline at 3 months after head and neck (chemo)radiation

- **Prevention**

- Avoid unnecessary irradiation to the uninvolved larynx (118). Mean larynx dose to be less than 35 Gy.
- Avoid unnecessary irradiation to the uninvolved pharyngeal constrictors. This does not impair tumor control and is associated with a low rate of dysphagia at 1 year posttreatment
- Mean dose to the uninvolved pharynx to be less than 40 Gy; Pharyngeal constrictor avoidance is contraindicated in the following situations
 - Grossly positive retropharyngeal lymph node(s);
 - Tumor involvement of the posterior pharyngeal wall.
 - • Avoid transoral surgery for T4 base-of-tongue tumors • The consequences of prophylactic gastrostomy tube placement are controversial and subject to institutional bias. Avoidance of gastrostomy tube placement has been reported as a means to prevent long-term dysphagia.

Screening

- All patients (even those who report no swallowing difficulty) should be evaluated by a speech language pathologist (SLP) for a formal swallowing evaluation prior to the initiation of head and neck radiation.
- Patients can be instructed to do a series of exercises during treatment to promote strength and mobility of key swallowing musculature. ● All patients should be evaluated by the SLP after the completion of head and neck radiation.

● **Treatment**

- Appropriate swallowing rehabilitation can eliminate aspiration, decrease the risk of pneumonia, and successfully return more than 75% of select patients who aspirate to oral intake years after treatment (122).
- Serial esophageal dilation can open radiation-related esophageal strictures even in cases of complete or near-complete closure

Evidence

- Prevention starts with treatment planning. The supraglottic and glottic larynx should be contoured as an organ at risk
- A mean dose level of less than 35 Gy to the uninvolved larynx is recommended in the setting of bilateral neck radiation
- Appropriate swallowing rehabilitation is encouragingly successful—even years after treatment. Practitioners with head and neck practices should be familiar with frequent referrals to an SLP and/or speech/swallowing center.

Dental Issues and Osteoradionecrosis (ORN) of the Jaw *Dental QOL*

- . Many patients have poor dentition at diagnosis, and poor dentition posttreatment increases the risk of ORN and infection.
- The reduced quantity and altered composition of saliva that is encountered after radiation treatment to the head and neck is known to increase the incidence of dental caries

● Screening

- Every patient who has received external beam radiation that delivers dose to either the oral cavity or a major salivary gland should be considered a “high risk” dental patient for the remainder of their life.
- High-risk dental patients should see a dentist at least every 3 to 6 months for routine cleaning and surveillance.
- Posttreatment tumor surveillance follow-up should include a detailed oral cavity examination for evaluation of recurrence/second primary and surveillance for ORN
- A panoramic scanning dental x-ray of the upper and lower jaw obtained in the dentist office (panorex) that demonstrates bone loss should be evaluated furtherRN

Treatment

- Good oral hygiene
- Regular rinses, brushing, and flossing.
- Rinses should be either nonacidic fluoride preparations or bicarbonate preparations.
- Brushing and flossing should be gentle and thorough.
- Antibiotics and conservative debridement for early and limited ORN There is no standard antibiotic regimen for ORN
- Antibiotic therapy should either be based on gram stain results or empiric to cover oral microbes.

- Conservative debridement
- Local wound irrigation; Curettage;
- Debridement
- Sequestrectomy
- Conservative debridement (141). Local wound irrigation; Curettage;
- Debridement;
- Sequestrectomy
- Hyperbaric oxygen (The most common side effects are myopia (reversible) and barotrauma) A randomized trial comparing hyperbaric oxygen versus placebo suggested that hyperbaric oxygen was associated with worse outcomes than placebo

- Pentoxifylline and tocopherol +/- clodronate
- Pentoxifylline is a methylxanthine derivative that exerts an antitumor
- necrosis factor (TNF)-alpha effect, increases erythrocyte flexibility, vasodilates, inhibits inflammatory reactions in vivo, and inhibits human
- dermal fibroblast proliferation.
- PENTOCLO regimen demonstrates a high rate of success in poor prognosis ORN
 - Pentoxifylline 800 mg;
 - Vitamin E 1000 IU;
 - Clodronate 1600 mg
- Two others days weekly:
 - Prednisone 20 mg;
 - Ciprofloxacin 1000 mg.

Hearing Loss

- *Timing*
- Interval between completion of RT and development of persistent sensorineural hearing loss (SNHL) is 1 to 2 years.
- Range of development of SNHL is 0.5 to 6 years.
- Late hearing loss is likely multifactorial.

Prevention

- Given the known ototoxicity of cisplatin, all patients scheduled to receive cisplatin require a baseline audiogram prior to the start of therapy (even if the patient professes that hearing is not difficult).
- Sensorineural hearing loss
- Cisplatin is highly ototoxic.
- Use of concurrent cisplatin should be limited to patients for whom there is a definite benefit.

- The cochlea/middle ear should be contoured as an avoidance structure
- Because the volume is small (often <0.5 cc if the cochlea alone is contoured), it should be evaluated as a mean dose function.
- The radiation dose limit recommendations are lower when cisplatin is used concurrently (150).
- – RT alone: Cochlea dose to be less than 40 Gy;
- – ChemoRT: Cochlea dose to be less than 10 Gy.

Voice Dysfunction

- Often presents as hoarseness, but can include garbled speech and any difficulty with pitch, quality, and clarity
- Late radiation cranial nerve (ie, CN X or XII) dysfunction can appear many years after the completion of therapy, causing speech difficulties
- **Prevention**
- All patients should see an SLP prior to the initiation of head and neck cancer treatment for speech exercise training
- ● Dose avoidance to the glottic larynx and supraglottic larynx: Mean dose of less than 35 Gy is typically recommended

Screening

- All patients should be evaluated by the SLP after the completion of head and neck radiation.

Treatment

- Voice therapy
Patients who receive voice rehabilitation posttreatment report better self rated voice function .
- Injection laryngoplasty

Peripheral Neuropathy

- Neuropathic pain or weakness. Lhermitte's syndrome is a relatively common occurrence presenting as an electrical-type sharp pain running from the neck down to the upper extremities
- **Timing**
 - Median time to development of a brachial plexus injury is more than 2 years
 - Earliest reported injury is at 6 months.
 - Injuries are known to develop after 6 years since the completion of radiation.
- **Prevention**
 - Brachial plexopathy is a radiation dose-related phenomenon.
 - The brachial plexus should be contoured as an avoidance structure
 - Dose limit: V70 higher than 10%
 - Unclear if other aggravating factors can predispose to development of symptoms at a lower dose level (cisplatin chemotherapy, surgical manipulation, diabetes)

Screening

- Most common symptom is pain.
- Formal brachial plexopathy (pain, numbness, tingling, and weakness) is rare, even at high doses of radiation.
- Nerve conduction analyses of patients with suspected brachial plexus injury can confirm:

Demyelination resulting in reduced sensory conduction;

Differences in latency and amplitude between affected and unaffected arm;

Treatment

Reduced motor conduction nerve velocity.

There is no data that pentoxifylline reverses the symptoms of radiation-induced brachial plexopathy.

social worker).

Psychosocial/Economic Effects

Definition

Anxiety, mood disorders, fatigue, and depression are common in head and neck cancer survivors, although these important symptoms are sometimes overlooked. In addition, facial disfigurement, loss of function precluding normal social function (eg, eating in a restaurant), and lack of employment impact the posttreatment QOL.

Timing

- Many patients report psychosocial problems at diagnosis (ie, prior to treatment).
- Patient issues with body disfigurement and limitations with speech/swallowing/other normal daily functions are thought to improve over time (161) with the patience and compassion of family and friends.
- The economic impact of head and neck cancer is immediate. Attendance to daily radiation treatments is often impossible to reconcile with a work schedule, and often requires a leave of absence. Returning to work may take months after treatment is complete. The treatment itself is expensive, even in the setting of single modality therapy (162).

Prevention

Encourage support group participation—many centers have support groups comprising of head and neck cancer patients, caregivers, and family with a facilitator (generally a SLP and/or counselor and/or

Screening

- Patients with body image changing operations should be evaluated for consequences of the operation, even many years later.
- Factors that predict for depression .Tracheostomy and/or laryngeal stoma; Gastrostomy tube dependence; Continued smoking.

Treatment

- Hyperbaric oxygen does not seem to reverse the symptoms of radiation- induced brachial plexopathy

Improvement of functional aspects of the head and neck damaged by tumors and/or treatment can improve psychosocial outlook.

- Reports suggest that mental health services are severely underutilized among head and neck cancer survivors . Appropriate referrals are indicated.
- Many patients reported symptom improvement over time, but the interval to improvement may be 12 to 18 months from the completion of radiation.