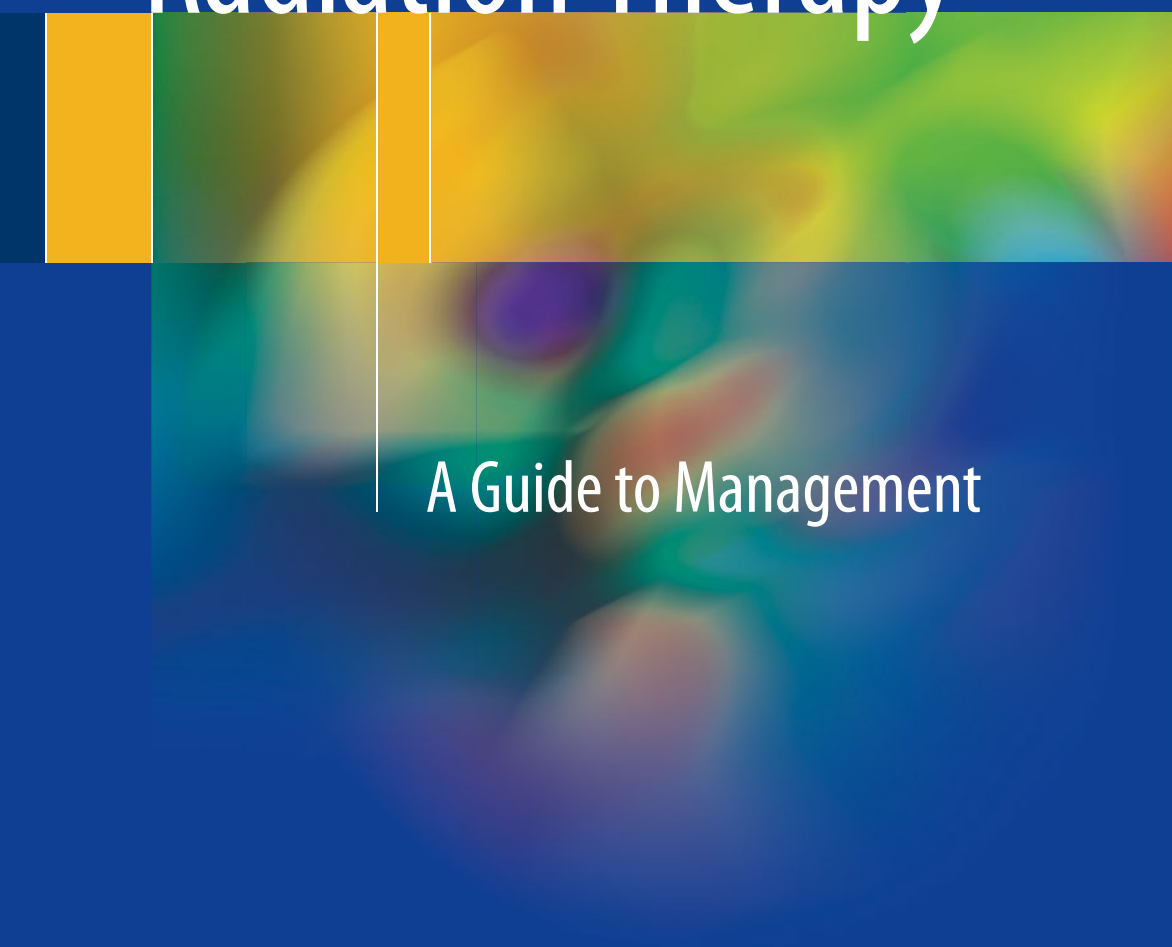
Ainaz Sourati · Ahmad Ameri
Mona Malekzadeh

Acute Side Effects of Radiation Therapy

A Guide to Management



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To my dear mother who I will forever be beholden to her.
To my loving husband, Arash, who I really appreciate his support and endurance through my most trying times.

Ainaz Sourati

To my love Zhila.

Ahmad Ameri

To my dear parents and my beloved son, Hooman.

Mona Malekzadeh

Foreword

Dichotomies in medicine are common, but it is nowhere more clearly demonstrated than in radiation exposure either used in diagnoses or in treatment as compared to excessive or unwanted radiation exposure either locally or systematically. Other dichotomies demonstrated in radiation injury include the separation between acute and late radiation damage, locally applied as contrasted to systemic or total body exposure, one or few radiation exposures vs. fractionated radiation exposures, and use of preventive or ameliorating agents applied before exposure in contrast to post-exposure treatments. All of these are important to our understanding of the effective, appropriate use of radiation as a treatment modality. This can only be ameliorated by accurate information about the causes, frequency, severity, and prevention or treatment of these radiation-associated conditions.

In the clinic, observed reactions to radiotherapy range from minor to serious and from temporary to permanent. Physician concern for these potential debilitating effects permeates the clinical practice of radiation and influences the selection of treatments on a day-to-day basis. Optimal utilization of radiation as a cancer therapy requires a clear understanding of the range of the major tissue sequela that can occur, including the risk of occurrence, natural history, and their management. This understanding leads to better clinical practice: greater confidence in recommending aggressive radiation treatment programs when appropriate or selection of other therapies when they are safer and equally effective.

Acute reactions of radiation therapy, the inflammatory reactions that occur as part of normal tissue reaction to radiotherapy, are often considered as an expected part of therapy, but they also may become debilitating to the patient during the treatment course. Understanding of the mechanism, timing of occurrence, preventable measures, and management of these side effects warrant discussion of their successful management, including ways to facilitate more comfortable therapy course for the patient.

In the era of multimodality therapy, it's also important to understand the risk factors of radiation therapy when combined with other modalities, i.e., systemic chemotherapy or biological agents. It is also important to realize the impact of other modalities as sole cause of side effect or as a co-positive impact along with radiation. Therefore, clinicians must be aware of these alternative possibilities and the method diagonals and modify them.

In this volume, the clinician-scientists of Shahid Beheshti University and Dr. Sourati and her associates have successfully provided to the readers the plethora of these concerns in a comprehensive yet relatively straightforward and simple text for day-to-day use of clinicians. Organ-specific effects are detailed as appropriate to understanding, minimizing, and managing radiation injuries. I congratulate them in their successful effort, and I am certain that many clinicians and their patients would significantly benefit from the information provided by these authors.

Maywood, IL, USA Bahman Emami, MD, FACR, FASTRO, FACRO

Introduction

Cancer is one of the leading causes of death worldwide [1]. Currently, cancer patients survive longer than they did more than two decades ago, and the population living with cancer is increasing. Understanding more about cancer radiobiology and major developments in radiation therapy technology play a critical role in increasing the life expectancy of these patients. Radiation therapies are used with three different concepts in cancer that are definitive, adjuvant, or palliative. It has been estimated that more than 50% of all cancer patients receive radiation therapy throughout the course of their disease [2]. With new technological advancements in imaging and radiation delivery, radiation therapy has been possible for more complicated cases, increasing the rate of radiation therapy in cancer treatments.

In addition to the tumor sterility and tumoricidal effects of radiation therapy, radiation has the potential to affect normal tissues, which includes tissue damage in radiation therapy fields or systemic side effects (e.g., hematologic side effects, fatigue). Physicians try to lower radiation therapy side effects by defining smaller targets and using more dedicated machines, but side effects continue to occur and their spectrum and severity are changing. As these patients live longer, more attention is directed on their quality of life.

Radiation therapy side effects are divided into acute and late. Late side effects occur 3 months after treatment completion, and acute side effects occur during treatment or within 3 months after treatment.

Late side effects can develop without dose thresholds, which include stochastic side effects, or with distinctive thresholds, which include deterministic side effects (e.g., neurologic effects, cardiac effects). Deterministic late side effects are dose-limiting and can be the result of the healing process following severe acute side effects. This kind of late side effects could be predictable, and efforts should be made to protect normal tissues [3].

Acute side effects are a type of deterministic effects, which have distinctive thresholds, and there is a direct relation with delivered dose and severity of resultant damage. These effects usually cause no limit in treatment dose because they occur in rapidly dividing cells, which have rapid cell repopulation; as a result, they are reversible. The main point in acute side effects is necessary actions for prevention and proper treatment in accordance with their severity to prevent radiation therapy disruption because treatment disruption can affect treatment results, particularly in tumors with rapid cell growth, which intensify cell growth inversely. Severe acute

side effects can also result in consecutive late effects. Using new techniques in radiation therapy (e.g., 3D-conformal radiation therapy, intensified modulated radiation therapy, image-guided radiation therapy) reduces normal tissue dose and consequently reduces treatment complications. However, the percentage of acute side effects is still noticeable because the dose threshold in these side effects' occurrence is less than late side effects. Furthermore, in some treatments, it is necessary to increase radiation dose to reach a definite complication (e.g., in locally advanced breast cancer after radical mastectomy, enough radiation must be delivered to reach dermatitis). We have to know the proper actions in approaching the complications in order to inhibit unwanted treatment disruption. Acute side effects may increase risk of late side effects, and prevention of these effects should be considered.

With respect to all points, acute side effects of radiation therapy are one of the most important issues in the treatment of cancer patients. Approach and management of these side effects are substantial to improve treatment results and increase patient compliance with treatment. We attempt to assemble the most common of these acute side effects in this book. In each part, we describe a summary of incidence, mechanism, symptoms, grading, and management of distinct acute side effects based on available evidence. Our main goal is gathering articles about each acute side effect for convenient and practical use for all involved in the radiation therapy process.

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Contents

Radiation Dermatitis

1

Anticancer properties of radiation were discovered by skin changes after exposure to radiation; initially, radiation was used for the treatment of skin diseases such as lupus erythematous. Skin cancer was the first cancer treated by radiation, and dermatitis accompanies radiation therapy since its discovery.

Radiation dermatitis is one of the most common adverse effects of radiation therapy. Approximately 90–95% [1, 2] of all patients treated with radiation therapy will experience a skin reaction at the treated area. Radiation dermatitis is especially seen in radiation therapy for breast cancer, head and neck cancer, lung cancer, and sarcoma due to the superficial position of these cancers and higher radiation doses to the skin. Various degrees of radiation dermatitis are experienced by patients undergoing radiation therapy. In most patients, the radiation dermatitis is mild to moderate (Grades 1 and 2); about 15–25% of patients experience severe reactions [3–5].

1.1 Mechanism

Radiation to the skin results in direct cellular injury and inflammatory cell influx. After the initial dose of radiation, cellular damage to epidermal basal cells, endothelial cells, Langerhans cells, and vascular components occur, and an inflammatory response in the epidermis and dermis develops following every subsequent fraction of radiation [1].

Initial cellular injury results from short-lived free-radical production and irreversible double-stranded breaks in nuclear and mitochondrial DNA [6]. Clumping of nuclear chromatin, swelling of the nucleus, nuclear disfiguration or loss of the nuclear membrane, mitochondrial distortion, and degeneration of the endoplasmic

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reticulum, as well as direct cellular necrosis and apoptosis, occur due to cellular damage. Repetitive cellular damage caused from each fraction of treatment does not allow time for cells to repair DNA damage [7–11].

Because of free-radical production, an inflammatory cytokine cascade is induced, and several cytokines and chemokines are produced including interleukins 1 and 6, tumor necrosis factor-α, and transforming growth factor-β [12]. These cytokines act on the endothelial cells of local vessels, which express adhesion molecules constitutively and induce migration of leukocytes and other immune cells from circulation to irradiated skin [13].

Reduction and impairment of functional stem cells induced by radiation lead to an alteration in the normal turnover of skin cells [6].

A prompt skin reaction may appear after exposure that is related to the inflammatory response, release of histamine-like substances, permeability and dilation of capillaries, and subsequent dermal edema. It presents with early transient skin erythema that can be seen within a few hours after radiation and subsides after 24–48 h [14].

After subsidence of initial erythema, the later phase includes additional edema, an increased dilation in capillaries, and erythrocyte extravasation, which resulted in an erythematous reaction. This phase is followed by thinning of the epidermis, damage to epithelial cells, degeneration of glands, reduced secretion of sebum, and sweat and clumps of exfoliated corneocytes (scales), which manifests as dry desquamation.

If damage to the basal cells and glands is more severe, epidermal necrosis, fibrinous exudates, and moist desquamation occur. The manifestation of moist desquamation results from the formation of small blisters in and around the basal layer of the epidermis that may also extend into the more superficial layers. The epidermis sloughs when these blisters rupture and coalesce, denuding the dermis and causing permanent epilation [15–17]. Finally, skin necrosis or ulceration of the full-thickness dermis may develop as the most severe damage of higher radiation doses [15, 16].

1.2 Timing

As noted above, a transient early erythema can be seen within a few hours of radiation, even after a single fraction of radiation (2 Gy) and subsides after 24–48 h [14]. The main erythematous reaction appears at about the second to third week (within 1–4 weeks) of radiation. Earlier reaction can be seen in patients with particularly sensitive skin. Effects typically continue to progress during treatment [18–20], and subsequently dry desquamation can develop after the third week or after a cumulative dose of 30 Gy, which is clinically characterized by dryness, scaling, and pruritus. Following 4–5 weeks (45–60 Gy) of therapy, moist desquamation may occur, which is characterized by serous oozing and exposure of the dermis [14]. Symptoms persist for the duration of radiation therapy and peak 1–2 weeks after treatment completion. At about 3–5 weeks after radiation, the skin begins to recover with epidermal regeneration and within 1–3 months (depending on the severity of reaction), complete healing occurs [1, 6, 18, 19, 21, 22]. Post-inflammatory

hyperpigmentation may persist for 5–7 weeks or even longer after radiation [20, 23]. Patient skin type may also influence timing and severity of radiation reactions, reflected by interindividual variation in skin presentation of radiation damage.

1.3 Sign and Symptoms

Mild dermatitis (Grade I) presents with erythematous skin accompanied by mild edema, pruritus, or pain. Dry, peeling skin (desquamation) and temporary epilation due to involvement of adnexal structures may occur (Fig. 1.1).

Moderate dermatitis (Grades 2 and 3) consists of tender or edematous reactions and moist desquamation (Fig. 1.2). The integrity of the dermis is impaired, and secondary infection with *Staphylococcus aureus* may occur (Fig. 1.3).

Severe dermatitis (acute radionecrosis) is rarely seen and may occur in the setting of very extensive superficial tumors treated with massive radiation doses over a very short period. It manifests as a very painful inflammatory or hemorrhagic plaque with deep necrosis, which can expose the muscles, tendons, and bones [19, 21, 22].

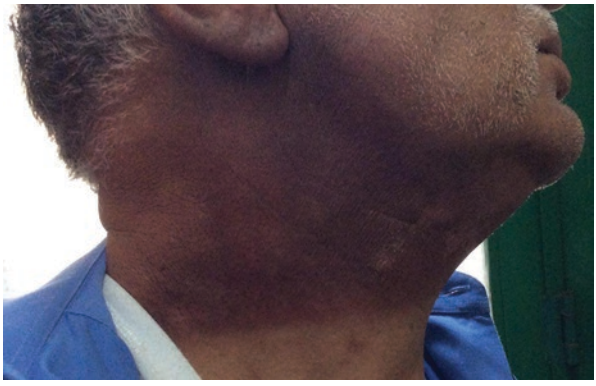

Fig. 1.1 Grade 1 dermatitis of neck after radiation therapy for laryngeal cancer

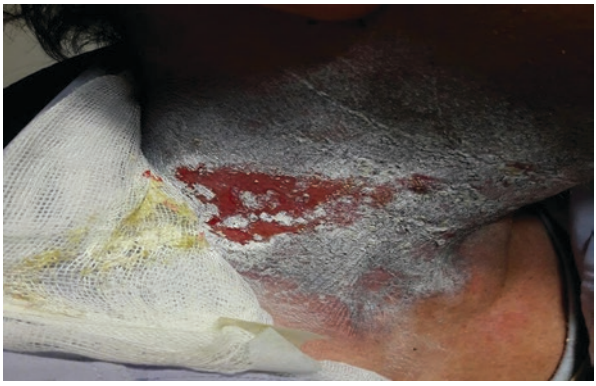

Fig. 1.2 Grade 2 dermatitis of neck after radiotherapy for nasopharyngeal cancer with multiple node involvement

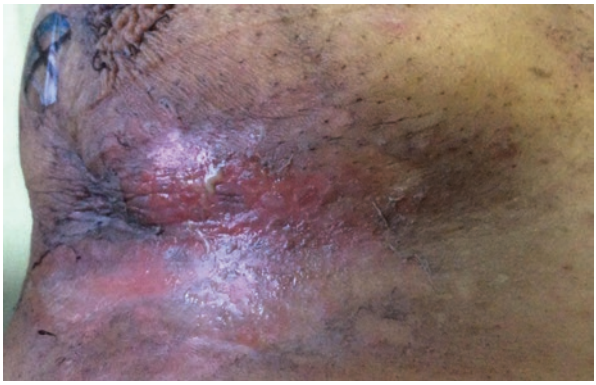

Fig. 1.3 Grade 3 dermatitis in inframammary fold after breast irradiation

Table 1.1 CTCAE v4.3 for dermatitis

	Definition
Grade 1	Faint erythema or dry desquamation
Grade 2	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema
Grade 3	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion
Grade 4	Skin necrosis or ulceration of full-thickness dermis; spontaneous bleeding from involved site

1.4 Scoring

The severity of radiation dermatitis is graded using several grading systems such as Common Terminology Criteria for Adverse Event (NCI-CTCAE grading), Radiation Therapy Oncology Group (RTOG) toxicity scoring system, and the Radiation-Induced Skin Reaction Assessment Scale (RISRAS).

Common Terminology Criteria for Adverse Event (NCI-CTCAE grading) is one of the most commonly used, and NCI-CTCAE v4.3 has been shown in Table 1.1 [24]. RTOG scoring is quite similar to NCI-CTCAE grading.

1.5 Risk Factors

Treatment and patient-related factors may affect incidence and severity of dermatitis.

1.5.1 Treatment-Related Factors Including

The higher total dose, higher dose per fraction, reduced overall treatment time, beam energy (depend on type and quality of the beam), higher volume and surface

area exposed, the junction between the electron and photon field, use of tissue expander and bolus material [25–27], concurrent systemic therapy with radiation (radiosensitizing drug such as paclitaxel, docetaxel, anthracyclines, dactinomycin, methotrexate, 5-fluorouracil, hydroxyurea, bleomycin, and cetuximab) [6, 28] are related to the development of radiation dermatitis.

Epidermal growth factor receptor (EGFR) is highly expressed in the epidermis, particularly in the proliferative basal cell layers, and has a major role in the regulation of multiple phases of epithelial biology, including cell cycle progression, differentiation, cell movement, and cellular survival; it also has an essential impact on the inflammatory reactions of the skin [29–31]. There is a reciprocal relationship between radiation and epidermal growth factor receptor inhibitors' (like cetuximab) effects on skin.

More severe radiation dermatitis is seen in patients receiving cetuximab plus radiation therapy than radiation therapy alone or even concurrent chemoradiotherapy [5, 15]. There is a slightly longer duration of radiation dermatitis (11.1 versus 9.4 weeks) [32] and an earlier onset of radiation dermatitis (week 1 or 2 compared with 3–5 weeks, respectively) [15], when cetuximab is added to radiation therapy. Dermatitis usually reveals rapid recovery with no scarring following the end of treatment of cetuximab plus radiation therapy [15]. A deferred cetuximab-induced acne-like rash appears within irradiated fields in concurrent treatment of cetuximab with radiation therapy (about 3–5 weeks after initiation of treatment versus 7–10 days, respectively). It seems that there is no significant relationship between the severity of cetuximab-associated acne-like rash outside irradiated fields and the severity of radiation dermatitis [32].

1.5.2 Patient-Related Factors Include

Demographic and behavioral factors, comorbid diseases, inherited disorders, and site of radiation therapy can affect incidence and severity of radiation-induced dermatitis [2, 33–41] (Table 1.2).

Table 1.2 Patient-related predisposing factors for radiation-induced dermatitis

Demographic and behavioral factors	Comorbid disease	Inherited disorders	Site of radiation therapy
Black race Obesity Female gender Advanced age Breast implant Smoking Poor nutrition	Actinic skin lesions Seroma aspiration after breast surgery Systemic lupus erythematosus Systemic sclerosis Juvenile rheumatoid arthritis HIV infection Diabetes mellitus Hypertension	Basal cell nevus disease Fanconi anemia Bloom syndrome Xeroderma Pigmentosum Ataxia-telangiectasia	Anterior neck Extremities Submammary Skin folds

Smoking seems to impair wound healing by cutaneous vasoconstriction [17].

The impact of increasing age on radiation dermatitis is related to decreased epidermal turnover resulting in extended healing times. Coexisting diseases like hypertension, diabetes, obesity, or malnutrition in older patients affect the severity and resolution of radiation dermatitis [17].

It has been reported that aspiration of a seroma following breast surgery may lead to damage to the lymphatic system, compromising wound healing and leading to a severe skin reaction during radiation therapy [41].

Patients with systemic lupus erythematosus (SLE), juvenile rheumatoid arthritis (JRA), and systemic sclerosis have significantly greater radiosensitivity and are at greater risk for developing radiation side effects. The presence of this connective tissue disease is considered as a relative contraindication to radiation therapy [42, 43].

Wound healing is complicated in patients with uncontrolled diabetes mellitus due to poor macrophage function including phagocytic activity, prolonged inflammatory phase, and greater risk of infection. Diabetes' effect on normal tissue reaction during radiation therapy needs further study [17].

There are a few rare genetic mutations that may predispose patients to severe radiation dermatitis, including mutations in the ataxia-telangiectasia gene. It has been suggested that unanticipated severe radiation dermatitis may indicate the presence of undetected genetic abnormalities in the ATM gene (ataxia-telangiectasia mutated) that can predispose patients to cutaneous complications [44, 45].

No studies have specifically investigated the effect of hemoglobin level on normal skin exposed to radiation therapy.

1.6 Diagnosis

Acute radiation dermatitis is a clinical diagnosis based on the finding of skin changes that shows a sharp demarcation of the skin changes and their limitation to the irradiated areas and the history of radiation therapy and its duration. A skin biopsy is usually not necessary for the diagnosis of radiation dermatitis [13].

Two important differential diagnoses of acute radiation dermatitis are radiation recall and cellulitis. Radiation recall is an acute inflammatory skin reaction limited to the area that was previously irradiated and occurs following cytotoxic agents or other drug administration. It occurs at least 7 days after radiation therapy and may occur weeks to years after radiation therapy [46–48]. Cytotoxic drugs such as docetaxel, doxorubicin, and paclitaxel have been associated with radiation recall. Radiation recall manifestations include a rash, dry desquamation, erythema, ulceration, hemorrhage, or even necrosis. Radiation recall generally resolves within 1–2 weeks after drug discontinuation. Patient's history of skin reaction following radiation treatment and medications will help to reach an accurate diagnosis [49].

Cellulitis is a bacterial infection of skin and subcutaneous tissues. It is characterized by localized erythema, warmth, swelling, pain, tenderness, fevers, and even purulent drainage. These clues can differentiate cellulitis from radiation dermatitis. However, radiation dermatitis is a predisposing factor of secondary cellulitis, and it

may be possible for both conditions to exist together. In this condition a culture from the wound may confirm the diagnosis of cellulitis. Empiric antibiotic treatment may also be helpful in these patients [49].

Eczema is a chronic, relapsing, inflammatory skin condition that is diagnosed by clinical presentation of symmetrical, pruritic, dry skin that persists for <6 months. Chronic eczema may exacerbate radiation dermatitis as both conditions are inflammatory in nature. Eczema may be distinguished from radiation dermatitis by its symmetrical distribution. In contrast, radiation dermatitis will only appear within radiation fields [49].

Recurrent or secondary tumors should be considered if atypical plaques and nodules develop within the radiation field. Although irradiated skin may present some difficulty in healing, a biopsy is useful in this clinical situation.

Atopic dermatitis [49], lichen planus [50], pemphigus [51, 52], and dermatophyte infection [53] rarely occur in the site of radiation therapy that clinical course, lesion distribution, and laboratory studies are helpful to distinguish from other diagnoses.

1.7 Prevention

1.7.1 General Measures

General recommendations for skin care in patients that are treated with radiation therapy include [13, 54]:

Washing the irradiated area daily with water and mild soap (pH-neutral agents) or normal saline then dry it and use a water-based moisturizer.
Wearing loose-fitting clothes.
Avoiding skin irritants such as perfumes and alcohol-based lotions and wax or other depilatory creams.
Avoiding extremes of heat and cold.
Avoiding sun exposure and use of sunscreen with a minimum SPF 30.

Currently, application of topical steroids is the only prophylactic intervention for radiation dermatitis protection suggested with a high level of evidence [55, 56]. Prophylactic application of topical steroids can reduce the severity of radiation skin reaction because of their anti-inflammatory effects (i.e., reducing the production of IL-1, IL-2, IL6 IFN-γ, TNF, and histamine and inhibiting leukocyte migration) [14, 57].

Low- to medium-potency topical corticosteroids (groups 4–6) such as mometasone furoate 0.1% or hydrocortisone 1% cream or methylprednisolone aceponate cream 0.1% or beclomethasone dipropionate spray are applied to the treatment field once or twice daily after each radiotherapy treatment [13, 58–61].

Treatment should be stopped if there is any exudate from the affected area [54] or if a skin infection is suspected.

Other protective options with primarily positive results that warrant further research on their efficacy in preventing and managing acute radiation dermatitis include:

1.7.2 Intensity-Modulated Radiation Therapy (IMRT)

There is some evidence suggesting that IMRT significantly reduces the severity and duration of radiation dermatitis compared with standard conventional technique [62–64].

1.7.3 Low-Level Laser Therapy

Low-level laser therapy is a form of phototherapy that induces the wound-healing process [65]. It has generated great interest in preventing radiation side effects such as dermatitis, xerostomia, or oral mucositis. The primary promising results of these trials warrant further research on its efficacy in preventing and managing acute radiation dermatitis [66].

1.7.4 Amifostine

Amifostine is a thiol that selectively protects normal cells from radiation damage by scavenging oxygen-derived free radicals. It has been shown that the severity of radiation dermatitis is significantly lower among patients receiving amifostine [67–69]. Further studies are needed to determine the impact and safety of amifostine as a cytoprotective agent against acute radiation dermatitis.

1.7.5 Ascorbic Acid

Ascorbic acid has antioxidant capacity and anti-free-radical action. No benefit of its topical application has been found for radiation dermatitis protection. However, oral ascorbic acid in breast cancer radiation therapy with a volume lower than 500 mL and in those that received a radiation dose between 107% and 110% of the prescribed dose showed positive results [70, 71].

1.7.6 Oral Zinc

Zinc (Zn) as an antioxidant has been evaluated in normal tissue protection studies against radiation injuries. There are primarily positive results for dermatitis that need further evaluation [72, 73].

1.7.7 Silver Leaf Dressing

Silver leaf dressing has antimicrobial activity and is another option proposed for radiation-induced dermatitis prevention. There are positive results about its efficacy [74–76] that should be confirmed in further studies.

1.7.8 MAS065D

MAS065D (Xclair) is a nonsteroidal water-in-oil cream that contains hyaluronic acid, shea butter (emollient), glycyrrhetinic acid (licorice extract with anti-inflammatory properties), *Vitis vinifera* (antioxidant activity), and telmesteine (anti-elastase and anti-collagen activity in vitro) [77]. MAS065D seems to be effective in the management of radiation dermatitis, but further studies are necessary [78, 79].

Oral proteolytic enzymes (e.g., products containing papain, bromelain, trypsin, and chymotrypsin) seem to be effective in protection against radiation dermatitis, and further evaluation is recommended [72, 80].

1.7.9 Soft Dressing or Barrier Film

It seems that prophylactic use of friction protections with soft dressing or barrier film in areas at risk such as the axilla, head and neck region, perineum, and skin folds could be an effective intervention for reducing skin reaction severity [81].

Other options without well-designed trial support include:

1.7.10 Hyaluronic Acid

Hyaluronic acid cream appears to reduce inflammatory response and oxidative free-radical damage and have been evaluated in radiation therapy studies as a preventive method for radiation dermatitis. Additional studies are required to clarify hyaluronic acid role as a preventive option in radiation dermatitis [82, 83].

1.7.11 Trolamine

A topically applied salicylates analgesic, this agent has been shown to promote the wound-healing process by recruitment of macrophages and enhancement of granulation tissue formation, which has therapeutic applications in dermatology. Current evidence does not support the use of trolamine for radiation dermatitis and requires more research to clarify its efficacy in prevention of radiation dermatitis [84–87].

1.7.12 Topical Sucralfate

Sucralfate is a topical drug that has been applied for the treatment of several types of epithelial wounds such as ulcers, inflammatory dermatitis, mucositis, and burn wounds. Some studies have evaluated the efficacy of sucralfate cream for prevention of radiation dermatitis with differing results. Current data do not support it to prevent radiation dermatitis [87–90].

1.7.13 Theta Cream

It contains glucan, Hydroxyprolisilane, and matrixyl with the immune system-modulating effects and tissue regeneration properties [91]. Evidence from a limited number of randomized trials does not support theta cream in radiation dermatitis prevention [92].

1.7.14 Dexpanthenol (Provitamin B5)

A stable alcohol form of pantothenic acid, dexpanthenol is converted in tissues to pantothenic acid, which is essential to normal epithelial function and enhances skin regeneration and wound healing [93–95]. Current evidence does not support the use of dexpanthenol for radiation dermatitis [92].

1.7.15 Calendula

Fabricated from a plant of the marigold family *Calendula officinalis*, *Calendula* has antioxidant and anti-inflammatory properties. Studies evaluating the efficacy of calendula in management and prevention of radiation dermatitis have mixed results that warrant further investigation [96, 97].

1.7.16 Pentoxifylline

A useful drug in a variety of vaso-occlusive disorders, pentoxifylline has anti-inflammatory properties. The pentoxifylline effects on acute skin reactions need to be determined in well-designed studies [98, 99].

1.7.17 Aloe Vera

An ancient herbal remedy and natural product, there are mixed results of its efficacy in radiation dermatitis protection that warrants more research before its extensive usage is recommended [100, 101].

1.7.18 Deodorant

Using deodorant did not demonstrate any effect on preventing radiation dermatitis development [102, 103].

1.7.19 Laughter Therapy

Laughter therapy may have a beneficial role in preventing radiation dermatitis. To confirm laughter therapy effect on radiation dermatitis, well-designed randomized studies with large sample sizes are required [104].

1.8 Management

Patients should be visited at least weekly during their radiation therapy course with regard of the skin reaction at each visit. The management of radiation dermatitis is guided by the severity of skin damage.

1.8.1 Grade 1 Dermatitis

For most patients, general skin care measures seem to be sufficient for ameliorating patient's symptoms. Patients should be educated on washing their skin gently with a mild soap (pH-neutral agents) or normal saline as a supportive care for erythematous skin. Washing reduces bacterial load and risk for infection.

Dry desquamation is managed by moisturizing the area with a thin layer of nonscented, hydrophilic, lanolin-free ointment or cream (e.g., Eucerin, Lubriderm) 2–4 times daily [49]. Topical moisturizers can act as a skin bolus and increase the radiation skin dose, so patients should be informed not to apply these products shortly before radiation treatment.

Pruritus or irritation can be controlled with mid-potency topical corticosteroids. Although there is insufficient information to support using topical corticosteroids (corticosteroids Group IV and V) in radiation-induced dermatitis, most practitioner is prescribing steroid for it. Topical steroid which is usually prescribed in radiation-induced dermatitis is listed in Table 1.3 [105].

Table 1.3 Topical corticosteroids used in radiation dermatitis

Group IV	Group V
Fluocinolone acetonide 0.01–0.2% Hydrocortisone valerate 0.2% Hydrocortisone butyrate 0.1% Flurandrenolide 0.05% Triamcinolone acetonide 0.1% Mometasone furoate 0.1%	Fluticasone propionate 0.05% Desonide 0.05% Fluocinolone acetonide 0.025%

Antihistamines do not seem to be effective in reducing pruritus related to radiation dermatitis [13].

Normal saline compress is applied up to four times daily and may help patients to clean their skin better and ameliorate symptoms related to inflammation. Patients are instructed to moisten gauze with warm or room-temperature saline solution and apply moist gauze to the affected area for 10–15 min. The gauze is removed and the wound is gently irrigated with normal saline and dried [54].

1.8.2 Grade 2–3 Dermatitis

In Grades 2 and 3 radiation dermatitis, in addition to general skin care measures, a number of topical applications can be helpful to reduce symptoms.

Patients with moist desquamation are at increased risk of infection and should be monitored for purulent drainage and fevers.

Moist desquamation typically is managed by wound dressings that provide the ideal moist wound-healing environment allowing for faster reepithelization, phagocytosis of bacteria, extracellular debris, and necrotic material, absorbing wound secretions, diminishing pain, and protecting the wound from contamination [6, 7, 106].

Dressings should be comfortable to increase patient compliance for prolonged use. They should also be able to absorb large amounts of serous leakage from the wound to prevent maceration of the surrounding healthy skin and must be removed without disturbing granulation and new tissue.

Various forms of dressings are available in clinical practice with no sufficient evidence to support particular types in the management of moist desquamation [13, 75, 107, 108]. Simple dressings alone are not recommended, due to the pain and trauma caused at dressing changes [41]. Hydrocolloids or hydrogels dressings have a traditional interest in the use of moist desquamation. However, a recent study that compared hydrogel versus dry dressing on healing time of moist desquamation found that healing time was significantly prolonged in the hydrogel group dressings without any improvement in patient comfort [109]. A new range of silicone foam skin dressings (e.g., Mepilex Lite) is currently available commercially with promising primary results [110].

Patients should be instructed to place normal saline compresses several times a day, applying a dressing after cleaning the wound and changing dressings frequently depending upon the severity of weeping.

When infection occurs, treatment should be done with topical and/or systemic antibiotics. Silver-based dressings are antibacterial and have proven to be effective for this purpose. Beta glucan or silver sulfadiazine cream may also be useful (but should only be applied after radiation therapy and after cleaning the irradiated area; caution use in patients with severe renal and hepatic impairment and patients with G6PD deficiency) [111]. In patients treated with concomitant chemotherapy or at increased risk of developing neutropenia, complete blood count should be checked. In patients with neutropenia or signs of sepsis, blood cultures should be obtained [15].

Nonsteroidal anti-inflammatory drugs can often be effective for pain management and can also relieve the discomfort associated with itching and swelling around the skin reaction.

Treatment interruption may be needed in Grade 3 radiation dermatitis depending on patient performance status, presence of sepsis or severe neutropenia, and the radiation oncologist's judgment [13].

Biologic preparations are investigated in some types of radiation dermatitis including the use of calcineurin inhibitors (e.g., pimecrolimus cream or tacrolimus ointment) for radiation dermatitis in patients receiving cetuximab [15] or topical granulocyte-macrophage colony stimulating for vulvar radiation dermatitis [112].

The effects of foam dressing with human recombinant human epidermal growth factor (rhEGF) [68] and granulocyte-colony stimulating factor (G-CSF) subcutaneously administered at the periphery of the wound [113] has been proposed in radiation dermatitis with moist desquamation. Further studies are required to evaluate optimal dosage, treatment scheduling, and confirming the mechanism of action of these agents.

Lianbai liquid is a Chinese remedy that has been reported to be effective in the treatment of Grade III acute radiation dermatitis and needs further evaluation [114].

1.8.3 Grade 4 Dermatitis

Grade 4 radiodermatitis is a rare complication. Surgical interventions are the treatment backbone. This grade should be treated with discontinuation of radiation therapy and surgical debridement, full-thickness skin graft, or myocutaneous or pedicle flaps [13].

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Hair Loss

2

Whenever the skin is irradiated, hair loss may occur as a side effect. Because hair loss of scalp induced by radiation of brain or head and neck cancer has a significant importance due to its effect on appearance (Fig. 2.1), we focus on scalp hair loss in this chapter.

Hair loss may be a temporary or permanent radiation side effect depending on radiation dose [1]. Temporary hair loss is typically observed in all patients undergoing whole-brain radiation therapy [2, 3]. Temporary hair loss with some areas of permanent alopecia is one of the common complications (more than 10 out of 100), in patients with primary brain tumors treated with cranial radiation therapy [4]. Permanent hair loss occurs in 50% of patients with the follicle dose of 43.0 Gy [5].

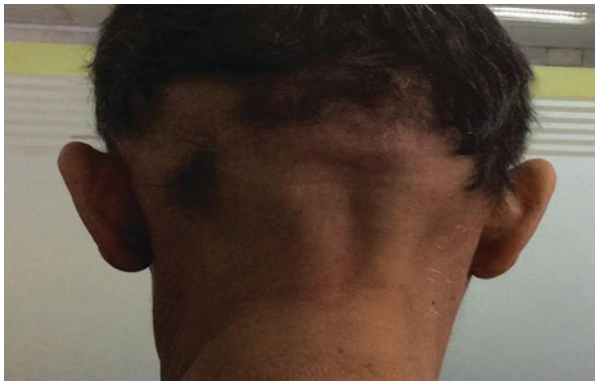

Fig. 2.1 Hair loss at posterior scalp after radiation therapy for sinonasal tumor that exposed to exit dose of antro-posterior radiation beam

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2.1 Mechanism

Radiation-induced hair loss is due to high susceptibility of anagen follicles to radiation.

Hair follicles are located approximately 3–5 mm below the scalp [6]. Hair growth has a cyclical process [7]. The three phases during the hair life cycle are anagen (active phase), catagen (transitional phase), and telogen (resting phase). Most hairs are normally in the anagen phase. During this phase, the bulb matrix cells are rapidly proliferating with high mitotic activity [8–10]. Any acute damage to actively dividing matrix cells of anagen follicles leads to abrupt loss of hairs called anagen effluvium. Chemotherapy and radiation therapy are common causes of anagen effluvium [8, 9, 11, 12].

Ionizing radiation primarily targets DNA and leads to double-strand DNA breaks [13, 14]. Radiation-induced DNA damage of hair follicular matrix cells causes apoptosis with increase in tumor-suppressor protein p53 levels in the matrix cells [15, 16].

2.2 Timing

Hair shedding may start as soon as 1–3 weeks after the first dose of radiation [17]. The hair follicle resumes normal cycling within a few weeks of treatment cessation [9] and usually resolves within 2–3 months after completion of radiation therapy [5]. Regrowth of hair may be sparser with different thickness or texture after treatment.

2.2.1 Risk Factors

Radiation dose is the most significant factor-related radiation-induced alopecia. Temporary alopecia can be detected after doses of about 2 Gy [18]. Permanent alopecia has been reported in a range of 0–80% (median risk 5%) of patients with dose of 36 Gy (2 Gy/fraction, 5 d/wk) and of 5–100% (median 15%) of patients with a dose of 45 Gy. Permanent alopecia occurs with a 7 Gy single-fraction dose [5].

Lower-beam energies, use of multiple overlapping beams, or use of fixation materials with high thicknesses can increase the risk of radiation-induced alopecia [5].

Previous or concomitant chemotherapy (alkylating agents most commonly reported) increase the risk of radiation-induced alopecia [5, 19].

Patients with personal history of alopecia may have a trend of developing permanent alopecia. Patient's age, family history of baldness, gender, tobacco use, and diabetes have not reported to correlate with alopecia [5].

2.2.2 Symptoms

Radiation therapy will generally cause alopecia limited to the treated area but may also occur in the adjacent area due to beam penumbra or at existing areas of the radiation beam.

Table 2.1 CTCAE hair loss scoring

	Definition
Score 1	Hair loss of <50% of normal for that individual that is not obvious from distance but only on close inspection; a different hairstyle may be required to cover the hair loss, but it does not require a wig or hairpiece to camouflage
Score 2	Hair loss of ≥50% normal for that individual that is readily apparent to others; a wig or hairpiece is necessary if the patient desires to completely camouflage the hair loss; associated with psychosocial impact

After hair loss, scalp is sensitive to radiation damage and radiation dermatitis may occur (see Chap. 1).

2.3 Scoring

Common Terminology Criteria for Adverse Events (CTCAE) v4.0 has defined two scores for hair loss of scalp (Table 2.1) [20].

2.4 Prevention

It has been shown that patients affected by hair loss have a poorer quality of life, lower self-esteem, and heightened self-consciousness [21, 22]. Novel strategies to decrease radiation-induced alopecia have been proposed. New radiation delivery techniques such as intensity-modulated radiation therapy (IMRT) or volumetrically modulated arc therapy (VMAT) for whole-brain radiation therapy (WBRT) are being evaluated to reduce the dose to the hair follicles [3, 23–25]. Primary results of these techniques are promising, which warrant further investigation.

Tempol, formally 4-hydroxy-2,2,6,6-tetramethylpiperidin-1-oxyl, is a membrane-permeable radical scavenger. Both the preclinical and clinical studies showed that topical application of tempol may be effective at preventing radiation-induced alopecia [26–28]. Larger studies are needed to evaluate its efficacy and safety in clinical practice.

Antioxidant compounds such as glutathione, lipoic acid, and antioxidant vitamins A, C, and E could act as natural radioprotectors and reduce the toxicity of radiation therapy. But possible tumor-protective effects of these nonselective free-radical scavengers are matters of great concern. Topical application of these antioxidants has been tested to reduce systemic absorption and subsequent tumor protection, but this does not seem to be able to eliminate the tumor-protective effect. Additional studies need to determine the safety of using these agents during radiation therapy [29].

Base on preclinical studies, systemic and topical application of prostaglandin E2, systemic administration of vitamin D3, topically applied vasoconstrictors, subcutaneously applied keratinocyte growth factor, *Panax ginseng* administration, and caffeine may protect hair follicles from radiation toxicity [30–34]. Further clinical trials should be conducted to prove the preventive effect of these agents on radiation-induced alopecia.

2.5 Management

General recommendations during treatment may be helpful for the patient to minimize scalp reaction including avoiding excessively hair combing, hair color and hair styling products, hair dryers, using baby shampoo or other mild shampoo and hair conditioner without any perfumes, and cutting hair to medium to short lengths [35].

Reconstructive surgery options can be considered in selective patients with post-radiation therapy and permanent alopecia based on alopecia area, size, patient's age, and prognosis [36].

Botulinum toxin type A (BTXA) is used successfully to treat radiation-induced alopecia in a case report, which warrants more studies to identify the mechanisms and efficacy of BTXA [37].

There are no reports about other hair loss treatments such as minoxidil or low-level laser therapy in the setting of radiation-induced hair loss.

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Radiation Brain Injury

3

Cranial irradiation has an important role in the treatment of brain tumors either with curative intent or for palliation. Cranial irradiation has a unique application in prevention of distant metastasis to brain parenchyma, and prophylactic cranial irradiation may be carried out in selected patients at high risk of neoplastic cranial involvement. Brain is also an organ at risk during radiotherapy of tumors which are located in base of skull and in some head and neck cancers. Cranial irradiation in any condition can cause brain injuries that are classified into three groups based on the timing of their occurrence after radiation exposure: acute (during radiation or up to 6 weeks after radiation), early delayed or subacute (up to 6 months after radiation), and late delayed (6 months or more after the completion of radiation). However in more trials, brain injury simply is defined as acute (within 90 days of the commencement of therapy) and late reactions (after 90 days of the commencement of therapy) [1]. Reports indicate that patients that undergo standard fractionated cranial irradiation and stereotactic radiosurgery may have acute brain reactions in the range of 2–40% [1–12]. However, up to 50% of patients with high doses per fraction (more than 3 Gy) to a large part of the brain may develop acute encephalopathy [3, 13].

Early-delayed reactions may present with worsening of primary symptoms or radiation somnolence syndrome (SS), which has been observed mainly after prophylactic radiation therapy for leukemia in children, with a mean incidence of 50% (in the range of 10–79% of these patients) [14–20].

It is important to differentiate brain tumor progression from radiation-induced acute injury. Pseudoprogression is defined as radiologic abnormality in postirradiation imaging because of radiation-induced injury that mimics tumor recurrence. Pseudoprogression occurs a few weeks up to 3–6 months after radiation therapy that is coincidental with early-delayed radiation reaction. The majority of patients with pseudoprogression are asymptomatic, but it can present with worsening of primary symptoms, transient cognitive decline, or somnolence syndrome [21]. Pseudoprogression incidence varies from 9% in patients treated with radiation

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therapy alone to 32% in patients undergoing chemoradiotherapy [22, 23]. Somnolence syndrome may develop in adults as a subacute reaction [24, 25] but have not been uniformly investigated.

3.1 Mechanism

Cranial irradiation causes vascular and cellular injuries. Endothelial cell damage, vasodilation, increased in blood-brain barrier permeability, cerebral edema, and consequent rise in intracranial pressure occur in early phase [3]. Oligodendrocytes are extremely sensitive to radiation. Subacute reactions are thought to be a result of oligodendrocyte depletion and transient demyelination [26, 27].

3.2 Timing

Brain edema could begin a few hours after the first treatment with a single dose of 2 Gy to a portion of the brain [28]. Symptoms of increased intracranial pressure or worsening of primary neurologic symptoms can occur and progress with additional fractions. With doses up to approximately 60 Gy, symptoms are usually mild and transient [29, 30].

Subacute reaction (somnolence syndrome, cognitive dysfunction, transient neurologic deficit) usually begins 4–8 weeks after treatment completion. The symptoms last from a few days to 6 weeks [14, 24, 31] and spontaneously subside over few weeks to months [20]; however, somnolence syndrome can cause long-term neurologic dysfunction [32].

3.3 Risk Factors

3.3.1 Treatment-Related Factors

Radiation therapy: Type of fractionation and fraction size, total dose [33], and field size [34] are important in the severity of acute brain toxicity. There are more acute cranial complications in the rapid course of radiation therapy with higher doses per fraction [5, 35] or multiple daily fractionated radiation therapy [1]. Risk of SS may be associated with the total dose of radiation [14] and fraction size [14, 18], but these results need further studies to be better defined [19, 36].

Combined treatment: Combination of surgery [7, 11] or radiosurgery [10] with fractionated radiation therapy seems to not significantly increase the acute complication, although surgery type (biopsy versus partial/total resection) may be a significant variable to predict the occurrence of acute brain toxicities [1]. Chemotherapy or radiation sensitizers during cranial irradiation are well tolerated without significantly increasing in acute brain toxicity [37–42]. No significant difference has been reported in the incidence of SS between patients that received radiation alone and

those that received irradiation and intrathecal methotrexate [15]. An obvious increase in pseudoprogression rate occurs in patients that are treated with chemotherapy and radiation therapy versus radiation therapy alone.

3.3.2 Patient-Related Factor

Age over 50, functional status, neurological function, and mental status have not been reported to be important in the occurrence of acute brain reactions [1]. Somnolence syndrome has not been related to patient factors such as age, initial white blood count [14], and anatomical site or histological type of brain tumor [43]. Glioblastoma patients with promoter methylation of the repair enzyme 06-methylguanine-DNA methyltransferase (MGMT) are at a higher risk of tumor pseudoprogression [23].

3.4 Symptoms

In the acute phase, all presenting symptoms are related to increased intracranial pressure including headache, nausea, vomiting, and mental status changes or an exacerbation of the symptoms or signs caused by the lesion being treated [44]. These symptoms can be controlled with medication and are transient with conventional fractionation (1.8–2 Gy/day given five times per week) to a total dose of 60 Gy to the whole brain or even higher doses to limited volumes [44]. However, in very few patients with higher doses per fraction (more than 3 Gy) to a large area of brain and in patients with significant pretreatment elevated intracranial pressure, cerebral herniation may occur.

Imaging including computed tomography (CT) scan or MRI in acute radiation brain injury is usually unremarkable and could differ from no clear changes to diffuse brain swelling (Fig. 3.1) [45].

Somnolence is referred to as excessive drowsiness or sleep [15, 46]. The somnolence syndrome is a collection of symptoms that consists of drowsiness, lethargy, fatigue, anorexia, headache, dysphagia, dysarthria, nausea, and vomiting and is sometimes associated with low-grade fever [36, 47–50]. Brain MRI may demonstrate nonspecific white matter hyperintensity [51]. The cerebral spinal fluid (CSF) analysis of these patients shows increased levels of protein and pleocytosis [17], and electroencephalogram (EEG) shows diffuse generalized slowing in electrocortical activity more than expected for all children that receive cranial radiation [52].

Somnolence syndrome in adults may manifest with some different symptoms from pediatric patients due to much greater dosage of radiation therapy applied in adults [47]. A transient worsening in primary symptoms (e.g., epileptic seizure, increased paralysis, etc.) can develop in addition to other classic symptoms of somnolence syndrome [47]. These symptoms may be severe enough to need supportive treatment and steroid administration [24]. A transient cognitive dysfunction may

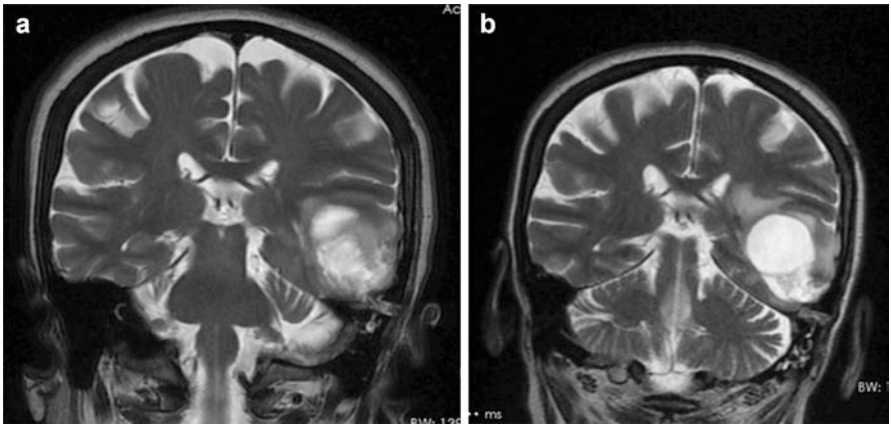

Fig. 3.1 Increased edema in a patient that treated with radiation therapy for glioblastoma multiform. (**a**) Before starting of radiation therapy, (**b**) 6 weeks after completion of radiation therapy

occur during 6–8 weeks after the end of radiation therapy [53]. MRI findings in the postradiation phase can vary from non-enhancing white matter hyperintensities on T2-weighted imaging, indicative of edema, to an increased size of contrast-enhancing lesions within or near the irradiated tumor volume due to radiation-induced endothelial damage and blood-brain barrier disruption [22, 45].

3.5 Diagnosis

The diagnosis of acute brain reactions is based on clinical picture and response assessment to steroid treatment.

Somnolence syndrome is characterized by excessive drowsiness or sleep accompanied by signs of elevated intracranial pressure such as headache, anorexia or nausea, and vomiting. It is diagnosed based on a group of symptoms that starts 4–8 weeks after radiation therapy, especially in children.

In patients with clinical deterioration after brain radiation therapy, distinguishing between tumor progression and radiation reaction is challenging. Imaging cannot help in this regard unless in new lesions appear outside the radiation field. Symptoms related to treatment injury usually respond to escalating or starting steroid treatment. Patients closely follow-up and reimaging at approximately 4-week intervals are a logical approach in these patients [30, 54]. Biopsy is an invasive action with confounding results and is not recommended in this setting. The value of metabolic imaging like positron emission tomography (PET) scan in this situation is unclear [55]. New functional MRI techniques such as magnetic resonance spectroscopy or diffusion-weighted and perfusion seem to be promising [56]. Further investigations are needed before they are incorporated into widespread use.

Table 3.1 RTOG/EROTC radiation-induced brain injury grading [57]

	Definition
Grade 1	Fully functional status (i.e., able to work) with minor neurologic findings, no medication needed
Grade 2	Neurologic findings present sufficient to require home case/nursing assistance may be required/medications including steroids/antiseizure agents may be required
Grade 3	Neurologic findings requiring hospitalization for initial management
Grade 4	Serious neurologic impairment which includes paralysis, coma, or seizures >3 per week despite medication/hospitalization required

Table 3.2 Somnolence syndrome scale of Littman

	Definition
None	No evidence of change in behavior
Minimal	Disturbance with some tiredness but activity not curtailed
Mild	Decreased activity and increased tiredness, may have a low-grade pyrexia
Moderate	Sleeping much of the day, decreased appetite, low-grade fever, most activities curtailed
Severe	Inactive, sleeping 18–20 h per day, low-grade fever, markedly decreased appetite, and only taking oral fluids

3.6 Scoring

Different scoring systems have been defined for radiation-induced injury. Two of them (RTOG/EORTC and Littman SS scale) are given in Tables 3.1 and 3.2.

Somnolence symptoms may be assessed by a patient-completed daily diary in which main symptoms like drowsiness, sleep, fatigue, lethargy, mental concentration, or appetite are scored by patients with visual analogue scales consisting of 100 mm long with opposing sensations [58]. Littman et al. [19] provided an observer-based scale (Table 3.2).

3.7 Prevention and Management

It has been recommended that pre-radiation corticosteroid administration should be considered in patients with significant peritumoral brain edema and who have symptomatic brain edema. Asymptomatic patients with minimal brain edema could be spared from pretreatment corticosteroids [59, 60].

A short course of corticosteroids may be helpful in patients with acute and subacute brain reaction to the irradiation.

Corticosteroids usually resolve the symptoms of somnolence syndrome; however, optimal steroid schedule for its management is still unknown [61]. The preventive effect of steroids [31, 36, 43] and antidepressants [62] to reduce the incidence of SS has been proposed. These results are needed to be tested in further studies before conclusion.

Dexamethasone is the drug of choice between steroids due to its long half-life, low mineralocorticoid activity, and a relatively low effect on cognition [63]. Dexamethasone causes general improvement in patient condition within 4–6 h [64, 65], and neurological improvement occurred within 24–72 h in majority of patients [66]; however, the pressure may not be consistently reduced until 2–4 days after initial dosing [67].

3.7.1 Dexamethasone Prescription

Prophylactic:
Dexamethasone (oral or parenteral): 4–16 mg daily for the first 2 weeks of radiation therapy [51, 59].
Therapeutic:
10 mg IV stat then 4 mg IM/IV every 6 h [51]

Corticosteroids have rapid and complete gastrointestinal absorption, and oral and parenteral dosing is equivalent. Parenteral therapy should be converted to oral therapy at the earliest appropriate opportunity [68].

The dose can be divided over 4 doses, but owing to its biologic half-life (about 36–54 h), dosing once or twice a day would be a rational practice [69].

Based on UptoDate "if dexamethasone dose of 16 mg is insufficient, the dose can be increased up to 100 mg per day."

A proton pomp inhibitor like omeprazole should be coadministered for gastric protection with concomitant use of NSAIDs or bisphosphonates in the immediate postoperative period, in those patients receiving unusually high doses of corticosteroids or previous history of gastrointestinal bleeding [70].

Some guidelines recommend *Pneumocystis carinii* prophylaxis with trimethoprim-sulfamethoxazole in patients with dexamethasone treatment during concomitant chemoradiation therapy [63, 71].

In patients with diabetic mellitus, additional medications during steroid therapy need to be increased based on blood glucose levels.

Higher doses of dexamethasone may be needed to control brain edema in patients with anticonvulsants (e.g., phenytoin, carbamazepine and phenobarbital), due to their ability to induce hepatic microsomes [70, 72]. In addition, serum phenytoin concentration may be interfered with by steroids [73].

After maximal clinical improvement, dexamethasone dose is reduced to the lowest effective dose and after the completion of radiation therapy is tapered over 2–4 weeks and discontinued [59, 74]. A gradual tapering of dexamethasone should be considered because dexamethasone doses used in brain tumor patients can suppress the hypothalamic-pituitary-adrenocortical axis when it is given for more than 2 weeks. More importantly, gradual discontinuation of dexamethasone can prevent rebound edema and recurrence of symptoms that may occur even with less than 14 days of treatment [68]. With less than 5–7 days of steroid use, treatment can usually be abruptly discontinued [75].

There are various steroid tapering guidelines in cancer patients. Guidelines for use of steroids in cancer patients recommend that steroids be discontinued abruptly if less than 4 mg per day of dexamethasone has been used for less than 3 weeks; otherwise, a gradual tapering is indicated [76]. BC Cancer Agency Cancer Management Guidelines for dexamethasone tapering recommends reducing by 4 mg every 5 days [71]. With any symptoms returning or worsening during tapering, the dexamethasone should be return to the previous dose [77].

Because of the corticosteroid complications, other agents that can reduce vasogenic brain edema without corticosteroid side effects are under investigation. Corticorelin acetate (a synthetic peptide formulation of the normal endogenous human corticotropin-releasing factor) [78–81], vascular endothelial growth factor (VEGF) receptor, tyrosine kinase inhibitors such as cediranib or monoclonal antibodies (e.g., Bevacizumab [82, 83], and selective COX-2 inhibitors [84] are some of these medications.

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Radiation Orbital Toxicity

4

The orbit contains the globe and connective tissues including extraocular muscles, orbital fat, eyelids, eyelashes, lacrimal gland, and lacrimal draining system. Different parts of the globe (e.g., the lens, iris, conjunctiva, sclera, retina, ciliary body, cornea, and optic nerve) have different sensitivities to irradiation. Some structures like the optic nerve respond to radiation in a chronic manner (late-responding tissue), and some like the conjunctiva and eyelids are acute-responding tissues. Some parts of the mentioned structures are very sensitive, and some of them like the lens and sclera are very resistant to radiation. The orbital area may be irradiated as the treatment target or as an organ at risk in the vicinity of the target. Radiation-induced acute side effects in this area require prompt attention to prevent long-term issues like ophthalmitis, permanent dry eyes, and impaired visual acuity. In this chapter, we will focus on more sensitive acute-responding tissues.

Most of the acute side effects of orbital radiation therapy have a mild severity, and there is often no need for treatment break [1–10]. These acute side effects (e.g., dry eyes, excessive tearing, conjunctivitis, transient periorbital erythema, and edema) have been reported in 30–50% of patients based on volume of the area within the radiation field [2, 3, 10–13]. Based on animal studies, the acute side effects of orbital radiation therapy in decreasing frequency include conjunctivitis, blepharitis, keratoconjunctivitis sicca, keratitis, and ulcerative keratitis [14].

The orbit is a small area that compared with its size, consists of a collection of many different structures as mentioned above. Each orbital structure has varying sensitivity to radiation effects and different signs and symptoms will develop at different times during radiation therapy. Here, the acute radiation effects will be reviewed for different orbital structures separately in each section.

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4.1 Blepharitis and Eyelid Dermatitis

The eyelid is a thin fold of skin and its response to radiation is more than skin at other sites. It also contains hair follicles in its free edge that are sensitive to radiation. Radiation blepharitis (eyelid edge inflammation), as a radiation dermatitis, begins with erythema followed by dry and moist desquamation (and rarely necrosis). Erythema takes approximately 2–4 weeks to develop after radiation exposure; it is usually transient and disappears rapidly. Moist desquamation of skin can develop after 5–6 weeks of radiation therapy (50–60 Gy in 1.8–2.2 Gy daily fractions). Healing is typically slow and may take up to 6–12 weeks [15, 16].

The following guidelines will provide comfort and healing of the periocular skin radiation-induced dermatitis and blepharitis [17]:

- Washing the eyelids with lukewarm water and mild soap and gently drying at least once daily.
- Applying an eyelid moisturizer, black tea soaks (soak tea bags in hot water, allow them to cool, lie down, and put them over the eyes).
- Avoiding extremes of heat and cold, skin irritants, and any eyelid rubbing or scratching friction.
- More severe dermatitis in eyelid skin may need a radiation break and should be treated like a skin burn using silver sulfadiazine ointment or similar medications.

4.2 Eyelash Loss

Loss of the eyelashes may occur (Fig. 4.1) with doses more than 10–20 Gy (1.5–2 Gy per fraction) [16, 18]. It may be temporary and regrowth after approximately 2 months [15] or may be permanent at radiation doses of more than 30 Gy [16].

Eyelash loss can result in irritation of the conjunctiva and cornea due to loss of the protective blink reflex. These complications are discussed below.

4.3 Conjunctivitis

Signs and symptoms of radiation-induced conjunctivitis include conjunctival injection, watery discharge, and discomfort that occur 1–3 weeks after the start of radiation treatment. Acute conjunctivitis is common with doses ≥30 Gy [11, 19]. Secondary infectious conjunctivitis (mostly bacterial or rarely viral) may also occur [20] (Fig. 4.1). A thicker, purulent, yellow-green discharge should raise suspicion for bacterial conjunctivitis [21].

Radiation conjunctivitis is a clinical diagnosis based on patient signs and symptoms including a red eye, discharge, and normal vision as well as exclusion of other diagnoses in patients with a history of irradiation to or near the orbit [21].

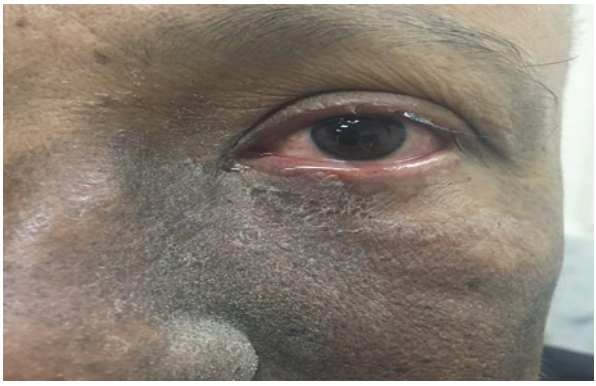

Fig. 4.1 Conjunctivitis and eyelash loss at the end of radiation therapy for advanced maxillary sinus undifferentiated carcinoma

The risk of conjunctival toxicity can be reduced by positioning the orbit out of the radiation field or reducing dose buildup on the conjunctival surface by higher beam energy or treating patients with the eye open during radiation exposure if eyes are irradiated from the anterior aspect of the orbit [20].

It is recommended that artificial tears be used 4–8 times daily to relieve the irritation caused by conjunctivitis [20].

Secondary infectious conjunctivitis should be managed as a primary form. Viral conjunctivitis is self-limited and topical antihistamine/decongestants may be needed for symptom relief. The efficacy of antiviral agents is not clear [22, 23]. Bacterial conjunctivitis is treated with a broad-spectrum topical antibiotic (trimethoprim with polymyxin B eye drops or erythromycin ophthalmic ointment). Gram stain or cultures generally are not carried out, and empiric antibiotics are usually prescribed [17, 24, 25].

4.4 Xerophthalmia

Tears are produced by the lacrimal functional unit consisting of the lacrimal glands, ocular surface (cornea and conjunctiva), eyelids, meibomian glands, and the interconnecting innervation [26, 27].

The tear film consists of three layers: mucous (inner layer), aqueous (middle layer), and lipid (outer layer).

The mucous layer is produced by conjunctival goblet cells and epithelial cells of the cornea and conjunctiva. The lacrimal glands consist of the main lacrimal gland and the accessory Krause and Wolfring lacrimal glands, which are located around the upper border of the tarsal plate and the conjunctival fornix, respectively. The aqueous component is secreted by these glands. The lipid component is secreted by the meibomian glands (at the rim of the eyelids inside the tarsal plate) and Zeis glands (anterior to the Meibomian gland, at distal eyelid margin) [28].

Radiation therapy leads to damage to the meibomian glands [29] and cause lacrimal gland acinar cell apoptosis and gland atrophy [30] or both [27]. Tear film aqueous and lipid deficiency develop due to dysfunction of lacrimal glands and Meibomian gland, respectively [20, 31].

With low-dose radiation therapy (about 24–25 Gy) of lymphoid lesions of the orbit and ocular adnexa, early mild radiation-induced xerophthalmia and chemosis have been noted in up to 50% of patients [12]. Irradiation of lacrimal glands to doses more than 30–40 Gy can lead to dry eye syndrome; the incidence increases dramatically with doses ≥50 Gy and doses greater than 60 Gy may cause permanent tear loss [20, 32, 33].

Diagnosis is based on characteristic symptoms and clinical appearance. Early effects are conjunctival inflammation, chemosis (swelling of the conjunctiva), and tear film instability with a resultant dry eye sensation [34]. Patients develop a red, painful, scratchy eye (foreign-body sensation), and photophobia. Severe problems may produce corneal desiccation, ulceration with bacterial infection, neovascularization, opacification, and ultimately perforation [35].

Xerophthalmia can be avoided by positioning lacrimal glands out of the radiation field, shielding them, or modifying dose distributions by using intensity-modulated radiation therapy (IMRT) [36, 37].

Supplemental lubrication or artificial tears are the mainstay of treatment for xerophthalmia; however, they act only as a replacement therapy without any effect on tear secretion. There are various artificial tear products with different formulations with no evidence suggesting a specific single brand being superior [38]. Preservative-free eye drops contain fewer additives and are generally recommended in the setting of extreme and long-term use of teardrop including severe dry eyes or multiple teardrop application daily due to lower effects of these products on the cornea and conjunctival epithelium [39].

In addition to artificial teardrops, there are other forms of supplemental lubrications like gels or ointments. Artificial tear ointments and gels offer longer-lasting relief but may blur vision [38].

There is no proven difference in efficacy between different topical dry eye treatments, including artificial tears, ointments, or gels [40].

Artificial Tear Prescription:
Solution: Instill 1–2 drops into eye(s) as necessary to relieve symptoms [39].
Ointment: Pull down lower lid of affected eye and apply 0.25 mL of ointment to the inside of the eyelid [39].

Stimulation of tear production has been seen by using topical sodium hyaluronate, cyclosporine, and tacrolimus, which increase the aqueous component of the tear layer and goblet cell density while also decreasing the inflammation process [41, 42]. These agents need to be studied in radiation-induced xerophthalmia. Oral pilocarpine could palliate dry eye and dry mouth symptoms in Sjögren's syndrome [43, 44] and has also been used in the management and prevention of radiation-induced xerostomia (see Chap. 7). But currently, there is no evidence for its application in radiation-induced xerophthalmia.

Topical anti-inflammatory agents (corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs)) are beneficial for selective patients with severe dry eyes [45], but there isn't sufficient evidence for their efficacy in radiation-induced xerophthalmia.

Autologous serum eye drops (with essential tear components for epithelial proliferation, similar properties of tears, and no additive preservatives) [46], punctal occlusion (mechanical blocking of the draining system) [47], and dry eye moisture chamber goggles (a chamber for protecting the dry eyes from the environment) [20], all have been suggested for severe dry eye treatment with some limitations in clinical use including need for frequent blood tests and potential risk of infection transmission in autologous serum eye drops, insufficient evidence of efficacy in punctal occlusion, and cosmetic concerns in wearing the moisture chamber goggles.

4.5 Corneal Toxicity

Acute corneal toxicity of radiation therapy can be secondary to radiation xerophthalmia or a primary effect of irradiation on the corneal surface epithelium, corneal stroma, and endothelium [20].

Secondary keratopathy due to tear film dysfunction is the common form of acute corneal toxicity and is presented by superficial punctate epithelial erosions or, in the case of severe dry eyes, corneal scarring [34].

Direct radiation injury can induce punctuate corneal erosions and corneal edema at doses of 40–50 Gy in 4–5 weeks and corneal ulceration at doses more than 60 Gy (with conventional fractionated radiation) and with 20 Gy delivered in a single dose [48].

Corneal damage is diagnosed clinically by signs and symptoms and eye examination including slit lamp exam. Patients usually present with photophobia, foreign-body sensation, tearing, pain, haloes, decreased vision, and red eye. In the penlight examination, conjunctival injection may be present. In slit lamp microscope examination, a corneal opacity or infiltration with corneal ulcers could be seen. The cornea may have a hazy appearance with corneal edema. Punctate epithelial erosions and corneal ulcers stain positively with fluorescein.

A corneal shield, which is placed between the lids and globe, could minimize corneal radiation dose and prevent toxicity if the treatment target is superficial to the cornea. These internal eye shields are used in radiation treatment planning of skin cancer near the eye and can give excellent protection from lower-energy X-rays and electron beams with energies ≥6 MeV [49, 50].

4.5.1 Treatment

4.5.1.1 Topical Lubricants (e.g., Ophthalmic Ointment)

Patient should be instructed to pull down the lower lid of the affected eye and apply a small amount of ointment once daily or more if needed [51, 52].

Some practitioners prescribe lubricant antibiotic ointment (e.g., erythromycin 0.5% ophthalmic ointment, polymyxin B/trimethoprim (Polytrim) ophthalmic solution, and sulfacetamide 10% ophthalmic ointment) [53].

4.5.1.2 Analgesics

Pain is common with corneal damage and is alleviated with oral nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen or narcotic analgesics (in severe cases). Topical NSAIDs (e.g., diclofenac 0.1%, ketorolac 0.4%), are administered by some practitioners in selective patients that request immediate pain relief or that cannot tolerate oral analgesics, but these topical agent have not been approved for this indication [54].

Patching and topical cycloplegics and topical anesthetics have not shown significant benefit for uncomplicated corneal abrasions [53].

4.5.1.3 Ophthalmologist Consult

Early ophthalmologist consultation is recommended and in the setting of significant vision loss, corneal infiltration or ulcer, vision worsening, or no improvement of symptoms with initial management, referring a patient to an ophthalmologist is necessary [53].

4.6 Iris Toxicity

Acute complications of radiation therapy in the anterior chamber are rarely reported, but transient early iritis can develop after single doses ≥10 Gy [20]. Iritis presents with pain, photophobia, red eye, and blurred vision and is distinguished from other causes of red eye by slit lamp examination (presence of leukocytes in anterior chamber) [55]. There is little published evidence about management of radiation iritis. Ophthalmologic consultation should be considered early in these patients.

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Ear Toxicity

5

The acute ear complications of radiation therapy include external, middle, and inner ear injuries. The acute external ear complications include otitis externa or skin reactions involving the preauricular region, the auricle, and the external auditory canal that occur in about 28% of head and neck cancer patients treated with radiation therapy [1]. The acute middle ear complications that include mastoiditis, Eustachian tube dysfunction, consequential otitis media, and transient conductive hearing loss occur in 40–45% of head and neck cancer patients during or after radiation therapy [2, 3]. The acute inner ear complications include sensorineural hearing loss (SNHL) and tinnitus [4]. SNHL may occur early after treatment in up to 50% of patients with head and neck tumors treated with radiation therapy [5–7].

5.1 Mechanism

The external ear is a tube covered by skin that conducts sound waves to the middle ear. Radiation effects on the external ear mimics the skin effects of radiation and for mechanism, timing, and symptoms (see Chap. 1).

The mechanism of radiation-induced otitis media is due to swelling of the mucosa following the radiation and subsequent obstruction of the Eustachian tube. The Eustachian tube obstruction results in resorption of the air oxygen and nitrogen from the middle ear, which results in negative pressure and tympanic retraction leading to conductive hearing loss. With further reduction of the negative pressure in the middle ear cavity, fluid transudation takes place resulting in serous otitis media [4, 8].

Stria vascularis in the inner ear is responsible for endolymph production and absorption. Stria vascularis injury after radiation exposure leads to endolymphatic hydrops and temporarily increased intralabyrinthine pressure, which could lead to ear fullness, hearing loss, tinnitus, dizziness, and vertigo [9].

Hearing loss may be conductive, sensorineural, or mixed type. Early hearing loss during radiation therapy is usually conductive due to Eustachian tube dysfunction and radiation-induced otitis media. The incidence of SNHL increases with time, and

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sensorineural or mixed-type hearing loss occurs either near the end of or shortly after the completion of radiation therapy. The sensory component of early hearing loss is usually related to stria vascularis degeneration and disturbances in normal perilymph and endolymph physiology [9, 10].

5.2 Timing

Acute otitis media usually occurs within a few weeks of radiation therapy. It is usually transient [1] and resolves within a few weeks after completion of the treatment [4].

SNHL may occur near the end of treatment or after the completion of radiation therapy and increase with time. SNHL may be transient or permanent. Transient SNHL could recover within 6–12 months; however, it may last over 12 months in a few cases [5].

Patients with no severe SNHL (less than 30 dB drop from baseline) and no post-irradiation serous otitis media have a good chance for recovery of sensorineural hearing within 6 months to 1 year. On the other hand, if severe SNHL develops or the SNHL persists beyond 1 year, it is likely permanent [5].

5.3 Risk Factors

No specific risk factor has been defined for radiation-induced ear toxicities. As with other organs, the maximum dose and ear irradiated volume could affect the prevalence and severity of toxicities. Background skin disease such as lupus erythematous and other autoimmune disease may cause more toxicity for the external ear. Previous middle ear disease such as otitis media or mastoiditis may also increase middle ear radiation-induced toxicities. Concomitant administration of chemotherapy may also increase the risk and severity of otitis in external ear (Fig. 5.1). Platinum-based regimens are used as induction or concurrent chemotherapy in locally advanced head and neck cancers and can potentially affect inner ear toxicity so the risk of SNHL may increase.

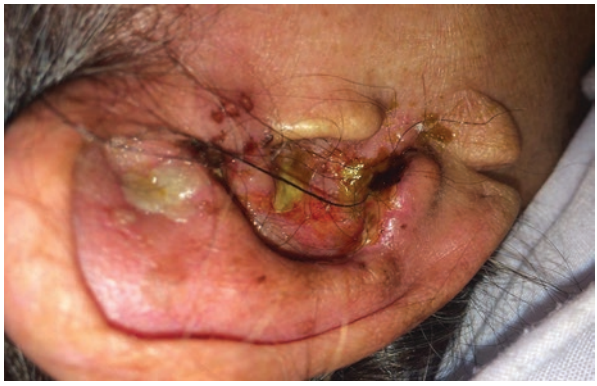

Fig. 5.1 External otitis in a patient treated with cisplatin-based chemoradiation of head and neck cancer

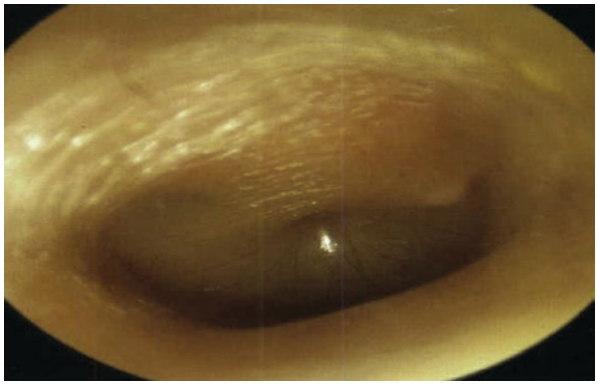

Fig. 5.2 Otitis media after chemoradiation for parotid tumors

5.4 Symptoms and Diagnosis

Symptoms of otitis media are conductive hearing loss, ear pain, fullness, and tinnitus in the affected ear [4]. As a result of radiation therapy, the tympanic membrane may become dull, retracted, bulged, and congested or may remain normal (Fig. 5.2) [3]. An inner ear injury can manifest with tinnitus, dizziness, vertigo, and high-frequency SNHL [5].

Diagnosis of these complications is based on patient symptoms and ear examination including otoscopic assessment. Hearing loss may be diagnosed by simple tests like general assessment of each ear with words spoken at various volumes or a tuning fork or by more thorough audiometry testing. A pure tone audiometer test offers an audiogram based on a person's ability to hear sounds with different loudness and pitches and characterizes the type and degree of hearing loss.

5.5 Scoring

No distinct grading system has been published for external, middle, and inner ear radiation-induced toxicities separately. Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) have defined the ear toxicity grading system, which considers all three parts as an organ (see Table 5.1) [11].

Table 5.1 RTOG/EORTC ear toxicity scoring

	Definition
Grade 1	Mild external otitis with erythema, pruritus, secondary to dry desquamation not requiring medication. Audiogram unchanged from baseline
Grade 2	Moderate external otitis requiring topical medication/serous otitis media/hypoacusis on testing only
Grade 3	Severe external otitis with discharge or moist desquamation/symptomatic hypoacusis/tinnitus not drug related
Grade 4	Deafness

5.6 Management

All patients that are undergoing radiation therapy to a portion of the temporal bone or any ear compartment should have pretreatment audiometric evaluation (pure tone audiometry, otoacoustic emission audiometry, tympanometry) [12]. Patients should be assessed again after the end of treatment or sooner, if the clinical situation warrants [13, 14], and then audiometric evaluation should be repeated based on patient symptoms at each visit.

All patients should be informed to maintain aural hygiene. Any traumatic actions to the ear canal like the use of a curette for cerumen removal should be avoided. The routine use of agents such as mineral oil or carbamide peroxide supplemented, as needed, with gentle irrigation is recommended to prevent cerumen impaction [13].

External otitis is a skin reaction to radiation exposure that commonly occurs during radiation therapy and resolves after the completion of treatment [9]. External otitis symptoms can be alleviated with over-the-counter analgesics and topical ear drops in our experience; however, there is no study evaluating the use of different topical medications in treatment of this complication during radiation therapy.

Corticosteroids (betamethasone or dexamethasone otic solutions) decrease inflammation and relieve ear pain [15]. Corticosteroids could be used 2–4 drops in the affected ear canal every 2 or 3 h. Patients should tilt the head to the affected ear, instill the drops, and keep this position for about 5 min [15].

Acetic acid drop changes the pH of the ear canal [16] and has antibacterial and antifungal properties [17]. The patient should be instructed to use acetic acid 4–6 drops every 2–3 h into the external auditory canal [17].

The combination of the hydrocortisone and acetic acid is available in the form of otic solution that can be used in patients with external otitis [16].

Perforated tympanic membrane is a contraindication to the use of any medication in the external ear canal.

Otitis media is generally treated symptomatically with analgesics and antipyretics.

Antipyrine and benzocaine otic solution is a combination solution containing antipyrine, benzocaine, oxyquinoline sulfate, and anhydrous glycerin that is applied as a local anesthetic for otitis media [18]. It can be used every 1–2 h as needed for pain relief with a sufficient amount of solution to fill the affected ear canal [19].

Aqueous lidocaine 2% can provide rapid pain relief in acute otitis media. Aqueous lidocaine is not available in a bottle with a dropper. Injectable lidocaine 2% can be used with a dropper [20].

Oral analgesics (e.g., NSAIDs, acetaminophen) can reduce acute otitis media pain much slower than topical medication [21]. Oral analgesics may be used in combination with topical agents such as lidocaine and benzocaine [18].

Middle ear ventilation tube insertion may be needed in the setting of long-lasting radiation-induced secretory otitis media (3–6 months) [22].

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Oral Mucositis

6

Almost no patients that are undergoing radiation therapy of head and neck cancers can run away from radiation-induced oral mucositis, especially if the oral cavity is included in the treatment target. Trotti et al. have confirmed the high incidence of induced oral mucositis in a systematic review with rates of 97% during conventional radiation therapy, 100% during altered fractionation radiation therapy, and 89% during chemoradiation therapy [1]. In a retrospective study of 204 head and neck cancer patients that received radiation therapy with or without chemotherapy, oral mucositis occurred in 91% of patients; the rates of mucositis grades 1, 2, 3, and 4 were 4%, 21%, 60%, and 6%, respectively [2].

Another study of 450 head and neck cancer patients that received radiation therapy with or without chemotherapy found that the majority of patients (83%) developed oral mucositis (mild in 19%, moderate in 35%, and severe in 28% of patients).

Oral mucositis has significant pain, dysgeusia, and odynophagia that can result in dehydration, malnutrition, and reduced quality of life scores.

Oral mucositis also can reduce radiation therapy tolerance and consequently affect treatment results. Unplanned breaks/delays in radiation therapy were reported in 2.4%, 15.8%, and 46.8% of patients with mild, moderate, and severe oral mucositis, respectively [3].

6.1 Mechanism

The oral mucosa is covered by stratified squamous epithelium. The basal layer of mucosal epithelium has columnar cells with rapid division properties to maintain a constant epithelial population as cells are shed from the surface [4]. The lamina propria underlies the epithelium, which consists of fibroblasts and connective tissue, capillaries, inflammatory cells (macrophages), and extracellular matrix [4, 5]. Radiation-induced oral mucositis is not a simple epithelial process and results from

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complex pathways embracing all different cellular and tissue compartments of the mucosa. It has been proposed that endothelial and connective tissue damage precedes epithelial changes in irradiated oral mucosa [5].

Radiation directly damages cellular DNA of rapidly dividing cells of the oral basal epithelium and cells in the underlying tissue [6]. Radiation also generates oxidative stress and reactive oxygen species (ROS) that lead to further tissue damage by activating a number of transcription factors such as nuclear factor-κB (NF-κB) in the epithelium, endothelium, macrophages, and mesenchymal cells. Subsequently, the upregulation of genes and the production of pro-inflammatory cytokines including TNF-α, IL-1β, and IL-6 occur, leading to an injury to the connective tissue, endothelium, and apoptosis of cells within the basal epithelium. Pro-inflammatory cytokines also activate molecular pathways that amplify production of TNF-α, IL-1, and IL-6 and resulted in further tissue damage (positive feedback loop).

Until this stage, the clinical appearance of mucosa seems to be normal, and only the thinning of the mucosa and edema related to acute vascular response may develop and cause early signs and symptoms of mucositis (mild erythema and burning sensation). But as radiation therapy continues, all events from the prior phase result in further injuries and loss of the basal epithelial stem cells with continuing cell loss from the mucosal surface, reducing the cellular population of the mucous membrane. Atrophic changes and breakdown of mucosa occur and patients experience obvious symptoms of mucositis [6–12].

The ulcerative phase of mucositis is accompanied by significant inflammatory cell infiltration. Beside the intrinsic factors, this phase may be affected by extrinsic factors that have reciprocal relation together. Damaged epithelium of the ulcerative mucositis is susceptible to bacterial colonization. Following the colonization with a mixed microbial flora, including mostly gram-negative bacteria, bacterial cell wall products penetrate the injured mucosa and increasingly stimulate pro-inflammatory cytokine release, amplifying the severity of mucositis and tissue injury [6]. When radiation therapy is completed, tissue repair begins with renewal of epithelial proliferation and differentiation and reestablishment of the local microbial flora [13].

6.2 Timing

In conventional fractioned radiotherapy (2 Gy per fraction daily), mucosal erythema with mild discomfort occurs within 1–2 weeks of treatment at doses of approximately 10–20 Gy [13]. Patchy pseudomembranous formation can develop after 2 weeks (20 Gy), and ulcerative radiation-induced mucositis often arises at doses of more than 30 Gy and peaks during the fourth to fifth week of therapy. This timing of symptom presentation is varied based on treatment schedule. In accelerated radiation therapy, mucositis reaches its peak within 3 weeks [11, 14]. The symptoms usually become more severe with treatment and remain for about 2–3 weeks after the end of therapy at its peak [2, 15]. Healing then begins and may take weeks to months (generally 3–6 weeks) to resolve [16]. However, chronic open wounds recognized as soft-tissue necrosis may occur in a few cases due to excessive depletion of mucosal stem cells depending on their recovery [17].

6.3 Risk Factors

Several factors have been identified for the development of more severe oral mucositis during radiation therapy. These factors could be related to treatment, tumor, and/or patient characteristics.

6.3.1 Tumor Site

Primary tumors of the oral cavity, oropharynx, or nasopharynx [16] increase the risk of oral mucositis due to including higher volumes of the oral mucosa and salivary gland in irradiation fields.

In the treatment planning of oral cavity, oropharyngeal, and nasopharyngeal cancer, a significant surface of oral mucosa includes in radiation field that increase the rate of oral mucositis. In the oral cavity, some areas, including the lateral borders and ventral surface of the tongue as well as the soft palate and floor of the mouth, have increased susceptibility to developing oral mucositis due to higher cell turnover rates. Instead, buccal mucosa has less sensitivity to radiation-induced mucositis [13].

Salivary gland radiation-induced injury leads to changes in quality (low production of glycoproteins and an increased acidity of saliva) and quantity of saliva (see Chap. 7) that inhibit the protective effects of saliva and increases the risk of developing mucositis [18].

6.3.2 Concomitant Systemic Therapy

When chemotherapy is combined with radiation therapy, both normal tissue and tumor response alter due to their additive effects. Both radiation therapy and antineoplastic agents disrupt normal cell division of the oral mucosa and result in increased oral mucositis incidence [13, 19, 20]. Dose, type, and schedule of systemic therapy all affect severity and frequency of mucositis in the setting of concurrent chemoradiotherapy (weekly versus every 3 weeks; cisplatin or paclitaxel are associated with higher rates of oral mucositis) [21, 22].

There is a paucity of data about oral mucositis rates when cetuximab is used concurrently with radiation therapy. Some proposed no exacerbation of the common mucositis associated with radiation therapy [23, 24], and others found an increase of oral mucositis compared to radiation alone or conventional cisplatin with radiation therapy [25–27]. Future clinical trials are needed to more precisely evaluate the incidence and severity of mucositis, the time of occurrence, and the impact on quality of life and treatment interruption of patients treated with cetuximab and radiation therapy.

6.3.3 Radiation Dose

Higher total radiation dose to the oral cavity and higher dose per fraction are significantly correlated to the grade of acute mucositis. It has been reported that patients with cancer of the larynx, hypopharynx, oral cavity, nasopharynx, or oropharynx

that are treated with radiation therapy with cumulative radiation dosage more than 50 Gy are at an increased risk for oral mucositis [3, 16].

With the introduction of high conformal radiation therapy, the correlation between the dose to the oral cavity and the severity of acute mucositis has been evaluated more precisely.

In a study of patients undergoing intensity modulated radiation therapy (IMRT) for head and neck cancer, it was demonstrated that a cumulative point dose of 39 Gy resulted in mucositis for 3 weeks or longer; mild severity and short duration of mucositis were found at cumulative point doses less than 32 Gy [28]. Another study found that the percentage of oral cavity volume receiving doses higher than 15, 30, 40, 45, and 50 Gy significantly correlated with acute mucositis grade [29].

6.3.4 Radiation Fractionation Schedule

Altered fractionation radiation schedules, such as concomitant boost or hyperfractionation seem to be associated with higher incidence of severe mucositis [15, 30–34].

6.3.5 Patient-Related Factors

The incidence of mucositis is related to various patient variables including younger patients, smoking, alcohol consumption, metallic dental restorations, preexisting periodontal disease, low body mass index, poor functional status, low leukocyte count, advanced disease and stage, a prior history of severe mucositis, and various comorbid conditions [3, 35–37].

It has been suggested that with increasing number of patient-related factors, the risk, duration, and severity of mucositis increases (see below).

Some argue that younger cancer patients have a higher rate of mucosal turnover that increases their susceptibility to mucositis [38].

The use of dental guards is proposed in the areas of metallic restoration because it reduces back scatter exacerbated radiation doses to adjacent mucosa caused by metallic restoration materials [13].

Genetic polymorphisms may be a susceptibility factor for radiation-induced mucositis (XRCC1 polymorphisms, NBN polymorphisms) [39, 40]. It has been seen that cytokine phenotype may be correlated to the risk of radiation-induced injury. During radiation therapy, an elevation in serum levels of cytokines IL-6, TNF-α, and IL-1β and low levels of IL-8 seem to correlate with mucositis severity [35, 41–43].

A weak correlation between high pretreatment epidermal growth factor (EGF) levels and decreased severity of mucositis has been seen that is suggestive of the protective EGF effect for oral mucosa damage [44]. Further study is needed to clarify cytokines and growth factors role in predicting, preventing and treating oral mucositis.

Suresh et al. evaluated a collection of patient-related risk factors and proposed a comprehensive tool to predict the probable incidence and severity of mucositis in head and neck cancer patients receiving chemoradiotherapy. In this suggested

system, patients are scored based on age > 40, erythrocyte sedimentation rate (ESR) >3-times the upper limit, albumin <3.0 g/dL, white blood count (WBC) less than 3000/μL, Eastern cooperative oncology group (ECOG) performance status (PS) of more than 2, stage III or higher disease, use of tobacco, and presence of any comorbid conditions. One point is given to each of these parameters. Scores of 3 or less and 6 or above predicted the differences in the incidence of mucositis [45].

6.4 Symptoms

The early signs of radiation mucositis are red appearance of the oral mucosa due to dilation of capillaries in the endothelial layer and reduced epithelial thickness. A whitish appearance may be seen due to transient hyperkeratinization prior to erythema. Patients are mostly asymptomatic or complain of a mild burning sensation or intolerance to spices or hot food in this early phase. Erythema (Fig. 6.1) is followed by fibrinous pseudomembranous formation, followed by erosion and ulceration (Fig. 6.2). Under the pseudomembranes, the epithelial surfaces are denuded, and hemorrhage occurs easily. Pseudomembranous ulcerative lesions are very

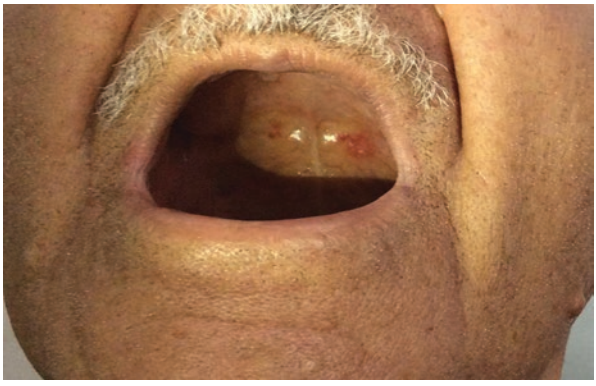

Fig. 6.1 Grade 1 of oral mucositis at second week (14 Gy) of radiation therapy

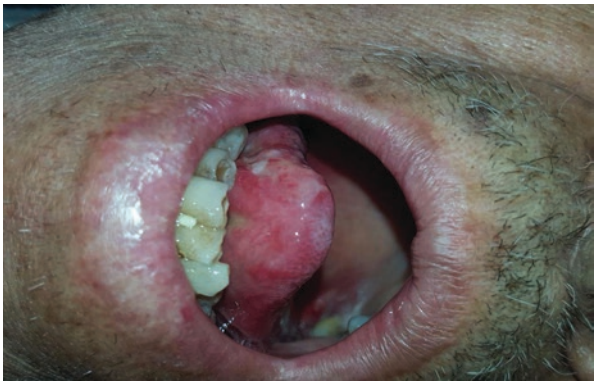

Fig. 6.2 Grade 2–3 of oral mucositis at fifth week (48 Gy) of radiation therapy

painful, and patients complain of severe pain and difficulty in chewing that interferes with their oral intake or speaking, eventually leading to weight loss.

Oral pain follows a similar pattern of objective clinical findings of oral mucositis but it may begin sooner and reach its peak earlier (between weeks 2 and 4) [2]. Correlation between patient-reported and clinical manifestations of mucositis is low in early parts of treatment [46].

Bacterial infection (usually gram-negative) or viral infections (such as herpes simplex virus (HSV)) and fungal infections (usually candidiasis) can sometimes be superimposed on oral mucositis [13, 37]. Infectious mucosal lesions often extend beyond the field of radiation. An infected oral mucosa usually manifests with a deep ulceration with a yellow-white necrotic center and raised borders. Fungal mucositis presents with white removable fungal plaques [13]; however, erythematous forms may occur and complicate the exact diagnosis [47].

6.5 Scoring

Patients undergoing radiation therapy to the oral cavity should be seen at least once a week. At each visit, patient symptoms and their oral intake should be assessed; their oral mucosa should also be examined.

A variety of assessment scales exist for measurement of oral mucositis. Three of the most commonly utilized scales (Table 6.1) for radiation-induced mucositis are toxicity criteria of the Radiation Therapy Oncology Group (RTOG), the European Organization for Research and Treatment of Cancer (EORTC) [48], the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) [49], and the World Health Organization (WHO) oral toxicity scale [50].

Table 6.1 RTOG, WHO, and CTCAE mucositis grading

	RTOG	WHO	CTCAE
Grade 1	Irritation/may experience mild pain not requiring analgesic	Mild Soreness ± erythema	Asymptomatic or mild symptoms; intervention not indicated
Grade 2	Patchy mucositis that may produce an inflammatory serosanguinous discharge/may experience moderate pain requiring analgesia	Moderate Erythema, ulcers; patient can swallow solid food	Moderate pain; not interfering with oral intake; modified diet indicated
Grade 3	Confluent fibrinous mucositis/may include severe pain requiring narcotic	Severe Ulcers with extensive erythema; patient cannot swallow food	Severe pain; interfering with oral intake
Grade 4	Ulceration, hemorrhage, or necrosis		Life-threatening consequences; urgent intervention indicate
Grade 5			Death

6.6 Prevention

Maintenance of good oral hygiene is critical to preventing oral mucositis. All patients should be informed of proper oral hygiene before starting treatment:

- Cleaning teeth with toothpaste and a soft toothbrush after each meal and at bedtime [51], using a mild-tasting toothpaste or a solution of 1 teaspoon of salt added to 4 cups (1 quart) of water (if not tolerating any toothpaste) [19].
- Dental flossing once daily.
- Dental screening at least several weeks before the beginning of therapy extractions and major surgeries should be planned 10–21 days and 4–6 weeks before beginning radiation therapy, respectively [52].
- Rinsing the mouth two to four times a day (1 tablespoon (15 mL) of oral rinse, swish in oral cavity for 30 s, then spit out).
  Recommended oral rinses [51]:
  - Water
  - Sodium chloride 0.9% for irrigation
  - Salt solution by adding a little salt (1/4 to 1/2 a teaspoon) to a cup of warm water
- Be aware that alcohol-based mouth rinses should be avoided.
- Moisten lips with a moisturizing cream.
- Adequate oral fluid intake (daily fluid intake of 8–12 cups, 2–3 L).
- Avoiding alcohol, tobacco, caffeine, fluid or foods with high sugar, highly acidic fluids and foods (e.g., lemon glycerin swabs, vitamin C lozenges), hot and spicy foods, and crunchy foods.

6.6.1 Prophylactic Interventions

Benzydamine is a nonsteroidal anti-inflammatory drug with local analgesic, anesthetic, and antimicrobial properties that inhibits pro-inflammatory cytokines including IL1 and TNF-α. It has been shown to reduce the severity and frequency of mucositis in patients with head and neck cancer undergoing radiation therapy. Benzydamine oral rinse appears to be effective in the prevention of radiation-induced oral mucositis in head and neck cancer patients [53–58]. Benzydamine (15 mL of oral rinse 0.15%) is used as a mouth rinse. It should be held or rinse within the mouth for at least 30 s, followed by expulsion from the mouth and try not to swallow, 3–4 times per day. It is recommended to begin the day prior to radiation therapy and continue during treatment.

Benzydamine is well tolerated. If patients complain of numbness or irritation or a burning sensation as result of benzydamine usage, diluting the liquid with an equal amount of warm water helps alleviate this issue. Other side effects are nausea and

vomiting, xerostomia, headache, cough, and pharyngeal irritation. It can be absorbed through the oral mucosa and should be used with caution in patients with renal impairment.

6.6.2 Prophylactic Intervention Under Evaluation

Intensity-modulated radiation therapy (IMRT) allows sparing a greater area of the oral mucosa from higher doses of radiation. However, an obvious superiority of IMRT to conventional three-dimensional conformal radiotherapy (3D–CRT) and conventional two-dimensional radiotherapy (2DRT) in the prevention of the acute oral mucositis is not established [59, 60].

Low-level laser therapy seems to be effective in the prophylaxis of radiation-induced oral mucositis [61–66]. As a noninvasive measurement, it can decrease the incidence and severity of oral mucositis [67]. Laser therapy modulates three main biological effects: an analgesic effect with increase in endorphin release and pain signal inhibition, an anti-inflammatory and wound healing properties with energy production at the mitochondrial level, and an increase in vascularity and regeneration of injured tissues [2, 63, 68]. It refers to local application of a high-density monochromatic narrow-band light source with the output power range from 5 to 500 milliwatts and a wave-length between 600 and 1000 nanometers [69]. It is a simple procedure that is administered immediately after radiation therapy and takes only about 6–8 min to administer. All is done extraorally unless intraoral lesions develop [47].

Glutamine is a nonessential amino acid in the body. Glutathione, a byproduct of glutamine metabolism, protects normal tissues against oxidative injury [70, 71]. Glutamine depletion may develop in cancer patients due to cachexia and normal tissue damage from radiation or chemotherapy [72].

It has been found that oral glutamine administered daily during radiation therapy can reduce the severity and frequency of oral mucositis in head and neck cancer patients. These results warrant further investigation in future trials [72–77].

Zinc renders multiple essential functions in the body such as cell proliferation, wound healing, free radical protection, immunity, and anti-inflammatory effects. It has been shown that oral zinc sulfate can prevent and cause delay in development of oral mucositis [78].

Payayor (*Clinacanthus nutans*) is a traditional herbal medicine originating from Thailand with anti-inflammatory and analgesic properties. There are some studies that support payayor as a prophylactic intervention for radiation-induced oral mucositis [79, 80]. However, no guideline for use exists currently due to insufficient evidence.

Calendula officinalis, commonly known as Marigold, possesses some anti-inflammatory and antioxidant properties. It has been suggested that *Calendula officinalis* can be effective in decreasing oral mucositis severity [81, 82].

Natural honey has been recently shown to be effective in reducing radiation-induced mucositis. Honey has immunomodulatory properties and antibacterial

activity and can accelerate wound healing. Honey is an easily available agent that warrants further trials to validate its effect [83–85].

Royal jelly is a secretion of hypopharyngeal and mandibular glands of worker bees with antioxidative, antibiotic, and anti-inflammatory action. Royal jelly could improve the signs and symptoms of oral mucositis and shorten healing time [86].

Granulocyte-macrophage colony-stimulating factor (GM-CSF) has been reported to regulate proliferation and maturation of leukocytes, macrophages, and dendritic cells. GM-CSF can improve wound healing by enhancing fibroblasts and keratinocyte growth [87].

Subcutaneous GM-CSF has been shown to decrease pain and severity of oral mucositis [88, 89]. However, topical administration of GM-CSF to treat radiation-induced oral mucositis has mixed results [87, 90, 91]. Saarilahti et al. studied topical use of GM-CSF and reported promising effects in prophylaxis of radiation-induced oral mucositis [92]. There are also conflicting data about effectiveness of subcutaneous GM-CSF in radiation-induced mucositis prophylaxis [93, 94].

Keratinocyte growth factor (KGF) is an epithelial cell growth factor expressed by fibroblasts and endothelial cells and has an important role in wound healing by increasing proliferation and maintaining integrity of epithelial cells and enhancing neovascularization and collagen deposition [95].

Primary results show that recombinant human keratinocyte growth factor Palifermin resulted in reduction of radiation mucositis with no stimulation of the proliferation of tumor cell lines [96–98], which needs further evaluation.

Oral recombinant human epidermal growth factor (rhEGF) has been shown to improve wound repair by stimulating epithelialization. rhEGF appears to be effective for the treatment of radiation-induced mucositis [99, 100]. Another growth factor with promising results in preclinical study is velafermin (recombinant human fibroblast growth factor-20, rhFGF-20) [101]. Further studies are needed to determine these agents' efficacy and safety for prevention and treatment of radiation-induced mucositis.

Amifostine is a thiol compound that selectively protects normal tissue from radiation effects [102]. Amifostine decreases the frequency and severity of xerostomia. The salivary preservation by amifostine may offer a protective effect against oral mucositis [17]. However, the amifostine studies for the prevention of oral mucositis offer insufficient evidence to support its use for this purpose. Additional investigation is needed to clarify the role of amifostine as an intervention for oral mucositis prevention [103].

Fluconazole (100 mg/daily) in head and neck cancer patients receiving radiation therapy can lead to decreased candida carriage and incidence of severe mucositis [5, 104–107]. Patients that are receiving head and neck radiation therapy are at increased risk of developing oral candida infection (17–29%) and colonization (93%) [108].

PTA is a multi-agent lozenge containing a mixture of polymyxin E, tobramycin, and amphotericin B and has a broad spectrum of antibacterial and antifungal effects. It has been used to prevent radiation-induced mucositis with inconclusive results. Results of the topical antibiotic approach in prevention of oral mucositis are insufficient and need to be further studied [109–114].

Chlorhexidine antimicrobial oral rinse is not recommended for the prevention of radiation-induced oral mucositis. It has no clinical benefit for the reduction or prevention of radiation-induced oral mucositis [18]. Chlorhexidine oral rinse is not well tolerated and may cause a degree of discomfort (e.g., taste alteration, burning sensation and teeth staining) without any clinical benefit [115].

Sucralfate is an oral ulcer coating complex of sucrose-sulfate-aluminum salt. Clinical trials found no significant advantage for sucralfate in the prevention or treatment of radiation-induced mucositis [116–120].

Prostaglandins are known to be cytoprotective. Misoprostol is a synthetic prostaglandin E1 analogue. Misoprostol mouthwash has been studied to prevent oral mucositis in head and neck cancer patients, and the data does not demonstrate a prevention benefit [121, 122]. There are limited studies for prostaglandin E2 application in the radiation-induced mucositis prevention and treatment that do not draw any conclusions.

Steroids have several effects on different systems of the human body and have been studied for radiation-induced oral mucositis prevention. Currently, there is insufficient evidence to support using systemic steroids for reducing the frequency or severity of oral mucositis [47].

Early morning radiation delivery has been shown to marginally reduce the severity of mucositis because of circadian variations in cell cycle proteins. The most radiosensitive phase of the cell cycle (G2-M) occurs in the late afternoon and evening in human oral mucosa [123, 124]. Currently, there is no recommendation for this observation in clinical practice [125].

Pilocarpine has not shown any preventive effect on oral mucositis during radiation therapy in head and neck cancer patients [125].

Supplemental antioxidants during radiation therapy have been proposed to protect the normal tissue and reduce side effects caused by radiation therapy. However, these antioxidants may act unselectively and protect cancer cells against the damaging effects of reactive oxygen species induced by radiation. Antioxidant supplement safety during radiation therapy is particularly controversial. The American Cancer Society and most other national nutrition guidelines recommend that patients with active cancer treatments limit the usage of supplements to obvious deficiency of essential agents [126].

RK-0202 (RxKinetix), an oral rinse, comprises the potent antioxidant N-acetylcysteine in a polymer matrix. RK-0202 has demonstrated primarily positive results in reducing the incidence of severe mucositis in patients treated with radiation therapy for head and neck cancer [127].

Vasoconstrictor agents such as phenylephrine with transient vasoconstriction, tissue hypoxia, and suppression of mucosal cell death during irradiation would prevent radiation-induced oral mucositis based on preclinical studies [128]. Further clinical trials should be conducted to prove the preventive effect of these agents on radiation-induced mucositis.

Caphosol (Cytogen Corp) is an electrolyte solution with high ionic content (Ca^{2+} and PO_4^{3-} ions) that help tissue repair by diffusing ions into the intercellular

spaces in the epithelium, thus permeating the mucosal lesion and modulate the inflammatory process. Recent studies did not find significant reduction in the incidence or duration of severe oral mucositis in patients receiving head and neck radiation therapy [129, 130].

Oxygen nebulization that uses high-flow oxygen could improve local mucosal oxygen content leading to angiogenesis, anti-inflammatory effect, and improved wound healing. It has been studied in patients with nasopharyngeal cancer to prevent radiation-induced mucositis with promising results. Future studies are required to better determine effectiveness [131].

Several herbal mouth rinses like Korean red ginseng [132], manuka (*Leptospermum scoparium*) and kanuka (*Kunzea ericoides*) [133], or chamomile [134] have been studied with a positive effect on the development of radiation-induced mucositis. Future investigation is needed to confirm the efficacy and safety of these products.

Persian traditional medicines have different compounds with various local and systemic effects on the mucosal surface and can theoretically be used to reduce mucositis [135]. One of the combinations (*Malva sylvestris* L and *Alcea digitata* (Boiss) Alef), which is effective in reducing xerostomia [136], has also been evaluated in a small randomized trial in our patients and primary results are promising (not published yet).

The mammalian target of rapamycin (mTOR) inhibition plays a role in the protection of normal oral epithelial cells from radiation-induced epithelial stem cell depletion. mTOR inhibition with rapamycin may have a potential effect on the prevention of radiation-induced mucositis [137]. Clinical studies need to evaluate rapamycin efficacy in this setting.

Mothers against decapentaplegic homolog 7 (SMAD7) is a protein encoded by the SMAD7 gene and has an antagonistic effect on transforming growth factor beta (TGF-β) and NF-κB signaling. Its prophylactic and therapeutic effects on radiation-induced oral mucositis as a well as its safety need to be determined in future studies [138].

Wobe-Mugos is a combination of proteolytic enzymes comprised of papain, trypsin, and chymotrypsin that has an anti-inflammatory effect. It seems not to be efficient in preventing radiation-induced oral mucositis [139].

6.7 Management

Principles of management consist of patient assessment, oral care, management of oral pain, treatment of secondary infection, and consideration of nutritional support.

6.7.1 Patient Assessment

All patients treated with radiation therapy should be seen as least once weekly, and the oral mucosa should be examined at each visit. In the patients with oral

mucositis, baseline grading of oral mucositis and the patient's general status should be determined. After initial assessment, decision-making about treatment protocol can be provided. Most cases can be managed in an outpatient setting except in the setting of grade 4 mucositis, fever (more than 38.3 °C), or severe neutropenia. Patients with inadequate fluid intake may require oral supplementation or IV hydration. Complete blood count is proposed in patients that have severe mucositis, fever, or at risk of developing neutropenia.

6.7.2 Mouth Care

Mouth care includes all measurements noted for maintaining good oral hygiene (see above), with intensity and frequency modification based on mucositis grading [140].

6.7.3 Management of Oral Pain

Pain management is the most important aspect of symptom control. Systemic analgesia may be prescribed in addition to topical agents in moderate to severe pain. Pain control can encourage patients to eat and drink more and wash the mouth more efficiently, resulting in improved medication effects.

6.7.3.1 Benzydamine Mouth Wash

Benzydamine can reduce the severity of oral mucositis and associated pain in radiation-induced oral mucositis [51, 141].

Benzydamine (15 mL of oral rinse 0. 15%) is used as a mouth rinse. It should be held in the mouth for at least 30 s, followed by expulsion (should not be swallowed), up to every 1–2 h.

Benzydamine is well tolerated. If patients complain of numbness or irritation or a burning sensation, dilution with an equal amount of warm water may reduce these symptoms. Other side effects are nausea and vomiting, xerostomia, headache, cough, and pharyngeal irritation. It can be absorbed through the oral mucosa and should be used with caution in patients with renal impairment.

6.7.3.2 Doxepin

Doxepin is a tricyclic antidepressant. Topical application is prescribed for pruritus and neuropathic pain [142]. Topical doxepin rinse has been shown to be an adequate analgesia for oral mucositis pain up to 4 h after application. Patients usually have good compliance; however, mild burning or stinging, unpleasant taste, and drowsiness could develop as common adverse effects [143].

Usage: oral rinse at a dosage of 25 mg (10 mg/mL × 2.5) diluted in 5 mL of water for 1 min 3–6 times per day.

6.7.3.3 Magic Mouthwash

Magic mouthwash usually contains at least three of these basic ingredients [144]:

– An antibiotic
– An antihistamine or local anesthetic
– An antifungal
– A corticosteroid
– An antacid

Magic mouthwash is used every 4–6 h, maintained in the mouth for 1–2 min before being either spit out or swallowed (in pharyngeal or esophageal involvement). It's recommended not to eat or drink for at least 30 min after using magic mouthwash [144].

There are various formulations for magic mouthwash with no standard mixture. Some of the more common formulations are defined here [145]:

- 80 mL viscous lidocaine 2%, 80 mL Mylanta, 80 mL diphenhydramine (12.5 mg per 5 mL elixir), 80 mL nystatin 100,000 U suspension, 80 mL prednisolone (15 mg per 5 mL solution), and 80 mL distilled water
- 1 part viscous lidocaine 2%, 1 part Maalox (do not substitute Kaopectate), and 1 part diphenhydramine (12.5 mg per 5 mL elixir)
- 30 mL viscous lidocaine 2%, 60 mL Maalox (do not substitute Kaopectate), 30 mL diphenhydramine (12.5 mg per 5 mL elixir), and 40 mL Carafate (1 gm per 10 mL)
- 100 mL dexamethasone (0.5 mg per 5 mL elixir), 60 mL nystatin 100,000 U suspension, 100 mL diphenhydramine (12.5 mg per 5 mL elixir), and 3 capsules tetracycline 500 mg

Different contributors of magic mouthwash are added for different purposes:

Diphenhydramine provides local analgesia but can exacerbate xerostomia.
Lidocaine also provides local analgesia.
Corticosteroids reduce inflammatory responses.
Nystatin is added as an antifungal agent.
Tetracycline as an antibiotic (inhibits bacterial protein synthesis).
Antacid (magnesium hydroxide/aluminum hydroxide) component to adequately coat the oral mucosa [54].

Side effects of magic mouthwash may include problems with taste, a burning or tingling sensation in the mouth, drowsiness, constipation, diarrhea, and nausea. Lidocaine can cause a gag reflex impairment and increase the risk of aspiration, mouth numbness, and tongue biting.

6.7.3.4 Gelclair

As an oral gel, Gelclair consists mainly of polyvinylpyrrolidone and sodium hyaluronate. It is indicated for the management of oral mucositis-related pain due to establishing a barrier over the oral mucosa [142].

Usage: Oral gel, available in 15 mL single-use packet, is poured into a glass. Then add up to two tablespoons or 40 mL of water, stir the mixture well and use immediately. Rinse for at least 1 min and spit 3 times a day or as needed. Do not eat or drink for at least 1 h following treatment; this may provide relief for up to 7 h.

6.7.3.5 CAM2028

CAM2028 is a bioadhesive barrier-forming lipid solution that can also act as a lipid-based drug carrier system for local and extended delivery of benzydamine. After application, lipid components spread in the oral cavity and form a barrier that protects the sore and inflamed mucosa. Recently, it has been shown that CAM2028, with benzydamine or without benzydamine, provides significant pain reduction for patients suffering from oral mucositis. Its effect begins within 5 min of application and is maintained for up to 8 h [146, 147].

Usage: Patients are instructed to spray a 0.15 mL-metered dose of the liquid into the oral cavity 1–3 times and to allow 5 min for the bioadhesive barrier to form before eating or drinking [146].

6.7.3.6 MF 5232

MF 5232 (Mucotrol) is a concentrated oral polyherbal gel wafer formulation with local analgesic, antioxidant and immunomodulatory activity, and wound-healing properties [148]. It has received FDA approval for pain relief associated with oral lesions [149]. The efficacy of MF 5232 therapy in radiation-induced mucositis management has been reported [148]. Further studies are required to confirm these positive results.

6.7.3.7 Acetylcysteine

Acetylcysteine oral rinse, as a mucolytic agent to reduce the viscosity of mucous secretions, is being studied to improve saliva thickness and painful mouth sores in patients with head and neck cancer undergoing radiation therapy [150].

6.7.3.8 Opiates

Low-dose opiates may be used in patients with inadequate pain relief with nonnarcotic topical agents. Oral, transdermal, or parenteral opiates may be used. Elixir should not be used because it contains alcohol, which exacerbates mucositis.

Constipation prophylactic laxatives should be considered in patients taking opiates [47].

Fentanyl has various forms that all can be used in patients with oral mucositis depending on patient preference. Transdermal fentanyl patch can deliver a steady-state dose through the skin and provide pain relief to cancer patients with less constipation and sedation than morphine [151]. The level of drug increase over 12–24 h and reach steady state in about 72 h. Oral transmucosal fentanyl is a sweetened

matrix of fentanyl that is dissolved in the mouth. It is effective for breakthrough pain and could be particularly useful in patients with mucositis. It has been demonstrated that oral transmucosal fentanyl citrate may provide more efficacious treatment options than morphine sulfate in treating breakthrough cancer pain [152, 153].

Fentanyl buccal tablet allows rapid absorption through the oral mucosa and produces a greater early systemic level than oral transmucosal fentanyl citrate. Fentanyl buccal tablet can be absorbed with a similar profile in patients with or without mild oral mucositis [154].

Mouthwashes with a morphine-containing solution can effectively decrease pain in oral mucositis associated with radiation therapy compared to magic mouthwash. More studies are required in this regard [155, 156].

Sublingual methadone has been proposed as an alternative of standard treatment for mucositis-related pain. Additional studies need to better illuminate the potential benefits of this formulation of methadone in radiation-induced mucositis [153].

Usage:

Morphine (opioid-naive patients): SC/IM; 5–10 mg q4hr PRN/IV; 2.5–5 mg q3-4 hr. PRN/oral; 15–30 mg PO q4hr PRN; 10–20 mg PR q4hr.

Fentanyl transdermal patch (12.5 mcg/hr., 25 mcg/hr., 50 mcg/hr., 75 mcg/hr., 100 mcg/hr): 25–100 mcg/hr., reapplied q72hr (or every 48 hr. administration may be needed in a few cases).

Initial patch is selected based on patient need for daily PO morphine dose, then decrease by 25–50%.

Oxycodone: 10 mg PO q12hr initially; increase by 25–50% gradually every 1–2 days, q12hr dosing interval should be maintained.

Methadone: 2.5 mg PO q8-12 hr.; increase slowly, then every 3–5 days.

6.7.3.9 Corticosteroids

Corticosteroids are useful [51] and are usually administered as a component of a magic solution. Hydrocortisone tablet (2.5 mg buccal tablets) can be used orally. Patients are instructed to dissolve the tablet slowly in mouth in contact with the ulcer three times daily.

6.7.3.10 Gabapentin

Gabapentin is an antiepileptic drug. It is an effective agent in the treatment of neuropathic pain. It also has an application for pain relief that is related to radiation-induced mucositis that seems to be successful [157].

Gabapentin begins at a dose of 600 mg and can gradually increase to 1800–3600 mg/day.

6.7.3.11 Other Analgesic Agents

Carmellose sodium paste [52]

Lidocaine 1% gel [52]

Choline salicylate dental gel [52]

Kaolin-pectin [158]

Codeine/acetaminophen (1–2 tablets dissolved in a little water) as a mouthwash up to four times daily [52]

Aspirin 300 mg (1–2 tablets dissolved in a little water) as a mouthwash up to four times daily [52].

6.7.3.12 Sucralfate

Sucralfate mouthwash is not recommended to be used to treat oral mucositis in patients receiving radiation therapy for head and neck cancer.

6.7.3.13 Phenytoin Mouthwash

Phenytoin mouthwash was compared with normal saline in patients with radiation-induced mucositis in a pilot study. Phenytoin mouthwash (1% solution) was more effective for pain control without significant efficacy on mucositis severity [159].

6.7.3.14 Low-Level Laser Therapy

Low-level laser therapy is a promising treatment therapy of oral mucositis that has been shown to reduce mucositis pain significantly [47, 160].

6.7.4 Antifungals

As was previously mentioned in Sect. 7.4, patients undergoing head and neck radiation therapy are at risk of developing candidiasis [108]. Fungal mucositis presents with white removable fungal plaques [13]; however, erythematous form may occur and complicate exact diagnosis [47]. The diagnosis is usually based on clinical suspicious and can be readily confirmed through identification of yeast forms on gram stain or KOH preparation of the scrapings [161].

Patients with early, mild presentation are treated with topical agents including nystatin or clotrimazole. Patients with moderate to severe candidiasis or recurrent disease are treated with more potent systemic agents including fluconazole and itraconazole [161].

Clotrimazole troches (10 mg oral troches): Dissolve 1 troche in the oral cavity 5 times a day for 14 days [161] (not tolerated in patients with xerostomia).

Nystatin oral suspension (100,000 U/mL): rinse mouth with 5 mL (400,000–6,000,000 units) four times a day. Swish in mouth and retain for 2 min, and then swallow or expectorate [161]. Continue treatment for at least 48 h after perioral symptoms have disappeared.

Fluconazole: 200 mg PO loading dose then 100–200 mg daily for 1–2 weeks [162]

Itraconazole oral solution: 200 mg daily for 1–2 weeks [162]

6.7.5 Antivirals

The incidence of herpes simplex virus-1 (HSV-1) infection has been estimated to be 29% in patients with mucositis during head and neck cancer radiation therapy, which is isolated from smears taken from patients with ulcerative mucositis [162]. The lesions present primarily as mucosal vesicles, which rupture spontaneously and

form ulcerative lesions. The early vesicular stage may be so rapid that it is not seen in immunocompromised patients [163].

Patients with oral mucositis that experience a prolonged course of mucositis with extreme pain or vesicular lesions, secondary HSV infection should be considered. The gold standard diagnostic test for HSV-related oral mucositis is isolation of HSV tissue culture (results usually take 2–7 days). A more rapid diagnostic test for mucocutaneous lesions uses staining of skin scrapings.

Treatment with oral or intravenous acyclovir or oral valacyclovir decreases the duration of viral shedding and improves the severity of oral mucositis.

Oral acyclovir: 400 mg three times a day for 7–10 days (five times a day in immunocompromised patients) [163]
Intravenous acyclovir (If oral intolerance develops): 5 mg/kg three times a day [163, 164]
Oral valacyclovir: 1 g three times a day for 7–10 days [164]

6.7.6 Feeding Tube/Nutritional Support

In patients with severe symptoms of radiation mucositis, oral nutritional is compromised and can lead to weight loss and nutritional depletion. Nutritional support and feeding tubes should be considered in these patients [3, 165].

For short-term access, nasogastric and nasojejunal tubes may be used; for longer-term access, gastrostomy, gastrojejunostomy, and jejunostomy can be placed. Percutaneous endoscopic gastrostomy is the method of choice unless in the setting of esophagitis, gastroparesis, aspiration pneumonia, or limited gastric volume that jejunostomy tube may be placed instead [166].

In patients without a functioning gastrointestinal tract due to obstruction, intractable vomiting, diarrhea, poor GI motility, short bowel syndrome or severe pancreatitis, and total parenteral nutrition may be appropriate [166].

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Xerostomia

7

Dry mouth (xerostomia) is one of the most common complications of radiation therapy in head and neck cancers due to the high radiosensitivity of the salivary glands.

Xerostomia is a common debilitating side effect of radiation therapy for head and neck cancers that affects chewing, eating, tasting, swallowing, tooth decay, and speaking. Xerostomia has a negative impact on quality of life in cancer patients.

It has been estimated that the incidence of acute xerostomia induced by radiation therapy of head and neck cancers is 60–90% depending on tumor site, irradiation technique, and time of evaluation; it is observed in 30% of patients with advanced cancer in need of starting a palliative care program [1, 2].

In regard to timing of radiation therapy, the incidence of xerostomia is 6%, 93%, and 83% before, during, and 1–3 months after treatment, respectively [3]. In regard to type of radiation therapy, xerostomia occurs in 81%, and 71% of patients underwent conventional head and neck radiation therapy during and 1–3 months after treatment, respectively. New radiation techniques such as intensity-modulated radiation therapy (IMRT) may spare salivary glands more than conventional therapies and decrease xerostomia rate and severity [3].

Moderate to severe xerostomia occurs in 60.2% of patients with nasopharyngeal carcinoma and in 32.9% of patients with other sites of head and neck cancer 3 months after treatment with intensity-modulated radiation therapy [4].

7.1 Mechanism

In order to understand the mechanism of xerostomia induction in radiation therapy, salivary gland physiology needs to be understood.

The terms of major and minor salivary glands refer to their anatomic size. There is a difference in the quality of content and quantity of production during different time points through the day, which may affect the clinical symptoms related to each salivary gland dysfunction.

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Normal salivary flow is highly variable and is usually 0.25 mL/min (1–1.5 L per day). A salivary flow of less than 0.12–0.16 mL/min is considered to be abnormal [5].

The parotid glands have only serous-secreting acinar cells and exclusively produce serous watery secretion. Up to 50% of stimulated saliva and approximately 20% of unstimulated saliva secretion volume comes from parotid glands secretion.

The submandibular glands have both serous and mucous acinar cell types (10% mucous cells and 90% serous cells) and produce a mixed serous and mucous saliva. They contribute 65% of unstimulated saliva secretion and 35% of stimulated saliva secretion.

The sublingual glands mainly have mucous acinar cells and produce predominantly thick, viscous saliva. They contribute less than 10% of unstimulated saliva volume.

The minor glands, which are distributed throughout the upper aerodigestive mucosa (e.g., labial, buccal, lingual, and palatinal mucosa), are mixed glands largely comprised of mucous acinar cells. The minor glands produce less than 10% of the total volume of saliva [6].

During the day, major saliva production in stimulated and unstimulated conditions is related to parotid and submandibular glands, respectively [7].These major salivary gland dysfunctions are major causes of xerostomia induced by radiation therapy.

Salivary glands are highly radiosensitive. Serous acinar cells of the salivary glands are well differentiated and have a slow mitotic rate and turnover, but they behave like acutely responding tissues to radiation and undergo interphase cell death by apoptosis [8, 9]. Mucous acinar cells of salivary glands have a lower radiosensitivity than serous acinar cells, and they have a trend to retain their function for some time later [10]. The parotid glands seem to lose more function than do the other salivary glands, resulting in a decrease in watery saliva and accumulation of sticky mucus. However, the difference in radiosensitivity between the parotid and submandibular/sublingual salivary glands is still controversial [11–13].

It has been found that saliva production reduces during the first days of radiation therapy. Membrane damage of saliva-producing cells confounding with receptor-mediated signaling pathways of water excretion and functional loss is responsible for the early hyposalivation. Cell death does not occur in the acute phase but is a late event [14].

Saliva is a complex fluid, mostly composed of water (99%) and a minority of various nonorganic and organic substances such as enzymes, hormones, antibodies, antimicrobial constituents, and growth factors. Saliva quality changes during radiation therapy, including increased viscosity, decreased transparency, yellow/brown discoloration, declined production of glycoproteins (e.g., immunoglobulin A), decreased salivary pH (from 6.8 and 7.0 to 5.5), altered salivary electrolyte levels (increases in the concentrations of sodium, chloride, calcium, and magnesium with slight potassium level change), and shift in certain intraoral microbial populations

(increase in *Streptococcus mutans* and species of *Lactobacillus*, *Candida* (primarily *Candida albicans*), and *Staphylococcus*, with parallel decreases in *Streptococcus sanguinis* and species of *Neisseria* and *Fusobacterium*) [13, 15–18].

7.2 Timing

Radiation-induced xerostomia usually initiates early during radiation therapy for head and neck cancers containing salivary glands within the radiation fields. When the radiation dose reaches 10–20 Gy with 2 Gy per day, which corresponds to the first to second week of treatment, a 50–60% decrease in salivary flow occurs, and the patient may begin to experience mild to moderate dryness of the mouth, which may progressively worsen over the course of treatment. After 7 weeks of radiation therapy, salivary flow decreases to approximately 20% and continues to further drop for more than 6 months after completion of treatment [11, 19, 20]. Some recovery is possible until 12–18 months after radiation therapy depending on the dose received by the salivary glands and the volume of the gland tissue included in the irradiation volume; there is also a compensatory hypertrophy of the non-irradiated salivary gland tissue. Xerostomia may rarely recover a few years after radiation therapy [19, 20].

Radiation-induced salivary gland damage may be reversible or permanent based on the radiation dose. With a dose less than 60 Gy, changes in the salivary glands, including edema and inflammation, are reversible. Although, for acceptable function, the radiation doses to salivary glands should be more lower than 60 Gy. When the dose exceeds 60 Gy, changes may be permanent, with fibrosis and glandular degeneration [13].

7.3 Risk Factors

The occurrence and severity of radiation therapy-induced xerostomia are dependent on radiation-related factors, mostly salivary gland radiation dose and volume within the radiation field [21]. Altered fractionation schedules' impact on the incidence of xerostomia is not clearly defined. It seems that accelerated and hyperfractionated radiation therapy both increase acute side effects of treatment including xerostomia [22].

Concurrent chemotherapy is associated with a significant risk of developing acute and late xerostomia [21]. However it has been shown in some studies that concomitant chemotherapy and intensity-modulated radiation therapy do not increase the incidence of acute or late xerostomia relative to intensity-modulated radiation therapy alone [23]. Concomitant cetuximab (a monoclonal antibody against EGFR) doesn't increase the xerostomia rate when it's prescribed concurrently with radiation therapy [24].

Patient age is also a contributing factor. With increasing age, the vulnerability of salivary glands to radiation injury and development of xerostomia increases [7]. It

should be noted that increasing age does not cause hyposalivation by itself [25]. The higher incidence of xerostomia in elderly patients is mainly due to their comorbidities and use of medications with the potential to develop xerostomia.

No significant association between the risk of developing xerostomia and ethnicity, marital, or socioeconomic status has been observed [21].

It has been proposed that the progression of xerostomia can be improved by mixing clinical and dose-volume factors. The mean dose given to the contralateral and ipsilateral parotid glands is the most significant predictors in multivariable normal tissue complication probability models for xerostomia. Age, financial status, T stage, and educational level are proposed clinical predictive factors for radiation-induced xerostomia. However some of these clinical datasets such as financial status and education may affect the patient-reported xerostomia, many of which need to be investigated before they are incorporated into the models [4].

The volumes of parotid and submandibular glands are decreased due to radiation therapy. The parotid gland volume reduces about 30% during radiotherapy. The lateral regions of the irradiated parotid glands move inward. The irradiated submandibular glands also shrink and move upward. Parotid shrinkage during treatment is accompanied by a decrease in tissue density consistent with a relative increase in fat over glandular tissue [26, 27].

Parotid gland density and volume variations during radiation therapy may possibly predict acute xerostomia. It has been found that a higher score of acute xerostomia is predicted by higher density and volume variations in the first 2 weeks of treatment. Further studies are necessary to definitively assess the potential of early density/volume changes in identifying more sensitive patients at higher risk of developing xerostomia [28].

7.4 Symptoms

Dryness is one of the most unpleasant oral symptoms that adversely affects all oral functions and compromises oral health. Patients may experience dry oral mucosa and thick, sticky saliva requiring them to adjust their diet and keep the mouth moist with water [1, 29].

Both acute and chronic xerostomia induce functional alterations such as chewing, swallowing, speaking, burning, and pain, with a propensity to bacterial and fungal infection, demineralization of teeth, and increase in caries, dysgeusia, gagging sensations, a fear of choking, and odynophagia. The patient may have bad breath secondary to food stagnation in the oral mucosa, gingiva, teeth, or tongue [30, 31].

Cheilitis, a fissuring or ulceration in the angles of the mouth and erythematous tongue due to damage to the dorsal epithelium, can also be seen in patients with xerostomia [29, 30].

Quality of life significantly worsens along with the severity of xerostomia. With each milliliter decrease in saliva secretion, the quality of life score decreases by 2.25% [32].

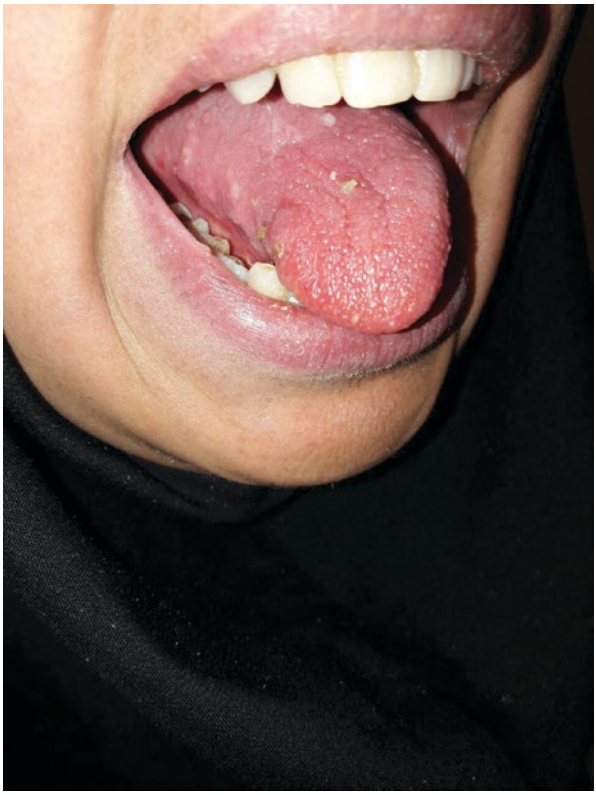

Fig. 7.1 Grade 2 xerostomia in tongue cancer 1 month after radiotherapy

7.5 Diagnosis

Xerostomia is a clinical diagnosis based on patient signs and symptoms (Fig. 7.1). The objective tests of salivary flow are not usually used for diagnosis because there is little correlation between patient symptoms and these tests. Therefore, clinical management should be based on patient symptoms [33].

There are some differential diagnoses including oral infections, bad oral conditions, and mucositis, which may be ruled out with a detailed history and clinical exam. However, they can all occur in association with each other.

7.6 Scoring

For measuring the severity of xerostomia, there are assessment tools based on patient- and observer-reported data.

Observer-based toxicity scoring is generally based on the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of

Table 7.1 RTOG/EORTC xerostomia scoring

	Definition
Score 0	No change over baseline
Score 1	Mild mouth dryness/slightly thickened saliva/ may have slightly altered taste such as metallic taste/these changes not reflected in alteration in baseline feeding behavior, such as increased use of liquids with meal
Score 2	Moderate to complete dryness/thick, sticky saliva/markedly altered taste
Score 3	–
Score 4	Acute salivary gland necrosis

Table 7.2 Michigan University xerostomia questionnaire

	0	1	2	3	4	5	6	7	8	9	10
Rate your difficulty in talking due to dryness											
Rate your difficulty in chewing due to dryness											
Rate your difficulty in swallowing solid food due to dryness											
Rate the frequency of your sleeping problems due to dryness											
Rate your mouth or throat dryness when eating food											
Rate your mouth or throat dryness while not eating											
Rate the frequency of sipping liquids to aid swallowing food											
Rate the frequency of sipping liquids for oral comfort when not eating											

Cancer (EORTC) grading scale (Table 7.1). Because of the low correlation between the measured salivary output and observer-reported xerostomia [34] and underestimation of the severity of xerostomia with these scoring systems [35], several xerostomia questionnaires have been developed to permit patient self-reporting.

One of the most validated patient self-reported questionnaires is xerostomia questionnaire (XQ), which was developed by the University of Michigan (Table 7.2). It consists of eight questions; patients rate each item on a scale from 0 to 10. Higher scores are related to more severe xerostomia [35].

7.7 Prevention

There are some preventive approaches for radiation-induced xerostomia, including more conformal radiation delivery technology, radioprotective agents, and even pre-irradiation surgical techniques [36, 37].

7.7.1 Amifostin

Available data show that amifostine significantly reduces the incidence of acute and long-term xerostomia. Amifostine, an organic thiophosphate agent, is a prodrug that is dephosphorylated by alkaline phosphatase in tissues after administration, converting it into its active form. This active form enters the cells and acts as a scavenger against free radicals. Amifostine concentrations in tumor cells are lower than normal tissue due to

lower alkaline phosphatase levels and the pH of tumors, and therefore normal tissue protection is provided [20]. However, amifostine's effect on tumor cell protection is still a concern that precludes it from extensive administration as a radioprotective agent.

Brizel et al. in a phase III trial randomized 303 patients that received conventional radiation therapy for head and neck cancers (both postoperative and as primary treatment) to receive amifostine daily before each fraction (200 mg/m^2 intravenously). They found that amifostine significantly reduced the incidence of grade 2 acute xerostomia from 78% to 51% and reduced the incidence of grade 2 chronic xerostomia from 57% to 34% without a difference in disease control or survival [38]. Amifostine was consequently approved by the US Food and Drug Administration (FDA).

Amifostine can be administered only with standard fractionated radiation therapy without chemotherapy and only when ≥75% of both parotid glands are exposed to radiation in the postoperative setting. Amifostine should not be administered in patients receiving definitive radiation therapy, except in the context of a clinical trial, because of insufficient data to exclude a tumor-protective effect in this setting [39]. Amifostine administration in the setting of concurrent chemotherapy with radiation therapy and in the setting of accelerated and hyperfractionated therapy has not been systematically studied [40–43].

7.7.1.1 Prescription

Each vial contains 500 mg of amifostine on the anhydrous basis, requiring reconstitution for intravenous infusion [44]. Prior to intravenous injection, amifostine is reconstituted with 9.7 mL of sterile 0.9% sodium chloride. The reconstituted solution (500 mg Amifostine/10 mL) is chemically stable for up to 5 h at room temperature (approximately 25 °C) or up to 24 h under refrigeration (2 °C–8°C). Amifostine is prepared in polyvinylchloride (PVC) bags and is available at concentrations ranging from 5 mg/mL to 40 mg/mL [45].

Standard amifostine intravenous administration: 200 mg/m^2 over 3 min once daily 15–30 min prior to radiation therapy [46, 47].

Amifostine can also be administered subcutaneously (unlabeled route): 500 mg once daily prior to radiation therapy [46, 48, 49].

Note: Because of rapid clearance from the blood and tissue, the drug needs to be delivered shortly before radiation therapy.

7.7.1.2 Contraindications

Hypersensitivity to aminothiol compounds or any component of the formulation.

7.7.1.3 Advers effects

Several adverse effects have been reported for amifostine including hypotension, nausea and vomiting, hypocalcemia, and cutaneous reactions.

Blood pressure should be monitored every 5 min during the infusion and thereafter as clinically indicated. The infusion of amifostine should be interrupted if the systolic blood pressure decreases significantly from baseline [45, 48].

Amifostine is a moderately to highly emetogenic agent, and antiemetic medications (including dexamethasone 20 mg I.V. and a serotonin 5-HT$_3$ receptor antagonist) should be administered prior to and in conjunction with amifostine [50].

Serum calcium levels at baseline should be checked and monitored in patients at risk for hypocalcemia, such as those with nephrotic syndrome or patients receiving multiple doses of amifostine for injection [45, 48].

Cutaneous evaluation of the patient prior to each administration and permanent discontinuation for serious or severe cutaneous reactions should be performed [44, 45].

7.7.2 IMRT

The volume of salivary tissue irradiated is related to the occurrence of xerostomia. With introduction of novel radiation therapy delivery techniques including intensity-modulated radiation therapy (IMRT), partial sparing of salivary glands may become possible, and thus acute and late xerostomia are significantly reduced [51, 52]. Mean dose to the parotid glands should be reduced as much as clinically possible. A mean dose of less than 20 Gy for at least one parotid gland or a mean dose of less than 25 Gy for both glands may prevent severe long-term xerostomia [53]. It has been suggested that the mean parotid dose for both sides together has a higher predictive value over considering each side separately [27].

The effect of amifostine combined with IMRT is not clear. It seems that the protective effect of IMRT in sparing saliva is much greater than the effect of amifostine [54, 55].

In patients that need bilateral radiation therapy of the head and neck including bilateral parotids within the radiation fields, the effect of IMRT in prevention of xerostomia is limited.

IMRT provides a way to spare all salivary glands and improves xerostomia-related quality of life during meals and at rest; however, the largest effect is still on xerostomia during meals [56]. As noted previously, the parotid glands are largely responsible for the stimulated saliva output, whereas the minor salivary glands and submandibular glands are mainly responsible for unstimulated saliva (lubrication in rest). The risk of xerostomia decreases or is even eliminated with sparing of at least one parotid gland and reduces with sparing of at least one submandibular gland [53]. It has been reported that a lower mean dose to the oral cavity (<40 Gy) and contralateral submandibular gland (<50 Gy) is each associated with lower patient-reported and observer-rated xerostomia [51].

7.7.3 Submandibular gland transfer

Another preventive approach is submandibular gland transfer. The submandibular gland is responsible for most of the unstimulated salivary volume, which is important in the subjective symptoms of xerostomia and oral homeostasis. Some argue that sparing the submandibular gland is preferable to sparing the parotid gland [29].

In this approach, a single submandibular gland is transferred into the submental space during a surgical procedure referred to as the Seikaly-Jha procedure (SJP). The borders of the transferred gland are marked with wire to help identify it during

radiation therapy and can be shielded from the radiation [57, 58]. The surgical method of transfer is a quick, easy, and simple procedure that can be done during surgical treatment of the primary tumor [20, 59–61].

The submandibular gland may be damaged during the transfer, and complete prevention cannot be achieved, although it is still superior to some other preventive options including pilocarpine in regard to median salivary flow and saliva consistency. It has been estimated that the submandibular gland transfer could reduce 69% of the risk of acute xerostomia. However, after radiation therapy, the salivary gland repaired itself and the rate of late xerostomia can reach 19% [62]. Local/regional recurrence and survival outcome after submandibular gland transfer seem not to be compromised; however there is some controversy and need for more evaluation [41, 63].

Submandibular gland transfer should be conducted on the gland of the contralateral side of the primary cancer. The procedure should not be performed for patients with cancer of the oral cavity, bilateral neck lymph node involvement, submandibular or submental neck lymph node involvement, or advanced neck disease (N3). For accurate selection of patients that are candidates for submandibular gland transfer, suspicious nodes and all level I lymph nodes (submental and submandibular) are dissected and sent for frozen section evaluation before transfer. If any of the nodes are involved with cancer, the transfer procedure should be abandoned [62].

Collectively, quality of life in head and neck cancer patients that are at risk of radiation-induced xerostomia may improve with submandibular gland transfer [58, 59, 63]. However, further studies are still needed to confirm the safety of this surgery.

7.7.4 Pilocarpine

Pilocarpine has been approved for postradiation xerostomia. The administration of pilocarpine during radiation therapy has been studied to prevent the subsequent development of xerostomia.

Pilocarpine hydrochloride is a muscarinic-cholinergic agent that can stimulate salivary glands [64–66].

Several studies have shown positive results of pilocarpine in the prevention of radiation-induced xerostomia, especially when the doses of whole parotid glands are more than 45 Gy. However, others have concluded that oral pilocarpine could not be recommended to prevent xerostomia in patients receiving radiation therapy for head and neck cancers [67].

It has been found that pilocarpine administration during radiation therapy can result in a significant improvement in unstimulated salivary flow at the end of treatment but not in stimulated flow. This observation can be explained with the mechanism of pilocarpine's protective effects [68]. Pilocarpine stimulates the residual function of salivary tissues outside the radiation fields, including non-irradiated parts of parotid and other major salivary glands/minor salivary glands, and it has no

protective effect in the glands that are completely irradiated [69–72]. Prominently unstimulated salivary flow is preserved.

The other hypothesis proposed for the mechanism of pilocarpine's protective effect is related to indirect inhibition of radiation-induced oxidative damage. Pilocarpine reduces heavy metals such as zinc, manganese, and iron, which are found in secretary granules, leading to reduction in intracellular leakage of proteolytic enzymes in secretary granules after radiation damage and reduction in subsequent serous cell autolysis [67, 70].

Data based on in vitro studies indicate that pretreatment pilocarpine administration does not protect tumor cells and has no effect on radiosensitivity of cell lines [73].

7.7.4.1 Prescription

Start pilocarpine 5 mg three times daily with irradiation, and continue until 3 months after the end of radiotherapy [74].

Available tablets: 5 mg, 7.5 mg

Taking with a high-fat meal reduces pilocarpine absorption. Give the medication with food if GI distress occurs.)

7.7.4.2 Contraindications

Hypersensitivity to pilocarpine or any component of the formulation, uncontrolled asthma, acute iritis or glaucoma, and severe hepatic impairment (adjust dose with moderate hepatic impairment) [75]

Pilocarpine should be used with extreme caution in patients that have chronic obstructive pulmonary disease and cardiovascular disease.

7.7.5 Acupuncture

Acupuncture has been investigated in the management of patients with xerostomia and demonstrated some benefits for improving salivary flow rates and reducing xerostomia-related symptoms. Based on these observations, the preventive approach of acupuncture has been recently addressed with promising results [76].

Low-level laser therapy refers to local application of a high-density monochromatic narrowband light source with the output power range from 5 to 500 mW and a wavelength between 600 and 1000 nanometers (like helium/neon with wavelength 632.8 nm or diode laser with various wavelengths 630–680, 700–830, and 900 nm) [77].

Low-level laser therapy may result in improvement of the salivary flow by stimulating salivary glands and the regenerative effect with an increase in the number of mitosis [78]. Although the use of a low-power laser may prevent xerostomia, it needs further study to be better implemented [78, 79].

Patients with Sjögren syndrome have been studied and shown that low-level laser therapy can be safely and effectively used in these patients to reduce xerostomia [80, 81]. However for detection of low-level laser therapy efficacy on radiation-induced xerostomia, long-term follow-up is necessary.

7.8 Management

Therapeutic interventions include supportive care, saliva supplementation, and the use of procholinergic salivary secretagogues.

7.8.1 Supportive Care

7.8.1.1 Oral Rinses

Oral rinses are recommended to keep the mouth moist and clean by removing debris.

Patients are informed to use 1 tablespoon (15 mL) of oral rinse such as normal saline (NS) or 1/2 teaspoon (2.5 mL) of salt in 240 mL of water to swish in the oral cavity for 30 s and then spit out [82]. Commercially available alcohol-containing oral rinses should be avoided due to their drying effect. Limited data have proposed that all Biotène products, which include a range of toothpastes, mouthwashes, mouth sprays, chewing gum, and gels, can improve many of the symptoms of radiation-induced xerostomia, but larger studies are needed to evaluate efficacy [83].

7.8.1.2 Chewing to Stimulate Secretion of Residual Glandular Tissue

Chewing is a stimulus for inducing salivary glands to secret more saliva, and chewing several times a day can be helpful in reducing symptoms [40].

7.8.1.3 Maintaining Adequate Nutrition

Patients may benefit from a nutritional consult and should be encouraged to moisten their foods by adding butter, mayonnaise, vegetable oil, yogurt ,or sauces and have a sip of a liquid after each bite, which helps chewing and swallowing. Patients should avoid foods high in sugar due to their susceptibility to dental caries, dry or spicy food, and excessively hot or cold beverages [40].

Xylitol is a natural sweetener product that differs chemically from other sweeteners like sorbitol, fructose, or glucose. It actually interferes with the growth of bacteria associated with tooth decay, and it is approved as a therapeutic sweetener by the Food and Drug Administration [40].

These patients should avoid irritating foods that are astringents or that may stick to the teeth [40].

Alcohol, tobacco, and large amounts of caffeine should be avoided due to their drying effect [82].

7.8.1.4 Drink Adequate Fluids

Patients should be instructed to always carry water with them and keep themselves well hydrated [82].

7.8.1.5 Protection from Dry Lips

Using topically applied water- or aloe-based lubricant after oral care, at bedtime, and as often as required is helpful [82].

7.8.1.6 Alleviating Nocturnal Symptoms

A mouth guard, a cold air humidifier in the form of a bedside vaporizer or household humidifier, or applying a small amount of dentifrice on smooth dental surfaces (especially using anti-xerostomia dentifrices) can alleviate the nocturnal oral dryness [15].

7.8.1.7 Keeping Appropriate Oral Hygiene and Dental Care

Patients should be instructed on tooth brushing, dental flossing, tongue brushing, and oral mouth rinsing with an appropriate antibacterial mouth rinse such as chlorhexidine and hexitidine several times a day.

7.8.2 Saliva Supplementation

Replacement therapy with artificial saliva or saliva substitutes can be used to lubricate the mouth. Various substitutes are available commercially that are formulated to mimic natural saliva [41]. They have short-term activity with no stimulating effect on salivary glands.

A variety of forms of products including solutions, sprays, gels, and lozenges are available. In general, they contain an agent to increase viscosity, such as carboxymethylcellulose or hydroxyethylcellulose, minerals such as calcium and phosphate ions and fluoride, preservatives such as methylparaben or propylparaben, and flavoring and related agents [41].

Artificial substitutes do not replace the antibacterial and immunologic protection of saliva and do not exclude the need for regular dental care and appropriate oral hygiene [11].

7.8.3 Acupuncture

Acupuncture may have a stimulating effect on saliva production and may be a useful treatment for some patients. The possible mechanism of acupuncture is related to parasympathetic central nervous system processes, which increase the concentration of salivary neuropeptides and modulate the complex process of salivary secretion. Another possible mechanism of acupuncture is stimulation of minor salivary glands present in non-irradiated buccal mucosa [15, 84, 85].

There are some studies that provide encouraging results for using acupuncture in xerostomia [84, 86–90], while others do not provide a statistically significant effect on the increase of salivary flow [91, 92]. Further research on acupuncture is necessary prior to the recommendation for widespread clinical implementation in xerostomia treatment.

7.8.4 Drugs

Patients with radiation-induced xerostomia may have a minimal response (mainly with an increase in resting saliva) to systemic sialagogues, but small increases in saliva may translate into subjective patient willingness [93]. Several therapeutic drugs have been used to treat xerostomia. Pilocarpine and cevimeline are two systemic FDA-approved sialagogues for the treatment of xerostomia [94]. In respect to radiation-induced xerostomia, pilocarpine is the sole sialagogue agent approved by the FDA [20].

Administration: 5 mg 3 times/day, titration up to 10 mg 3 times/day may be considered for patients that have not responded adequately (not to exceed 30 mg/day). After the administration of pilocarpine, salivary output increases rapidly, usually reaching a maximum within 1 h and returning to baseline at 3 h [31, 95–99].

Systemic administration of pilocarpine is associated with an increased risk of side effects (e.g., mild-to-moderate sweating, flushing, headache, nausea, urinary frequency, lacrimation, and rhinitis). Local administration of pilocarpine (topical pilocarpine) may be an appropriate alternative with a potential decrease in systemic side effects. Local stimulation of saliva more rapidly increases salivary production rather than systemic pilocarpine. Overall improvement of xerostomia seems to not be significantly different between oral and systemic pilocarpine. Further investigation is required to provide more definitive conclusions [72].

Cevimeline is a newer muscarinic agonist that has been studied in patients with xerostomia after radiation therapy for head and neck cancers with positive results [100]. Cevimeline (45 mg three times daily) studied in patients with radiation-induced xerostomia showed that 69% experienced an adverse effect, mostly mild to moderate in severity. The most frequent side effects were sweating, dyspepsia, nausea, and diarrhea [101]. There is no significant difference in overall increase of production of saliva with cevimeline or pilocarpine [102]. Based on animal studies, the central nervous system effects are more common with cevimeline than pilocarpine, but no clear difference was observed in respiratory and cardiovascular effects. Clinical trials are ongoing to determine the efficacy and side effects of both cevimeline and pilocarpine in the secretion of saliva for patients with xerostomia.

Bromhexine, a mucolytic agent, has been used by patients with radiation-induced xerostomia. However, pilocarpine has demonstrated superiority to bromhexine in improving xerostomia symptoms [103].

Bethanechol, with prolonged muscarinic and nicotinic-cholinergic activity, has also been used in patients with radiation-induced xerostomia with no significant difference in efficacy and side effects rather than pilocarpine [93, 104].

Malva sylvestris L and *Alcea digitata* (Boiss) Alef have been used as herbal remedies in traditional Persian medicine for their antitussive, antioxidant, expectorant, anti-inflammatory, antimicrobial, and laxative therapeutic effects [105]. They are useful for lubrication of the throat and lungs and in respiratory disorders. Studies have shown these plants to be immune stimulants that are useful in mucositis. This compound was compared with artificial saliva in a randomized trial [106].The herbal group showed a significant difference between the grade of dry mouth before and after intervention, but no change was observed for the grade of dry mouth in the artificial saliva group.

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Loss of Taste

8

A reduction in taste sensitivity (hypogeusia), an absence of taste sensation (ageusia), or a distortion of normal taste (dysgeusia) are well-known side effects in cancer patients that receive radiation therapy to the head and neck areas, and it has been reported in up to 100% of these patients [1–4]. The generic term of dysgeusia more commonly refers to any alteration in taste perception [5].

8.1 Mechanism

There are four basic taste intensities: salt, sour, bitter, and sweet. In addition to these basic tastes, a novel taste that is referred to by the Japanese word umami, which means delicious, has come to be recognized as a "fifth taste." Umami is found in a diversity of foods (e.g., fish, meat, milk, tomato, and some vegetables), which is created by the combination of glutamate with 5′-ribonucleotides [6–8].

The sense of taste is mediated by the taste buds. They are found in the oral cavity, primarily on the dorsum of the tongue in the circumvallate, fungiform, and foliate papillae and on the palate, lips, cheeks, pharynx, epiglottis, larynx, and upper part of the esophagus [9, 10].

The taste bud is an onion-shaped epithelial structure with 50–100 tightly packed cells, including taste receptor cells, supporting cells, and basal cells [11]. Each taste bud opens to the epithelial surface via a small opening called the taste pore [12].

Taste receptor cells have short microvilli, which emerge from the apical region (outer end) of the taste cells to a taste pit below the inner taste pore. Taste receptor sites are located on membranes of microvilli. The microvilli are the portion of the cell that is exposed to the oral cavity [13]. The pore enables molecules and ions taken into the mouth to reach the receptor cells inside [12].

The taste receptor cells contact with afferent sensory neurons at their inner ends.

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A nutritional, or trophic, interaction (i.e., one cell emits a substance that a second cell needs to grow) between the nerve fibers and taste buds exists. The interruption of the nerve fibers results in the disappearance of the taste buds [12].

Each of the different tastes is perceived in an individual taste bud with specific receptor cells that respond to distinct chemical stimuli. Furthermore, the diverse sites of the tongue surface are sensitive to a distinctive taste. For example, the anterior (tip) tongue is most sensitive to sweet or salty stimuli, while the lateral edges and posterior aspects of the tongue respond predominantly to sour and bitter substances, respectively. However, there is a concept that each taste cell and each site of the tongue surface may be sensitive to more than one taste [14], and all four different tastes can be perceived in all areas where taste buds are located [15].

The mechanisms involved in taste loss during radiation therapy are complex. Functional loss of taste buds occurs following radiation therapy due to the taste-cell microvilli or their membrane injuries. Membrane damage causes interruption of the synaptic contacts, impairment of taste bud trophic function of the nerve, and taste bud atrophy [12, 16, 17]. Functional loss of taste buds precedes cell loss, which occurs later following radiation therapy [12, 18].

Direct mucosal and epithelial cell damage of radiation results in desquamation of the surface epithelium. The epithelial thickness is increased, the taste pores are covered, and the total area of the taste pores is also decreased [14, 19].

8.2 Timing

Alteration in taste is an early and rapid response to radiation and often precedes mucositis [20]. Increase in taste thresholds begins from treatment with as little as 2–4 Gy and rises exponentially with a cumulative dose of about 30 Gy (3 weeks), 2 Gy per fraction. Rate of loss then slows down as the patients' acuity approaches nil at >30 Gy [18]. Subjective complaints of taste also are started early after the beginning of the treatment, approximately 1–2 weeks after the initiation of treatment [3, 21, 22]. Perception of bitter and acid flavors is more susceptible to impairment than perception of salty and sweet flavors [23].

The clinical impairment pattern of umami taste has been investigated. Umami taste declines during the third week after the start of radiation therapy and improves after treatment conclusion [6, 24].

Loss of taste is usually transient. Patients often experience normal or near-normal levels of taste within 1 year after radiation therapy, although it can sometimes take a few years, or even a residual reduction in taste acuity may permanently remain [20, 23, 25–32].

A permanent loss of taste can occur at the dose of about 60 Gy [28, 33]. However, due to the adaptation of the patient to the sensory loss, a minority of patients complain of taste loss [11].

8.3 Risk Factors

The proportion of the tongue that is contained within the radiation fields and the irradiation dose delivered has a significant correlation with the taste loss [12, 15, 34, 35]. A correlation between the tongue area that irradiated and the taste sensation mostly lost has been observed [18].

The presence of saliva plays a significant role in the normal taste acuity by transport and solubility of gustatory stimulants and protection of the taste receptors. Saliva production may be reduced by radiation therapy and affects taste sensitivity [11, 13, 20, 26, 34, 36].

Other factors that have some influence on the incidence or severity of loss of taste caused by irradiation are malnutrition or specific vitamin or mineral deficiencies like zinc deficiency [37] and destruction of the taste buds by the tumor [9]. Head and neck surgery by a reduction of the total number of taste buds or around the chorda tympani or glossopharyngeal nerve [2, 38] can also affect acuity of taste. Chemotherapy drugs [12, 39], oral mucositis [40], and infection [5] can exacerbate radiation-induced dysgeusia. Systemic disease like liver and kidney disorders, endocrine disorders, diabetes mellitus, psychological disorders, and central nervous system disorders, smoking, and alcoholism can also decrease taste [2, 41].

8.4 Symptoms

Irradiation of the taste buds typically leads to partial (hypogeusia) or complete (ageusia) inability to taste or an abnormal taste (dysgeusia) [18]. These taste abnormalities lead to the decreased hedonic aspect of food intake, decreased appetite, and reduced nutrient intake, leading to anorexia and weight loss [2, 18, 21, 37, 42].

The nature of the taste sensation modifies the volume and character of saliva. Loss of taste and failure of adequate salivation may explain difficulty in swallowing reported by some affected patients [37].

8.5 Diagnosis

Loss of taste may be a subjective response, which patients may indicate a presence of any subjective awareness of it.

Subjective awareness of taste loss and the presence of any distress caused by taste impairment (e.g., decreased enjoyment of food and appetite) can be assessed by using taste questionnaires [2], and objective detection of taste loss and recognition of the thresholds for each taste quality can be determined in each patient by the increase in threshold above the upper limit of normal and the lowest concentration of a solute that the patient distinguishes as different from water, respectively [9, 21, 43–45].

Table 8.1 CTCAE. V4.03 for taste

	Definition
Grade 1	Altered taste but no change in diet
Grade 2	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste

8.6 Scoring

Common Toxicity Criteria for Adverse Effect (CTCAE), version 4.03, scoring system has just defined two grades for taste abnormalities [46] (Table 8.1).

8.7 Prevention

Prevention of taste loss can be obtained by the modification of radiation therapy including normal tissue shielding or placement of these tissues outside the radiation field by means of field arrangements or repositioning prostheses (e.g., tongue depressor) [47] or advanced radiation therapy technique (e.g., intensity-modulated radiotherapy) [48, 49].

The effect of amifostine on taste loss is inconclusive. The administration of amifostine may produce reductions in the severity of taste loss. However, the total frequency of dysgeusia can be more frequent among patients given amifostine than among controls [50, 51]. Further studies are needed in this regard.

All actions for prevention of xerostomia may be effective in reducing radiation-induced taste loss [48] (see Chap. 7).

There are a lack of data and controversial results on the effects of zinc supplementation in prevention/treatment of taste alterations in cancer patients (see Sect. 8.8).

8.8 Management

In most instances, taste gradually returns to normal or near-normal levels within 1 year after radiation therapy. Because of this transitory aspect, there is usually no need for special treatment [25], but clinicians can help their patients by offering counseling to improve their distressing symptoms. Dietary counseling and patient education can result in improved nutrition status and prevent weight loss.

Patients should be instructed about methods to increase taste, including preparing foods with strong taste and creating an attractive presentation of foods. Patients should be encouraged to avoid the use of tobacco and/or alcohol and management of hyposalivation and poor oral hygiene.

The assessment for taste alterations includes a thorough dietary history, eating habits, current appetite and desire for food, and weight measuring for comparison to baseline [52]. Nutritional counseling estimates each patient's current nutritional status, calculates increase in energy and protein requirements to

overcome deficits, and provides the therapeutic diet based on personal eating patterns and preferences, which are adjusted to the individual's needs. Dietary counseling corrects patient diets with appropriate manipulation and consideration of foods with appealing taste, color, and smell; oral nutritional supplements may be added to the diet only in patients with inadequate food intake for more than 5 days or BMI < 18.5 [53, 54].

In the setting of significant weight loss (>2% loss in 1 week), patients should be evaluated by a registered dietician [52]. A dietician provides an individualized and intensive dietary counseling based on standard nutrition protocol, the Medical Nutrition Therapy (Cancer/Radiation Oncology) protocol of the American Dietetic Association (ADA), to maintain and/or improve a patient's energy and protein intake [55–57].

In general, 25–30 kilocalories per kilogram body weight per day and 1–1.5 g of protein per kilogram per day are appropriate for those of normal weight. For those that are hypermetabolic or need to gain weight, 30–35 kilocalories per kilogram or greater and 1.5–2.5 g of protein per kilogram may be necessary [58].

Energy requirements can be calculated using various formulas, which give more precise estimates of resting energy expenditure. The Harris-Benedict equation is practical and reliable for measuring metabolic rate. The equation is used to estimate the basal energy expenditure (BEE) based on weight, height, and age [59]. To estimate daily energy requirements, basal requirements were multiplied by a 1.5 activity factor [60].

In men:

$$BEE = 66.5 + (13.75 \times kg) + (5.003 \times cm) - (6.775 \times age).$$

In women:

$$BEE = 655.1 + (9.563 \times kg) + (1.850 \times cm) - (4.676 \times age)$$

Zinc plays an important role in taste perception [61]. Zinc deficiency results in structural changes in taste buds cells, changes in the number and size profile of taste buds, and decrease in related nerve sensitivity [62, 63]. The effects of zinc supplementation in prevention/treatment of taste alterations in cancer patients are controversial. Some have found that the administration of zinc sulfate (45–50 mg orally three times daily) in cancer patients that had received radiation therapy to the head and neck region is an effective approach both in the prevention and correction of taste abnormalities [2, 3, 21, 64]. However, some found no statistically significant effect of zinc sulfate therapy on radiation-induced taste alterations [65]. Further studies with longer follow-ups and with different doses of zinc supplementation are needed in this regard.

The use of megestrol acetate (480 mg/day) during radiation therapy may be effective in the improvement of loss of taste, appetite, and reversing malnutrition. Further evaluation of its effect on radiation-related complications and patient outcomes is needed [66].

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Laryngeal Edema

9

Laryngeal edema occurs when the larynx is included in the treatment field and may impact the voice. Laryngeal edema accompanied by hoarseness is a common acute side effect in radiation therapy of laryngeal and hypopharyngeal carcinoma and whenever the neck is irradiated [1]; however, no studies have reported its incidence as an acute side effect. It has been estimated that 15–59% of patients with head and neck cancers develop grade 2 or higher laryngeal edema within 2 years after radiation therapy [2].

9.1 Mechanism

Ionizing radiation generates free radicals and produces various reactive oxygen species (ROS) that result in DNA damage and changes in the local microenvironment through the activation of cytokine cascades and influx of inflammatory cells [3, 4]. These processes cause inflammation, hyperemia, and erythema of the laryngeal mucosa.

The larynx has many mixed serous-mucinous-type glands that lubricate the larynx with thin mucus secretion and is essential to phonation. Radiation induces atrophic changes in laryngeal glands leading to changes in the quantity and quality of secretions, poor lubrication of the vocal folds, and subsequent voice problems [5, 6].

9.2 Timing

Laryngeal edema may occur during the first 2–3 weeks of radiation therapy and continue to increase to the end of treatment. Recovery begins 3 weeks after treatment completion and may require 6–12 months to subside.

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9.3 Risk Factors

The incidence of acute laryngeal edema increases with total dose, field size, tumor stage, smoking, supraglottic laryngectomy, and chemotherapy administration [2, 7–10].

9.4 Symptoms

In the acute phase, laryngeal edema related to radiation causes phonation dysfunction (Fig. 9.1) that rarely is severe enough to cause serious dysphagia or compromise the airway [11]. Dryness of the laryngeal mucosa makes it sensitive to develop referral ear or throat pain.

9.5 Scoring

RTOG Common Toxicity Criteria for acute laryngeal side effects is based on clinical criteria and has been shown in Table 9.1 [12].

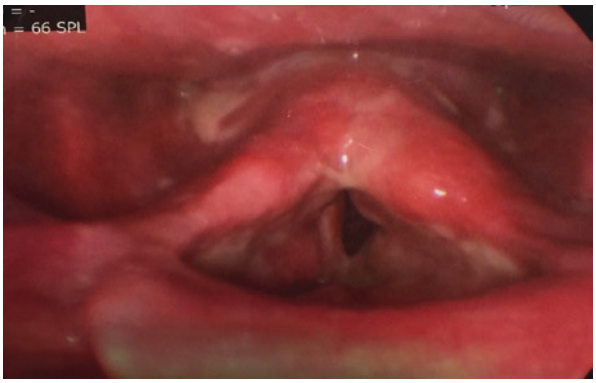

Fig. 9.1 Laryngeal edema 7 days after full dose 3DCRT for recurrent true vocal cord SCC

Table 9.1 RTOG common toxicity criteria for laryngeal toxicity criteria

	Definition
Grade 0	No change over baseline
Grade 1	Mild or intermittent hoarseness/cough not requiring antitussive/erythema of mucosa
Grade 2	Persistent hoarseness but able to vocalize/referred ear pain, sore throat, patchy fibrinous exudate, or mild arytenoid edema not requiring narcotic/cough requiring antitussive
Grade 3	Whispered speech, throat pain, or referred ear pain requiring narcotic/confluent fibrinous exudate, marked arytenoid edema
Grade 4	Marked dyspnea, stridor, or hemoptysis with tracheostomy or intubation necessary

9.6 Prevention

The volume of larynx in radiation field receiving high dose of radiation should be kept as low as possible to minimize the edema. The investigators suggested that the percentage of laryngeal volume receiving more than 50 Gy and the mean laryngeal dose should be ideally constrained to less than 27% and 43.5 Gy, respectively [13]. Smoking and alcohol consumption will increase the risk of severe laryngeal edema, and patients should be encouraged to cease smoking and alcohol consumption.

9.7 Management

Exacerbating behavior such as smoking and alcohol consumption should be discontinued. Voice rest is recommended to all patients.

In patients with moderate to severe or persistent laryngeal edema unresponsive to conservative treatment methods, treatment with steroids and occasionally antibiotics may be necessary [2].

In patients with severe laryngeal edema leading to compromise airway, temporary tracheostomy should be considered [10].

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Radiation Pneumonitis

10

Radiation pneumonitis (RP), the acute manifestation of radiation-induced lung injury, is one of the main dose-limiting toxicities among patients receiving thoracic radiation therapy. It has been reported to occur in 13–37% of patients receiving definitive external beam radiation therapy for lung cancer [1]. Radiation pneumonitis development following radiation therapy for other cancers actually depends on lung volume, which is included in various irradiated volumes and dose parameters. Some other factors such as smoking, background lung disease, or combined modality treatments are also important risk factors for radiation-induced pneumonitis. The incidence of radiation pneumonitis is lower in Hodgkin disease (3%) [2] and breast cancer patients (1%) [3] compared with lung cancer patients. Diagnosis and indications for therapeutic intervention are in a major controversy that will be discussed in the next few paragraphs.

10.1 Mechanism

The first changes that are induced by radiation are increased vascular permeability and exudation of proteinaceous material in the alveolar space [4]. Capillary endothelial cells are very sensitive to ionizing radiation, and their damages are manifested by detachment of cells from their basement membrane, which is followed by blood flow turbulence and thrombosis formation. Following endothelial cell injury, capillary permeation increases, fibrin-rich exudate leaks into the alveoli, and a hyaline membrane is formed, which impairs gas exchange. Ionizing radiation can also damage alveolar cells, which are manifested by depletion of type I pneumocytes and hyperplasia of type II pneumocytes, in the context of the alveolar epithelium regeneration process [5]. On the other hand, type II pneumocytes are also known to be damaged by radiation therapy, resulting in release of surfactant into the alveolar space and detachment of the pneumocytes from their basement membrane [6]. Later, the alveolar exudate clears, fibroblasts migrate into the alveolar walls, and the alveolar septa are thickened.

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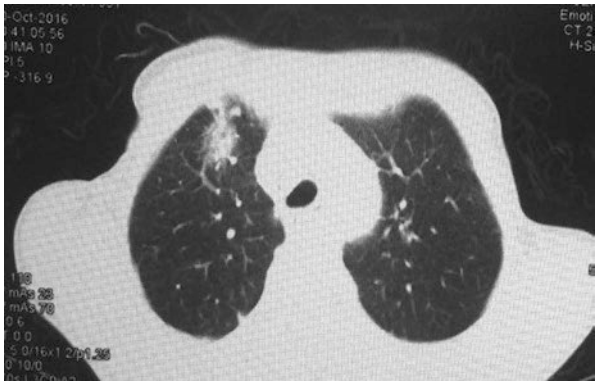

Fig. 10.1 Radiation-induced pneumonitis in a patient with bulky Hodgkin disease at 2 months after mediastinal radiation therapy

10.2 Timing

Although pathologic changes in lung tissue occur in the initial 24–48 h after radiation, those changes are undetectable both clinically and radiologically. Radiation pneumonitis occurs typically within 6 months after a course of radiation with a peak onset at 1–3 months but may be seen as early as 1 week, especially in patients receiving high total dose [7]. In some cases, no symptoms are present, and the diagnosis is made by imaging alone (Fig. 10.1).

10.3 Risk Factors

10.3.1 Volume and Dose Parameters

Nontarget lung dose and irradiated volume should be lowered as much as possible. Different dose and volume parameters (mean lung dose, V5, V10, D15, V20, etc.) have been evaluated to predict probabilities of radiation pneumonitis, but no definitive dose and volume limits have been accepted as an optimal limit or parameter. The percentage of lung volume exceeding 20 Gy (V20), percentage of lung volume exceeding 30 Gy (V30), and mean lung dose (MLD) are the most predictive parameters evaluated in several studies. It has been shown that the risk of radiation pneumonitis is less than 20% when MLD is less than 20 Gy [8], less than 8% when V20 is 31% or lower [9], and less than 6% when V30 is 18% or lower [10]. These parameters are in respect of both lung volumes; however, a significant correlation was recently found between these parameters when ipsilateral lung volume is considered and radiation pneumonitis rates have been reported [11].

10.3.2 Fractionation Schedule

The use of twice-daily fractionation has been shown to reduce the risk of radiation pneumonitis compared with administration of the same total daily dose as a single fraction [12].

Most dose volume parameters have been studied in areas of conventional fractionated radiotherapy of lung cancer, and with increasing use of stereotactic body radiation therapy with a large fraction size for lung cancer, well-designed studies are needed to define new parameters for radiation-induced pneumonitis.

10.3.3 Chemotherapy/Hormone Therapy

The administration of chemotherapy concurrently or before radiation therapy appears to increase the risk of radiation pneumonitis compared to radiation therapy alone [13, 14]. It has been shown that concurrent taxane-based chemoradiation therapy increases the radiation pneumonitis risk more than cisplatin-based chemotherapy regimens [15]. Additionally, chemotherapy administration with certain agents (e.g., taxanes, anthracyclines, gemcitabine, etoposide, or vinorelbine), following radiation therapy, can cause radiation-induced pneumonitis that is an inflammatory reaction within the previously treated radiation field [16].

There is conflicting data about correlation of hormonal therapy including tamoxifen and aromatase inhibitors and radiation pneumonitis risk. Some found no positive effect of these agents on radiation pneumonitis risk; however, some reported a significant correlation [14, 17, 18].

10.3.4 Smoking

There are also different results reported about smoking effects on radiation pneumonitis risks [10, 19]. Surprisingly, some have shown that active smokers had a lower frequency of radiation-induced pneumonitis.

10.3.5 Other Factors

Adequate data are not available for some variables including age, sex, tumor site, Karnofsky performance status, comorbid lung disease, pulmonary function test, and biological markers such as plasma cytokine levels and transforming growth factor beta 1 (TGF-β1).

10.4 Symptoms

Dyspnea is the most common symptom, occurring in as many as 90% of cases. Dyspnea is frequently accompanied by a dry cough, which occurs in about 50–60% of cases. A low-grade fever is occasionally reported, which can be more pronounced in severe cases. Some patients complain of chest pain with breathing, malaise, and weight loss. Sensation of chest fullness usually develops 1–3 months after completion of radiation therapy.

10.5 Diagnosis

Radiation pneumonitis is a diagnosis of exclusion. Physical findings are usually not prominent, but occasionally moist crackles, a pleural friction rub, or evidence of consolidation may be present. There is no specific lab test to predict the development of RP. Some patients might have a mild polymorphonuclear leukocytosis, elevated ESR, serum LDH, and CRP, but these findings are nonspecific.

Chest X-ray and computed tomography are the most commonly used modalities for assessing RP. The most common finding on CXR in early phases is perivascular haziness, which often progresses to patchy alveolar-filling densities [20]. Pleural effusions or atelectases are also sometimes seen. These changes occur shortly after completion of radiation therapy, peak at 6 months, and become stable by 12 months. One of the most characteristic features of radiation pneumonitis and fibrosis is that these radiologic changes are confined to the outlines of the field of radiation (Fig. 10.1). However, the use of oblique beam angles and the development of newer irradiation techniques such as three-dimensional conformal radiation therapy and intensity-modulated radiation therapy can result in an unusual distribution of these findings [21].

Computed tomography (CT) is more sensitive than chest radiograph in detecting subtle lung injury following radiation treatment but is not required to make the diagnosis of RP. The most common findings on CT are ground-glass opacities in the acute phase and traction bronchiectasis, volume loss, and consolidation in the late phase [22].

Pulmonary function test (PFT) in patients with radiation pneumonitis usually reveals a reduction in lung volumes and diffusing capacity of the lungs for carbon monoxide (DLCO), but these changes are nonspecific [23].

Bronchoalveolar lavage and transbronchial biopsy are not useful in the diagnosis of radiation pneumonitis but can be used to exclude other causes of pulmonary infiltrates.

10.6 Scoring

Common Toxicity Criteria for Adverse Effect (CTCAE) (Table 10.1) [24] and Radiation Therapy Oncology Group (RTOG) (Table 10.2) [25] have defined five grades for radiation-induced pneumonitis with some differences.

Table 10.1 CTCAE v4.03 for pneumonitis

Grade 1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
Grade 2	Symptomatic; medical intervention indicated; limiting instrumental activity of daily life (ADL)
Grade 3	Severe symptoms; limiting self-care ADL; oxygen indicated
Grade 4	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)
Grade 5	Death

Table 10.2 RTOG grading for radiation-induced pneumonitis

Grade 1	Asymptomatic or mild symptoms (dry cough); slight radiographic changes
Grade 2	Moderate symptomatic fibrosis or pneumonitis (severe cough); low-grade fever; patchy radiographic changes
Grade 3	Severe symptomatic fibrosis or pneumonitis; dense radiographic changes
Grade 4	Severe respiratory insufficiency; continuous oxygen therapy/assisted ventilation
Grade 5	Death

10.7 Prevention

There are several agents reported to have preventive effects on radiation pneumonitis.

Amifostine is a thio-organic prodrug that is believed to scavenge harmful free radicals and shield normal tissues from the toxic effects of chemotherapy and radiotherapy. It is approved for use as a cytoprotectant, relieving problems of dry mouth (xerostomia) in patients with head and neck cancers undergoing radiotherapy. Multiple randomized trials have assessed the role of amifostine in preventing RP, with contradicting results [26–28]. The largest study was performed by the Radiation Therapy Oncology Group; the incidence of grade ≥3 pulmonary toxicity was not statistically different between patients receiving amifostine and those that did not [29]. Current guidelines do not advise amifostine for prevention of radiation-induced pneumonitis.

Pentoxifylline is an immunomodulator that is used primarily for patients with intermittent claudication. In one small randomized study, the use of pentoxifylline (400 mg three times daily) resulted in a noticeable reduction in grade 2 or 3 pulmonary toxicity (20% vs. 50%), as well as the measured diffusing capacity after 6 months of follow-up [30].

Captopril is an angiotensin-converting enzyme inhibitor that has been shown to reduce the development of radiation-induced fibrosis in rats [31], although no such protective effect has been demonstrated in humans.

There is lack of high-quality evidence on the management of radiation pneumonitis, and no prospective controlled studies have evaluated the efficacy of current therapies for radiation pneumonitis in humans.

Treatment for acute radiation pneumonitis is mainly supportive. Patients that are asymptomatic with radiographic abnormalities do not require treatment, and patients with mild symptoms are generally treated with cough suppressants including codeine and benzonatate.

Despite the lack of solid evidence, oral corticosteroids have been the mainstay of therapy for radiation pneumonitis, often with dramatic results. Although the starting dose and tapering schedule are undefined, based upon clinical experience, dose of approximately 60 mg or 1 mg/kg of prednisone is given for 1–2 weeks, followed by a slow taper over 4–8 weeks. The dose is tapered slowly because some patients experience a rebound pneumonitis with a faster tapering schedule. In some cases, symptoms and radiographic abnormalities tend to recur with discontinuation of therapy, and patients might need to maintain a low-dose prednisone schedule for more extended periods of time [32].

When prednisone dose exceeds 20 mg a day for greater than a month, prophylaxis for Pneumocystis pneumonia is recommended. It is worthy to mention that established fibrosis is irreversible and will not improve with glucocorticoid therapy.

Azathioprine and cyclosporine may be considered in patients that do not tolerate glucocorticoids or that have disease refractory to glucocorticoid therapy based on small case series [33].

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Pericarditis

11

Pericarditis is the most common acute presentation of radiation-induced heart disease. The incidence of pericarditis in patients with irradiation for different targets within and around the thorax is estimated around 5% on average and even less; indeed, with improvement in radiation treatment techniques, its incidence has decreased from 25% to 2% [1–3]. Clinically significant pericarditis is observed just in a limited percentage of patients after mediastinal radiation therapy [4].

Radiation-induced pericarditis most commonly occurs in Hodgkin and non-Hodgkin lymphoma and breast cancer patients [2]. It's probably related to the incidence and survival of these malignancies. The risk of pericarditis is higher when the target volume for radiation therapy is in the mediastinum, and it will decrease with increasing distance between the target volume and the mediastinum and heart. Site and size of mediastinal lymphadenopathies are important factors in the incidence of pericarditis for lymphoma patients. With effective chemotherapies, target volumes and pericarditis rate have decreased in patients with lymphoma after mediastinal radiation. Besides these, pericardial manifestations have also decreased in lymphoma as well as breast cancer by radiation technique improvements [5, 6].

Pericardial effusion has been reported in one third of esophageal cancer patients following definitive chemoradiotherapy [7]. Wei et al. showed that pericardial effusion will develop in 73% of patients if more than 40% of the heart volume receives more than 30 Gy of radiation [8].

Although acute pericarditis is usually self-limited, the crucial point is the progression into chronic pericarditis and/or constrictive pericarditis in 10–20% of patients. However, chronic pericarditis may occur in some patients without any history of acute pericarditis [9, 10].

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11.1 Mechanism

After mediastinal radiation therapy, there are some acute and chronic effects on the heart. Pericarditis is a dominant side effect among acute radiation-induced cardiac complications, and the essential factors in the acute phase are tumor necrosis factor (TNF) and interleukins (IL) (i.e., IL-1, IL-6, and IL-8) that cause neutrophil infiltration within the tissues [11]. Delayed radiation-induced pericarditis is generally the consequence of an acute inflammatory process followed by fibrin deposition. Injury is primarily initiated by microvascular damage, which causes episodic ischemia. The next stage is neovascularization with abnormal and permeable vessels, which lead to worsening of ischemia and fibrosis progression [12].

Fibrous thickening, pericardial adhesion, and effusion are pathological findings after radiation to the heart and pericardium. These findings are secondary to microvascular and mesothelial cell injuries. On the other hand, plasminogen activator decreases, and considering its usual role in fibrinolysis, high levels of fibrin are expected [13]. Pericardial effusions have high amounts of protein and fibrous adhesions and are also accompanied by high levels of serum inflammatory markers during the acute phase [10]. Mononuclear cells infiltrate the pericardium 2 days after radiation exposure in optic microscopy. Other histologic findings are bizarre fibroblasts (with abnormalities in the nucleus and cytoplasm), sclerosis of small vessels, and fat necrosis of the pericardium [14].

11.2 Timing

Acute pericarditis is uncommon, and it can present during or after radiation. It is usually detected by subclinical pericardial effusion [11, 15]. The presentation of pericarditis during the first year after radiation therapy, known as acute pericarditis, is usually a self-limited and benign disease [16], although it has been named radiation-induced late pericardial disease by others [15].

11.3 Risk Factors

Several factors increase the risk of radiation-induced pericarditis, but the percentage of irradiated pericardial volume and mean pericardial dose are the most important [3]. The percentage of cardiac silhouette irradiated could be as an index of pericardial volume. Other risk factors are the nature of radiation source and duration and fractionation of radiotherapy. There are some studies that determine the predictive parameters for radiation-induced pericarditis and pericardial effusion. Daily dose per fraction more than 3 Gy has been shown to correlate with pericardial complications [17, 18]. Mean dose to pericardium is a predictive factor for pericardium injury, and 27 Gy is a proper cutoff point in most studies [6, 8, 17].

11.4 Symptoms

As a common manifestation of acute pericarditis, patients present with chest pain, which usually includes characteristic pleuritic chest pain. This is accompanied by low-grade fever, dyspnea, and tachycardia [10]. Pericardial friction rub can be found on physical examination [13].

Patient signs and symptoms could be categorized into six groups depending on time elapsed from radiation exposure [19]:

1. Acute pericarditis during radiation therapy, which presents with nonspecific symptoms including chest pain, fever, and EKG abnormalities.
2. Late pericardial disease, which occurs during the first year of radiation therapy [15].
3. Delayed pericarditis, which presents from months to years after radiation treatment (most references include the second half of late pericarditis timing). In this group of patients, the most common presentation is dyspnea; some others develop pericardial pain. Tamponade may also rarely occur in these patients [2]. Pulsus paradoxus (decreasing peripheral arterial pulse paradoxically during inspiration) is characteristic of tamponade [4].
4. Pancarditis, which manifests as heart failure, is difficult to control. It is a rare compilation of heart radiation during the acute phase because of the delayed effect of radiation on the myocardium.
5. Constrictive pericarditis usually develops several years after radiation [15]. Kussmaul's sign (jugular venous distention on inspiration) is seen in constrictive pericarditis and less frequently in cardiac tamponade [4].
6. Asymptomatic pericardial effusion, which is an incidental finding by echocardiography.

11.5 Diagnosis

Considering positional pleuritic chest pain as a hallmark feature of acute pericarditis, an EKG is usually the first diagnostic study obtained. Diffuse ST elevation with or without PR interval depression could be seen, but sinus tachycardia may also be seen [15].

Chest radiography in patients with pericardial effusion may show cardiomegaly.

It is easy to detect loculated or generalized pericardial effusion by echocardiography by measurement of echo-free pericardial space. There are other signs on echocardiography (e.g., collapsing right atrium and ventricle in end-diastolic and diastolic phase, respectively) [4].

By using computed tomography (CT), pericardial effusion and thickening are showed and, in comparison to MRI, is more sensitive to detect constrictive pericarditis [4]. Normal thickness of the pericardium is less than 2 mm on CT scan and

MRI. Thickened pericardium could be enhanced after IV contrast injection, which is a sign of inflammation and is used to differentiate between constrictive pericarditis and restrictive cardiomyopathy [20].

Serum inflammation markers, such as white blood cell count, erythrocyte sedimentation rate (ESR), and serum C-reactive protein (CRP), are usually elevated; serum cardiac troponin I levels may be minimally elevated. CRP as an acute phase protein can help in treatment monitoring in most patients that have elevated levels of this marker [21].

In patients with malignant tumors and pericardial effusion, at least three differential diagnoses should be considered. One of them is heart failure with pericardial effusion, which is secondary to low cardiac output. Another is malignant pericardial effusion, which could be accompanied by other metastases and is confirmed by positive cytological examination for malignant cells. A third differential diagnosis is hypothyroidism, which may be due to radiation to the thyroid [2].

11.6 Scoring

Pericardial effusions and pericarditis have been scored in Common Toxicity Criteria for Adverse Effect (CTCAE v4.03) as shown in Tables 11.1 and 11.2 [22]. In this scoring system, no grade 1 has been described for pericardial effusion, and pericardial tamponade is grade 4 at least.

RTOG scoring also classifies acute radiation heart effect into four grades (Table 11.3) [23].

Table 11.1 CTCAE, version 4.03, scoring system for pericardial effusion

	Definition
Grade 1	
Grade 2	Asymptomatic effusion size, small to moderate
Grade 3	Effusion with physiologic consequences
Grade 4	Life-threatening consequences with urgent intervention indicated
Grade 5	Death

Table 11.2 CTCAE, version 4.03, scoring system for pericarditis

	Definition
Grade 1	Asymptomatic, EKG, or physical findings (e.g., friction rub) consistent with pericarditis
Grade 2	Symptomatic pericarditis (e.g., chest pain)
Grade 3	Pericarditis with physiologic consequences (e.g., pericardial constriction)
Grade 4	Life-threatening consequences with urgent intervention indicated
Grade 5	Death

Table 11.3 RTOG/EORTC radiation toxicity grading for cardiac toxicity

	Definition
Grade 1	Asymptomatic but objective evidence of EKG changes or pericardial abnormalities without evidence of other heart disease
Grade 2	Symptomatic with EKG changes and radiological findings of congestive heart failure or pericardial disease/no specific treatment required
Grade 3	Congestive heart failure, angina pectoris, and pericardial disease responding to therapy
Grade 4	Congestive heart failure, angina pectoris, pericardial disease, and arrhythmias not responsive to nonsurgical measures

11.7 Prevention

Multidisciplinary approach should be considered in the management of patients with cancer. In some centers, cancer patients are evaluated by cardiologists with respect to cardio-oncology history taking, physical exam, chest X-ray, and electrocardiography with strain and are routine, and based on these patients, risk is determined [1].

Lowering the pericardium-irradiated volume and dose without any defect in treatment is an essential step in reducing the probability of pericardial side effect development. Emami et al. published data on normal tissue tolerance by using TD 5/5 and TD 50/5 parameters. TD 5/5 is the dose associated with a 5% risk of complications within 5 years, and TD 50/5 is the same but in 50% of patients. Considering pericarditis as the end point, TD 5/5 in conventional radiation therapy is about 60 Gy for one third of the heart, 45 Gy for two third, and 40 Gy for the whole volume of the heart. For TD 50/5, these doses, respectively, change to 70, 55, and 50 Gy. In patients with predicted long survival, TD 5/5 is determined much lower (25 Gy), corresponding to other cardiac complications [15].

If we consider two-dimensional planning of radiation therapy, by radiation to more than 50% of the heart, we will observe an increase in the risk of pericarditis. In three-dimensional planning, the volume of pericardium that receives ≥30 Gy (V30) is a main determinant. In order to prevent pericardial injury, it is recommended to keep mean pericardial dose less than 26 Gy or pericardial V30 less than 46% [24] although there are some challenges in defining heart volume [9].

Radiation-induced pericarditis occurs in less than 15% of patients by keeping the mean dose to the pericardium less than 26 Gy [11].

Using modern techniques in radiation therapy, cardiac exposure has changed. In breast cancer, irradiation on deep inspiration (unassisted or by using some devices for active breathing control) and even breast board significantly reduces dose and volume of irradiated heart. Another factor for decreasing heart dose is using electron beam irradiation, especially for internal mammary nodes if indicated [13]. Breast radiation therapy in prone position is also helpful to reduce irradiated pericardium volume [5].

By using IMRT, more heart volume is irradiated by lower dose, but high-dose volume decreases [1].

11.8 Treatment

Acute pericarditis is usually self-limited, and half of the patients do not require any intervention.

Patients are usually treated in the outpatient setting unless they have high-risk features such as fever (temperature >38°C), leukocytosis, a large pericardial effusion (echo-free space >20 mm), cardiac tamponade, acute trauma, immunosuppressed state, concurrent oral anticoagulation, failure of nonsteroidal anti-inflammatory drug (NSAID) therapy, elevated troponin levels, and recurrent or incessant pericarditis, all of which mandate hospitalization [21].

Forty percent of symptomatic patients are good responders to the rest and NSAIDs.

Colchicine is suggested for patients with acute pericarditis as an adjunct to NSAID therapy and sometimes is sufficient in relieving pain in patients with acute pericarditis and preventing recurrences [11, 16, 21].

The important practical point is that this presentation is not a reason for radiation therapy discontinuation, although a reduction in dose should be considered [11, 19].

Different NSAIDs with various dosages are recommended:

Aspirin: 500–1000 mg every 6–8 h (range 1.5–4 g/day).
Ibuprofen: 600 mg every 8 h (range 1200–2400 mg/day).
Indomethacin: 25–50 mg every 8 h; start at the lower end of dosing range and titrate upward to avoid headaches and dizziness.
Naproxen: 500–1000 mg every 12 h may be used if tolerated and clinically indicated and may increase to 1500 mg daily for a limited time (<6 months).

For geriatric patients, the lowest dose and frequency are recommended.

In patients with renal impairment and a creatinine clearance (CrCl) ≤30 mL/min, NSAIDs are not recommended. Aspirin is slightly safer than others in these patients, but it's not recommended if CrCl is less than 10 mL/min.

NSAIDs should be also used with caution in hepatic impairment. Prophylaxis with proton pump inhibitors is also an important treatment to implement.

Uncomplicated treatment continues for 1–2 weeks. However, symptom and CRP normalization should be considered [25].

Pericardiocentesis may be performed for patients with persistent symptomatic pericardial effusions. The approach to recurrent pericardial effusions would be surgical by either a pericardial window or pericardiectomy [2].

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Esophagitis

12

Radiation esophagitis is an acute dose-limiting toxicity associated with radiation treatment that decreases the patient's compliance for treatment completion.

Incidence of acute esophagitis has been reported in about 29% of patients with thoracic radiation therapy [1] and in 93% of patients undergoing thoracic chemoradiation therapy [2]. Severe esophagitis requiring nutritional support or radiation therapy breaks has been reported in 1–4% and 22–45% of patients that are treated with radiation therapy alone or chemoradiation therapy, respectively [3, 4].

12.1 Mechanism

The luminal side of the normal esophagus is lined by mucosa. The mucosal layer contains epithelium, lamina propria, and muscularis mucosae. The esophageal epithelium is a nonkeratinizing, stratified, squamous epithelium and contains rapidly dividing cells situated in the basal layer [5].

Radiation therapy affects the basal epithelial cell layer and limits the proliferation rate of the basal epithelium, causing mucosal thinning, ulceration, and initiation of the inflammatory response resulting in congestion, edema, or erosion [6].

12.2 Timing

Acute radiation esophagitis begins on the second to third week after initiation of irradiation (20–30 Gy). Generally, with single daily fractions of 2.0 Gy radiation therapy, grade 1 esophagitis first appears in the second week, and grade 2 and higher

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esophagitis begins during the third week of the treatment. As treatment continues, the rate of symptomatic esophagitis increases. Patients experience grade 3 esophagitis during the fifth week of treatment [7].

Esophagitis often recovers within 4–6 weeks of treatment completion. The duration of symptomatic esophagitis is longer for intensive treatment (hyperfractionated radiation therapy or concurrent chemotherapy) [8].

12.3 Risk Factors

The most significant predictors of acute esophagitis are concurrent chemotherapy [9–13] and hyperfractionated radiation therapy, especially in the setting of concurrent chemotherapy with hyperfractionated radiation therapy [12, 14–17].

It has been reported that the use of chemotherapy concurrent with irradiation is associated with a nearly 12-fold greater risk of developing severe esophagitis [18]. Sequential chemotherapy seems not to significantly increase the risk of esophageal radiation injury [3, 4, 14, 19]. The incidence of esophagitis in chemoradiotherapy is also dependent on chemotherapeutic agents used. Cisplatin-based regimens are generally associated with a lower rate of significant esophagitis compared with protocols using paclitaxel [7, 20, 21].

Radiation regimen schedule is an important factor in the rate of esophagitis. Higher radiotherapy dose per fraction [22] and increasing the number of daily fractions induce more severe esophagitis.

A number of studies evaluating dosimetric factors have shown that percentage of esophagus volume receiving 10–60 Gy [7, 9, 23–30], mean esophageal dose [24, 25, 31], the maximal esophageal dose [11, 13, 32], esophageal surface area receiving 55 Gy [9], and higher length of the esophagus in the radiation treatment field (with some contradictory results) [6, 15, 33] are all associated with acute esophagitis.

A recent systematic literature review concluded that the valuable dosimetric parameters predicting the occurrence of acute radiation esophagitis in patients receiving concurrent chemoradiotherapy include maximum esophageal dose, mean esophageal dose, and esophageal volume receiving 20, 30, 50, and 55 Gy [34].

It is well known that with the similar dosimetric parameter consideration, only a small proportion of patients develop esophageal toxicity. Individual variability in radiosensitivity should be further investigated to identify genetic variations modulating the development of radiation esophagitis. In this regard, it has been observed that patients with the transforming growth factor-beta1 (TGFβ1)509 CC genotype [35], heat shock protein beta-1 (HSPB1) CC genotype [36], and single nucleotide polymorphisms (SNPs) in inflammation-related genes including three PTGS2

(COX2) variants rs20417, rs5275, and rs689470 [37] are at greater risk for developing radiation esophagitis.

It has been shown that one of the most significant risk factors for dysphagia during chemoradiation is the maximal grade of neutropenia. Indeed, the nadir of the neutrophil granulocytes during treatment is strongly associated with developing and severity of esophagitis [17, 38]. Patients with higher pretreatment platelet counts and lower hemoglobin levels as a preexisting systemic inflammatory state have greater rates of radiation esophagitis [39].

There are individual case reports demonstrated that patients with human immunodeficiency virus (HIV) may experience unusually severe radiation-induced esophagitis [40, 41].

Other factors proposed to be associated with acute esophagitis include the pretreatment body mass index [30].

Patient's gender, age, performance status, and histology are not significantly correlated with esophageal toxicity [6, 42].

12.4 Symptoms

Radiation-induced esophagitis presents with retrosternal or substernal burning sensation, pain, odynophagia, dysphagia, and anorexia. Weight loss could occur and nutritional support may be needed. Rarely, with severe esophagitis, patients may develop obstruction, perforation, or fistulas.

12.5 Scoring

The Radiation Therapy Oncology Group (RTOG) and European Organization for Research and Treatment of Cancer (EORTC) have defined four grades for radiation-induced esophagitis (Table 12.1) [43].

Table 12.1 RTOG/EORTC esophagitis grading

	Definition
Grade 1	Mild dysphagia or odynophagia (may require topical anesthetic or nonnarcotic analgesics and a soft diet)
Grade 2	Moderate dysphagia or odynophagia (may require narcotic analgesics and puree or liquid diet)
Grade 3	Severe dysphagia or odynophagia with dehydration or weight loss >15% from pretreatment baseline requiring NG feeding tube, IV fluids, or hyperalimentation
Grade 4	Complete obstruction, ulceration, perforation, and fistulization

12.6 Diagnosis

Radiation esophagitis is a clinical diagnosis in patients with dysphagia or odynophagia, that is, receiving thoracic irradiation. In patients with symptoms progressing after completion of radiation therapy despite the optimal treatment, endoscopy should be considered to establish the diagnosis and rule out other etiologies like infectious or fungal esophagitis.

12.7 Prevention

Prediction of esophagitis severity allows prevention of esophagitis with treatment deintensification and other measurements. Various dose constraints are proposed to predict radiation-induced esophageal toxicity that should be considered in treatment planning.

It has been shown that esophagitis as an inflammatory process results in elevated ^{18}F-fluordeoxyglucose (FDG) positron emission tomography (PET) uptake in the postradiation period, which correlates to the treatment planning dose distribution. Using posttreatment ^{18}F-FDG-PET scans allows for developing a quantitative biological model to improve the accuracy of esophagitis prediction based on planned dose [44]. Also an increase in FDG uptake during radiation therapy from pre-radiation may predict radiation esophagitis and provides the opportunity for treatment planning modification [45].

Advances in the radiation delivery with intensity-modulated radiation therapy (IMRT) may allow radiation oncologists to prescribe higher doses to tumors with normal structures being spared such and keep the incidence of radiation-induced esophagitis quite low when the esophagus is not the treatment target [11, 46].

Amifostine is an organic thiophosphate compound that offers selectively normal cell protection from radiation-induced damage and also chemotherapeutic agents by scavenging oxygen-derived free radicals [47]. It seems that amifostine administration can protect the normal esophageal mucosa from radiation-induced injury and delay the onset of esophagitis and reduce its severity and incidence.

In a multicenter trial of 146 patients with advanced lung cancer treated with a daily fractionated radiation therapy to a total of 55–60 Gy with or without daily amifostine administration reported that the incidence of esophagitis grade 2 or higher was 42% in the radiation therapy alone group versus 4% in the group with amifostine administration during 4 weeks of treatment [48].

Amifostine administration seems to reduce severe esophagitis and analgesic intake in patients undergoing chemoradiation therapy without compromising treatment outcomes [20, 49–51]. Further studies are required to determine the optimal amifostine combination with therapeutic strategy.

Glutamine supplement administration during thoracic irradiation appears to postpone onset and reduce the severity of radiation esophagitis [52]. Further investigation of this agent may therefore be warranted.

Oral sucralfate solution has been compared with placebo as prophylaxis in a prospective trial and didn't prevent esophagitis development, although it had significant gastrointestinal side effects [53].

12.8 Management

Acute esophagitis is managed symptomatically.

Dietary modification that should be recommended to all patients are:

Eat frequent meals with small pieces throughout the day instead of three large meals.
Eat soft foods that are warm or at room temperature.
Drink enough liquids.
Avoid hot or spicy foods, acidic foods, and hard and crunchy foods.
Avoid alcohol and tobacco.

Pain is managed with topical analgesics (e.g., viscous lidocaine), NSAIDs, or narcotics.

If patients complain of reflux symptoms, antacids, proton-pump inhibitors, or H2 receptor blockers could be effective.

In the setting of severe dysphagia or odynophagia with significant weight loss, short breaks from radiation therapy have been proposed. Feeding tube or parenteral nutrition may be needed for these patients (see Sect. 6.7.5).

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Radiation Gastritis

13

Radiation-induced gastritis occurs in about 30–50% of patients undergoing radiation therapy whenever the stomach is included in radiation fields as the main target or an organ at risk (e.g., during radiation treatment of lymphoma, neoplasm of lower esophagus, stomach, biliary tract, pancreas, testis, or including of thoracic stomach in radiation field after gastric pull-up procedure) [1–4].

13.1 Mechanism

The gastric walls consist of mucosa, submucosa, muscularis, and serosal layers. The gastric mucosa is the mucous membrane layer of the stomach, which contains the glands and gastric pits. The epithelium of the mucosa has gastric pits (mucous membrane invaginations), and lamina propria contains gastric glands. There are three types of gastric glands including cardiac glands, which produce lysozyme and mucus, fundic and body glands, which produce hydrochloric acid, pepsin, and intrinsic factor, and lipase and pyloric glands, which produce lysozyme and mucin [3].

Each fundic gland is divided into three segments: the isthmus, neck, and the gland proper. The main epithelial cell types of the gland are the precursor mucous neck cells, the parietal or oxyntic cell (secrete hydrochloric acid), and the chief or zymogen cell (produce pepsinogen). The surface of the mucous membrane is covered by a single layer of mucous cells. These cells secrete mucous and develop the gastric mucosal barrier [5].

Several types of endocrine cells are found throughout the gastric mucosa and produce histamine, gastrin, and somatostatin.

Irradiation produces marked mucosal and submucosal edema, ulcerative or erosive lesions, and changes in the quality and quantity of gastric secretion [2, 6].

The early changes in gastric mucosa include mucosal and submucosal edema and inflammation, endothelial cell swelling, and capillary dilation, which could be demonstrated after 20–25 Gy of radiation dose [3].

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With higher doses, more severe injuries could occur including gastric erosion or ulcer. The gastric ulcer developing rate increases with doses above 45 Gy (25–30% of patients) [6]. The degree of gastric acidity in radiation ulcers is variable. In some cases, the acidity is somewhat increased; in the majority, it is normal or even subnormal [1].

Radiation initially reduces surface mucous cells due to their relatively short lifespan. So breakdown of the mucosal barrier, net flux of electrolytes into the gastric lumen, and back diffusion of the luminal hydrogen ion occur. Mucosal histamine is released and stimulates secretion directly from the glandular cells, and a transient increase in acid secretion during the radiation therapy exhibits [5, 7].

After the initial gastric hypersecretion, secondary mucosal damage occurs and induces coagulation necrosis of glandular cells, denudation of glandular epithelium, cystic dilatation of the glands and a reduction of the gastric glands, and the volume of gastric secretion and its content change [7]. A significant reduction in the secretion of hydrochloric acid and pepsin develops. The degree and duration of the radiation effect on gastric secretion depends on radiation dose and biologic differences [8]. It has been reported that gastric acidity may suppress or significantly decrease with doses of less than 20 Gy [9]. Some have suggested that chief cells are more radiosensitive than are parietal cells, and gastric acidity suppression occurs first due to damage to the pepsinogen-secreting chief cells; parietal cells are more resistant and are depressed later [10]. Another reason for gastric acidity suppression is reduction in gastric histamine content [11]. A decrease in gastric acidity occurs within 4–6 weeks after completion of radiation therapy [12].

13.2 Risk Factors

The severity and frequency of the acute gastric lesions depends upon the total dose received by the stomach. The radiosensitivity of stomach seems to be higher than the small and large intestine [13]. The gastric ulcer never occurs following less than 45 Gy. When the radiation dose exceeds 45 Gy, the incidence of gastric ulcer is 25–30%. With higher radiation dose, the more serious the gastric damage may occur, leading to penetration hemorrhage and perforation [6]. The risk of perforated ulcers increases with doses greater than 60 Gy [14].

Chemotherapy may also increase the gastric injuries induced by radiation.

With the exception of unknown factors of individual sensitivity, there is no report of patient factor effects on frequency of the acute gastric lesions [9, 11, 14].

13.3 Timing

Gastritis will develop in the second and third week of irradiation (20–30 Gy) [15]. Patients may experience nausea, epigastric distress, and uncommon vomiting, and these symptoms last for only a few hours after each fraction of radiation. Later with higher radiation doses, more severe symptoms including epigastric pain may occur.

Symptoms usually resolve 1–2 weeks after completion of the radiation therapy. Occasionally the mild epigastric distress or dyspepsia persists for months or even years [3].

Ulceration occurs from 1 month to 6 years with an average of 5 months after radiation therapy [6].

13.4 Symptoms

Epigastric distress, anorexia, nausea, vomiting, and pain are more common symptoms of radiation gastritis [10, 16].

Acute ulceration may be seen shortly after radiation therapy. The usual symptoms of ulcer are present, but food and antacids usually afford no relief [6]. The most severe symptoms appear when ulcers are accompanied by perforation or obstruction, usually 1–2 months after irradiation [14].

13.5 Diagnosis

The diagnosis of radiation-induced gastritis is based on clinical suspicions in patients that received radiation therapy with stomach at least partially within the treatment portal. Barium meal examination and gastroscopy may be needed in some patients with severe symptoms or no response to initial treatment.

Radiation therapy in patients that have a tumor in the stomach like lymphoma may lead to destruction of deeply infiltrating tumor and result in gastric perforation. These conditions should be considered in distinction of radiation-induced injuries [17].

13.6 Prevention

There is no prophylactic agent available to mitigate the acute gastric injury. Reducing the irradiated volume specially for higher doses (when the stomach is not the treatment target) is the best way to minimize gastritis probability, and new techniques could help radiation oncologists in this way, although there are no definitive data about dose-volume constraints for partial volume irradiation of stomach. Doses of 45 Gy to the whole stomach are associated with ulceration in 5–7% of patients [18].

13.7 Management

Medical management with antacids (H2 blockers and proton pump inhibitors) is usually used in patients with gastritis symptoms.

Nausea and vomiting are treated with antiemetics. The management of radiation-induced nausea and vomiting is discussed separately (see Chap. 20).

Radiation-induced gastric ulceration less often responds to the medical management than the usual peptic ulcer disease, and due to higher frequency of complications in these ulcers, early surgical intervention is indicated in patients who do not respond to medical management [17].

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Radiation-Induced Liver Disease

14

Radiation-induced liver disease (RILD), historically called radiation hepatitis, has been reported in 6–66% of patients whose livers are irradiated based on radiation dose, exposed liver volume, and baseline liver function [1, 2]. Abnormalities in laboratory liver function tests may be found on routine evaluation of patients when RILD is mild, but in severe cases, liver dysfunction may affect the treatment course and eventually threaten patient's lives.

14.1 Mechanism

The histologic hallmark associated with RILD is veno-occlusive disease (VOD). It is characterized by severe congestion of the sinusoids in the central portion of the lobules with sparing of the larger veins [3].

The pathogenesis of RILD is unknown. Some possible mechanisms have been proposed. It has been postulated that radiation damages the sinusoidal and vascular endothelial cells, which initiates the coagulation cascade leading to fibrin accumulation and clot formation. The fibrin network is replaced by collagen deposition and resulted in progressive fibrous obliteration of small hepatic veins [3, 4]. Irradiation induces the dysregulated activation of myofibroblastic hepatic stellate cells, increasing some cytokine expression like TGF-β1 (transforming growth factor) and hedgehog (Hh) pathway activation (an essential pathway for tissue remodeling), [5] which are important in the development of fibrosis following exposure to radiation. GDC-0449 targets the Hh signaling pathway, and this suppressed Hh signaling may lead to reduced proliferation of progenitor cells and fibrosis in irradiated livers [5].

Finally, hepatic vessels occlude, resulting in vascular leakage, distorted dilated sinusoids, and congestion with erythrocyte trapping, causing central zone hypoxia and hepatocyte death [6].

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A cluster of NF-κB-regulated cytokines, including TNF-α, are induced by radiation and increase the sensitivity of hepatocytes to radiation and induce cell apoptosis [7].

After 4 months, an effective circulatory system within the liver has apparently developed leading to the disappearance of congestion and restoration of hepatic cells [8].

14.2 Risk Factors

Radiation treatment factors have a strong correlation with RILD. Mean radiation dose to the liver and volume of liver exposed to more than 30–35 Gy of radiation are directly related to RILD occurrence [9, 10]. Emami et al. found a <5% rate of RILD when the mean whole liver dose is ≤30 Gy in patients without preexisting liver disease or primary liver cancer. The mean liver dose should be ≤28 Gy in those patients with preexisting liver disease [11]. However, part of the liver could be safely treated with higher doses with acceptable complications. Dose per fraction is an important factor in the development of RILD. Altered fractionated radiation therapy with large fraction sizes decreases liver tolerance [12].

The combination of chemotherapy agents with whole liver radiation seems to decrease liver tolerance [13, 14], although studies with use of fluoropyrimidines [15–18] or partial liver radiation have not been reported to significantly increase hepatic complications of combination therapy.

Baseline liver function is an important factor in predicting the occurrence of RILD. Cirrhotic livers have a lower tolerance for radiation. It has been reported that patients with worse Child-Pugh Class (B vs. A) and chronic hepatitis B carriers are at higher risk for developing RILD [9].

Patients with elevated liver enzymes during radiation therapy are at risk for developing RILD [12]. Such liver abnormalities are presumably related to self-limited liver inflammation [19].

Primary hepatobiliary carcinoma is associated with a significantly increased risk of RILD compared with a diagnosis of liver metastases; this could be related to preexisting cirrhosis or hepatitis in patients with hepatobiliary carcinoma [20].

Other factors associated with elevated risk of RILD include prior transcatheter arterial chemoembolization (TACE) [12], portal vein tumor thrombosis [21], tumor stage [12], and male gender [22].

14.3 Timing

RILD typically occurs 4–8 weeks after the completion of treatment, although it has been described as early as 2 weeks and as late as 7 months afterward [3].

14.4 Symptoms

In severe cases, patients develop rapid weight gain, increase in abdominal girth, liver enlargement, right upper quadrant discomfort, ascites, and jaundice [3]. Physical examination reveals ascites and hepatomegaly in moderate to severe cases, although in mild cases these signs are detectable only by ultrasound or abdominal CT scan [3]. Serum alkaline phosphatase is predominantly elevated (more than twice the upper limit of normal or baseline value), with minimal increase or relatively normal levels of aspartate transaminase (AST) and alanine (ALT) (in the range of twofold above normal) and bilirubin [3, 19].

In patients with intrahepatic cancer, decreases in alkaline phosphatase because of tumor response may mask alkaline phosphatase elevation resulting from RILD [23].

In patients with hepatitis and cirrhosis, nonclassic-type RILD with markedly elevated serum transaminases (>5 times the upper limit of normal) rather than elevated alkaline phosphatase or a decline in liver function (measured by a worsening of Child-Pugh score by 2 or more) and jaundice can occur, indicating severe radiation-induced injury to hepatocytes [19].

Reactivation of viral hepatitis has been reported in patient who underwent radiation therapy; however, its role in RILD pathogenesis is unclear. Elevation of transaminases rather than commonly reported increase in alkaline phosphatase is seen in hepatitis B carrier patients and implies radiation injury of hepatocytes rather than bile ducts [9]. It has been suggested that the risk of hepatitis B reactivation is decreased with prophylactic antiretroviral therapy [19].

Thrombocytopenia has been reported in children studies related to congestion of the portal bed and spleen and secondary hypersplenism [24].

14.5 Scoring

Most research uses the Cancer Therapy Evaluation Program and Common Terminology Criteria for Adverse Events (CTCAE) to evaluate liver toxicity after radiation therapy [25]. The Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0, defines grades 2, 3, 4, and 5 liver dysfunction as jaundice, asterixis, encephalopathy or coma, and death, respectively. No grade 1 has been defined (Table 14.1) [19].

Table 14.1 CTCAE.V3 liver dysfunction criteria

	Definition
Grade 1	–
Grade 2	Jaundice
Grade 3	Asterixis
Grade 4	Encephalopathy
Grade 5	Death

14.6 Diagnosis

Patients with typical clinical picture and history of recent radiation therapy to the liver included in treatment field have a high likelihood of having RILD.

In patients with intrahepatic cancer, progression of cancer should be ruled out before making the diagnosis of RILD. An abdominal CT scan and paracentesis of the ascites are typically performed as part of the differential diagnosis [3].

Ascitic fluid obtained by paracentesis is consistent with a transudate feature (the serum to ascites albumin gradient > 1.1) with cytological negativity for malignant cells [26].

Irradiated liver in RILD appears hypodense on non-contrast CT scans. This CT finding is limited to radiation fields with well-defined linear margins in partial liver irradiation with more than 45 Gy [27, 28]. The sharp margins of demarcation are not seen in patients that received radiation through several non-axial and non-coplanar portals. The hypodensity of the irradiated area most likely correlates with changes of increased water content resulting from either edema or vascular congestion [29]. On contrast CT scans, irradiated areas are hypodense on the portal venous phase due to hypoperfusion and decreased contrast inflow and become hyperdense on the delayed phase obtained 4 min after contrast injection due to decreased venous drainage and stasis [30]. Maximal effect of radiation on liver appearance in CT images is seen 2–3 months after completion of therapy and is reversible with return to normal appearance [29].

The area of low density on CT has high signal intensity on the T2-weighted and low intensity signal on the T1-weighted sequence of MR images [27, 31]. Contrast enhancement of the irradiated area could be seen in MRI imaging after administration of gadopentetate dimeglumine (Gd-DTPA) due to the increased capillary permeability and chondroitin sulfate iron colloid (CSIC) due to hypofunction of the reticuloendothelial system [32].

The irradiation area has diminished function that could be detected with radioisotope scan as the area with decreased radioisotope uptake. These functional scans have the potential to quantify hepatocyte function to distinguish functional regions of hepatocytes from nonfunctional zones. Technetium (^{99m}Tc) sulfur colloid (SC) single-photon emission computed tomography is used as the imaging modality to image liver function, and there is a correlation between differential SC uptake and varying doses of radiation delivered [33].

14.7 Prevention

Prevention of RILD is paramount due to its fatal potential.

Three-dimensional treatment planning offers the potential to determine the liver radiation dose and volume, RILD risk could be estimated using dose-volume histogram (DVH) parameters, and modification of treatment planning should be considered if the RILD risk is high enough.

With the availability of intensity-modulated radiotherapy (IMRT), stereotactic body radiotherapy (SBRT), and image guidance in radiation treatment planning, radiation can be delivered with better liver sparing.

Coa et al. recently have proposed a risk assessment strategy for radiation treatment planning and re-optimization of the plan during therapy for intrahepatic radiation treatment. The assessment of the patient's individual portal vein perfusion dose-response function during therapy and prediction of residual liver function after radiation could allow for detection of patients at high risk for RILD and adjusting the treatment plan [34, 35].

Amifostine is an organic thiophosphate that was developed to selectively protect normal tissues against the toxicities of chemotherapy and radiation. Systemically or regionally, administration of amifostine effectively protects hepatocytes from ionizing radiation damage without compromising the antitumor effect of radiation. Feng et al. observed that the use of amifostine allows for a higher dose of whole liver radiation to be safely administered and suggested the possibility of using amifostine in combination with radiation for patients with focal liver disease undergoing intensity-modulated radiotherapy or stereotactic body radiotherapy for focal liver tumors [36, 37].

Theoretically, anticoagulation may exert a protective effect against acute radiation injury by precluding fibrin clot formation and decrease the hepatic congestion. Lightdale et al. observed a possible protective effect for warfarin in a small group of Hodgkin's disease patients [23]. Further evaluation of anticoagulation effect on radiation hepatic injury appears warranted.

Exposure to ionizing radiation enhances production of reactive oxygen species and decreases the levels of antioxidant in liver, whereas selenium and vitamin E supplementation can modulate the changes in liver. Gençel et al. observed significant decrease in oxidative stress in rat liver with selenium and vitamin E administration prior to a 7 Gy exposure relative to control animals [38].

14.8 Management

Treatment of RILD is primarily supportive and involves the use of diuretics for fluid retention, analgesics for pain, paracentesis for tense ascites, correction of coagulopathy, and steroids to prevent hepatic congestion [39].

Most patients respond to this therapy and symptoms resolve over the subsequent l–2 months. A minority of patients develop jaundice, progressive ascites refractory to paracentesis and diuretics, and coagulopathy. Although some of these patients may recover, a substantial fraction will die due to liver failure [3].

Thrombolysis using tissue plasminogen activator (rh-tPA) and heparin remains unproven for the treatment of hepatic veno-occlusive disease due to the risk of bleeding in VOD and suboptimal response rate [40]. tPA/heparin should not be used in patients with severe VOD with multi-organ failure (MOF) and should be given early in VOD [39].

Defibrotide is a deoxyribonucleic acid derivative extracted from mammalian organs that has fibrinolytic and antithrombotic properties. It has been successfully used to treat severe hepatic VOD with MOF in patients that have received cytotoxic chemotherapy in preparation for bone marrow transplantation. Investigations of defibrotide appear warranted in the setting of radiation-induced liver injury [39, 41, 42].

Radiation will cause hepatocyte injury and suppress liver regeneration. Hematopoietic stem cells or hepatocytes with normal regenerative potential would proliferate and repopulate the liver; it has been suggested that G-CSF-mobilized $CD34^+$ hematopoietic stem cells (HSCs) [43] and transplanted hepatocytes [44] may ameliorate radiation-induced damage to liver by the ability to engraft into liver tissue and generate hepatocytes.

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Enteritis

15

Acute gastrointestinal complications occur in 80% of patients in pelvic radiation therapy [1]. The small intestine appears to be more sensitive to radiation than the colon and rectum [2] and is also more frequently exposed incidentally to radiation during treatment of adjacent organs because of its situation within the peritoneal cavity.

Different intestinal side effects were reported in the Postoperative Radiation Therapy in Endometrial Cancer (PORTEC-2) Trial, which found that among 214 women with endometrial cancer treated with external beam radiation therapy after total abdominal hysterectomy and oophorectomy, the rates of diarrhea, fecal leakage, rectal blood loss, and bloating were all increased from the baseline at a rate of 22%, 5.3%, 1.8%, and 0.7% at 1–4 weeks after the end of treatment, respectively [3].

In a study of 107 patients with gynecologic, urologic, or gastrointestinal cancer within the pelvis that underwent radiation therapy, acute gastrointestinal toxicities were assessed during the treatment. It was found that 94% of patients developed altered bowel habits, 80% loose stool, 74% frequency, 65% difficult gas, 60% pain, more than 48% distress, 44% tenesmus, more than 40% restrictions in daily activity, 39% urgency, 37% fecal incontinence, and 40% required antidiarrheal medication [4].

15.1 Mechanism

The intestinal epithelium is a single layer of columnar cells containing crypt-villous units. Villous protrusions increase the absorptive surface of the small intestine. Undifferentiated rapidly proliferating stem cells are in crypts that are dividing and converted to other differentiated cells including enterocytes that migrate to the villous epithelium. The crypt-villous units are substantially degenerated in organization after radiation injury.

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Radiation initially induces mitotic arrest in stem cells. Cryptal surface cell layers become swollen with nuclear shrinkage and degenerative cytoplasmic changes and necrosis occur. Villi become shortened with a decrease in enterocyte cell number and microvilli length and number, leading to absorptive capacity reduction. Acute inflammatory reaction, leukocyte migration (mostly polymorphonuclear leukocytes and eosinophils), increased microvascular permeability, hyperemia, and edema all occur causing tissue damage and mucosal breakdown, and, ultimately, ulceration will develop [2]. Small bowel bacterial overgrowth also may occur during pelvic radiation therapy in some patients and is likely related to gastrointestinal symptoms [5].

Damaged epithelium results in impaired absorption of bile salts, fats, carbohydrates, proteins, and vitamin B12 during radiation therapy [6].

The small bowel motility pattern also changes during radiation therapy. The exact mechanism of this change remains unclear. Some proposed mechanisms are related to alteration in neurotransmitters release, activity and sensitivity, mucosal injury, and change in water and electrolyte absorption or alterations in the function of the smooth muscle cells [7, 8].

15.2 Timing

Symptoms such as cramping and diarrhea usually develop about 1–2 weeks after the start of radiation therapy (5–12 Gy in fractionated radiation therapy) [9, 10], and its peak is reached by the fourth to fifth week [10]. Symptoms gradually decrease in severity within 2–6 weeks after treatment [11, 12], but it could last longer [13].

15.3 Risk Factors

Radiation dose and the volume of small bowel exposed to radiation correlate with incidence and severity of acute enteritis [14, 15]. Small bowel loops are freely moving within the peritoneal cavity, and defining exact dose-volume parameters that are consistent during the entire course of radiation therapy is not possible. Kavanagh et al. found that severe acute small bowel toxicity could be prevented if the volume of small bowel receiving radiation doses more than 15 Gy is kept under 120 mL (D15 < 120 mL) when bowel loops are contoured as normal tissue volume; however, if the entire peritoneal cavity is considered as small bowel volume, the volume receiving more than 45 Gy should be kept under 195 mL (D45 < 195 mL) [9].

Chemotherapy concomitant with radiation therapy increases the risk of all grades of acute enteritis, especially higher grades [16–18]. A systematic review of acute and late toxicity of concomitant chemoradiation for cervical cancer has reported a twofold increase in acute grade 3 and 4 gastrointestinal toxicities in patients treated with chemoradiation therapy rather than radiation alone [18].

Inflammatory bowel disease (IBD) is a known risk factor for small bowel radiation-induced toxicity, though very scant data are available. Irradiation can

exacerbate IBD symptoms; IBD also increases the acute and late side effects of radiation therapy significantly. Acute gastrointestinal toxicity that results in radiation cessation was more than 20% in a retrospective study of 28 patients with IBD that underwent external beam abdominal or pelvic irradiation, and there was no difference in acute toxicities between patients with Crohn's disease and ulcerative colitis. It is recommended that radiation should be used with caution in these patients [19]. If the radiation therapy is mandatory, efforts should be made to spare the normal gastrointestinal tissue. Selecting appropriate patient position, computed tomography (CT) simulator with contrast agent, and using more conformal treatment techniques are effective to determine gastrointestinal tract irradiated volume and doses.

Previous abdominal surgery is related to risk of acute enteritis due to a larger volume and fixed loop of small bowel within the radiation field [20, 21]. Type of surgery may be important in this view. In a retrospective study of 120 patients with rectal cancer that received chemoradiation, severe radiation-induced diarrhea was more common in patients with sphincter-preserving procedures versus abdominoperineal resection [22].

Low body mass index [14] and female gender [22] have been reported to be associated with radiation-induced enteritis.

Diabetes, hypertension, age, field design, and number (two-, three-, or four-field technique) have not been reported to significantly increase acute toxicity of pelvic radiation [11].

15.4 Symptoms and Diagnosis

Acute injury to small bowel manifests mainly with diarrhea with or without abdominal cramping during or shortly after radiation therapy. The diarrhea secondary to acute radiation enteritis may be associated with decreased absorption of bile salts, vitamin B12, lactose, fat, and more rapid small intestinal transit [13]. Nausea and vomiting, bloating, and loss of appetite may occur [10, 13]. Weight loss can be a secondary finding. Rarely, obstructive symptoms or bowel perforation due to profound acute enteritis may occur and require surgical intervention, especially in patients with underlying inflammatory disease [23].

15.5 Scoring

Radiation Therapy Oncology Group (RTOG) and European Organization for Research and Treatment of Cancer (EORTC) have classified all symptoms related to lower gastrointestinal and pelvic tissue in the single scoring category (Table 15.1) [24].

Diarrhea is the main symptom of radiation-induced enteritis, and Table 15.2 shows the Common Terminology Criteria for Adverse Events (CTCAE) v4, which classifies diarrhea into five grades [25].

Table 15.1 RTOG/EORTC lower gastrointestinal toxicity

	Definition
Grade 1	Increased frequency or change in quality of bowel habits not requiring medication/rectal discomfort not requiring analgesics
Grade 2	Diarrhea requiring parasympatheticolytic drugs (e.g., Lomotil)/mucous discharge not necessitating sanitary pads/rectal or abdominal pain requiring analgesics
Grade 3	Diarrhea requiring parenteral support/severe mucous or bloody discharge necessitating sanitary pads/abdominal distention (flat plate radiograph demonstrates distended bowel loops)
Grade 4	Acute or subacute obstruction, fistula, or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion

Table 15.2 CTCAE v4, diarrhea scoring

	Definition
Grade 1	<4 stools per day over baseline; mild increase in ostomy output compared to baseline
Grade 2	Four to six stools per day over baseline; moderate increase in ostomy output compared to baseline
Grade 3	≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL (activities of daily living)
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

15.6 Prevention

Frequently, different volumes of small bowel have to be included in irradiation portals when abdominal or pelvic tumors are treated with radiation therapy. It should be attempted to reduce the bowel volume in radiation portals or at least exclude from high-dose exposure by various techniques such as patient positioning, use of a belly board, treatment with a full bladder, or using multiple-field techniques [26–28].

Prone positioning on belly-board devices is an appropriate way to spare the small bowel in both 3D-CRT (conformal radiation therapy) and IMRT (intensity modulated radiotherapy) treatment plans [29, 30], although it may increase large bowel volume in the treatment field when the limited arc technique is used [29].

With the introduction of new techniques for radiation delivery like IMRT, small bowel volume with high radiation doses and resultant radiation toxicity have decreased [31–34].

A number of surgical techniques have been applied for bowel exclusion from the radiation field in patients with postoperative pelvic radiation therapy that have used prosthetic materials (e.g., absorbable mesh or saline-filled tissue expanders) or omentum [35–37]. These interventions are not routinely used in many centers [10].

European Society for Medical Oncology (ESMO) clinical practice guideline recommends using systemic sulfasalazine at a dose of 500 mg administered orally twice a day to prevent radiation-induced enteropathy in patients receiving radiation therapy to the pelvis.

There are many preventive options that have been discussed in the literature but cannot be recommended due to insufficient evidence [38–46].

Elemental nutritional formulas, low-lactose, low-fat, and low-fiber diets, and probiotic preparations currently cannot be considered in clinical practice as prophylactic interventions until better determination of their safety and efficacy is made [42].

Amifostine [39] and vitamin E [40] before radiation therapy as well as angiotensin I-converting enzyme inhibitors (ACEi) and 3-hydroxy-methylglutaryl coenzyme A reductase inhibitors (statins) [41] during radiation therapy appear to provide protection against lower gastrointestinal toxicity. These primary promising results need to be established in future studies.

Glutamine is a major source of energy for intestinal epithelial cells and is necessary for cellular proliferation, mucosal cell integrity, and immunological protection of the small bowel [46, 47]. A protective effect of oral glutamine on the small bowel mucosa has been suggested in several studies with contradictory results [43–46]. There is insufficient data to draw a definitive conclusion.

Different cytokines and peptides have been evaluated for protecting the gastrointestinal tract from radiation side effects. The protection effects of insulin-like growth factor-I (IGF-I) on small intestinal mucosal radiation damage have been proposed in animal studies that need further evaluation [48–51]. Several other agents including immunomodulators (e.g., orazipone, interleukin-11) [37, 52], trophic agents like glucagon-like peptide-2 and its dipeptidyl peptidase-4 (DPP-IV) resistant analog teduglutide [53], and other growth factors [54, 55] are proposed to modulate small intestine injury.

A circadian diurnal variation in the number of apoptotic cells in the intestinal crypt has been shown in animal studies to affect radiation-induced enteritis frequency [56, 57]. In a randomized study of 229 patients with cervical carcinoma that were treated with radiation therapy in the morning (8:00–10:00 AM) or evening (6:00–8:00 PM), the overall incidence and severity of diarrhea in patients increased with the morning treatment as compared with the evening [38]. Currently there is no recommendation for this observation in clinical practice.

15.7 Management

The key point in the approach to patients with radiation-induced diarrhea is determining the severity of diarrhea and patient's general condition. Mild to moderate diarrhea without any other significant symptoms and signs can be treated in the outpatient setting with dietary modification, antidiarrheals, and antispasmodics (see below). All of these patients should be examined every 24 h [58].

Patients with severe diarrhea or persistent mild to moderate diarrhea or presence of some cautionary factors such as fever, dehydration, severe abdominal cramping, nausea and vomiting, sepsis, neutropenia, or blood in the stool should be hospitalized to be immediately worked up with complete blood count, stool exam and culture, serum electrolyte and renal function test and aggressive treatment with octreotide, antibiotic therapy, and fluid and electrolyte replacement, as indicated [58].

15.7.1 Dietary Modification

Patients should be encouraged for maintenance of adequate hydration (35 ml/kg/day) and eating small, frequent high-protein food. Chocolate, alcohol, caffeine, sorbitol-containing substances, beans, high osmolar beverage, foods with insoluble fiber including skins of fruits and raw vegetables, whole-grain and multigrain foods, strong spices, and extreme hot/cold food should be avoided. A transient lactose intolerance may occur in up to 45% of patients that respond to the avoidance of milk and milk products (a lactose-restricted diet) [5, 13, 59]. Fat malabsorption also occurs in many cases that provides a rationale for the use of low-fat diet [10]. Soluble fiber may help build stool consistency (e.g., fruits without skins, oat, bran, and barley) [59].

15.7.2 Antidiarrheals

Loperamide is often used as a first-line antidiarrheal agent. If diarrhea does not respond to the use of loperamide after 48 h, octreotide has been shown to be effective [10]. It has been reported that octreotide seems to be more effective than diphenoxylate and atropine in the treatment of radiation-induced diarrhea [60].

Loperamide should be started with an initial dose of 4 mg, then 2 mg after each loose stool or every 4 h; treatment should be continued throughout the duration of radiation therapy with standard dose. If diarrhea does not resolve after 24 h, increasing the dose 2 mg every 2 h should be considered, not to exceed 16 mg/day (8 mg/day for self-medication). These patients should be further assessed with stool analysis and blood work-up. Oral supplementation or intravenous hydration may be indicated in patients based on their general condition, lab test results, and dehydration status. Treatment delay may be required based on physician judgment. If no improvement has been seen within 48 h, loperamide is discontinued and second-line treatment with octereotide 100 μg subcutaneously (SC) three times daily will start [10, 59, 61].

Cholestyramine is a nonabsorbable high molecular resin that binds bile salts irreversibly. Some studies have supported cholestyramine efficacy in the treatment of acute and chronic diarrhea in patients treated with radiation therapy [62, 63].

It has been observed that the inhibition of prostaglandin biosynthesis by sulphasalazine agents may relieve diarrhea caused by other reasons than radiation, and this led to assessing aspirin in radiation-induced diarrhea. There is limited evidence in this regard and no guideline recommended for its use [62, 64, 65].

15.8 Antispasmodics

An anticholinergic antispasmodic agent could alleviate bowel cramping.

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Radiation Cystitis

16

Radiation cystitis is a complication of pelvic radiation therapy that patients encounter when treated for bladder cancer or other pelvic cancers.

There is a wide range of radiation cystitis incidence because of variation in radiation technique, time-dose-volume parameters, the subjective nature of the symptoms, and diversity in collecting and reporting patient data between studies that evaluated radiation cystitis [1].

Up to 70–90% of patients with bladder cancer experience acute genitourinary symptoms during radiation therapy [2–19]. Prostate cancer is the second most common reason for radiation-induced cystitis (41–100%) [20–30], followed by cervical cancer (20–25%) [31–35] and rectal cancer (35–53%) [36, 37].

16.1 Mechanism

The bladder wall has three well-defined layers including the mucosa (urothelium, basement membrane, and lamina propria), the muscularis propria, and the adventitia/serosa.

Human urothelium is considered a transitional epithelial tissue that its cellular differentiation increased from basal cells at basement membrane to surface cells of superficial or apical layer [38]. Surface cells known as umbrella cells are joined to each other with tight cell membrane junctions. The apical surface of umbrella cells is almost entirely covered by rigid plaques (known as the asymmetric unit membrane or AUM) consisting of a group of transmembrane proteins called uroplakins (UP), i.e., UPIa, UPIb, UPII, and UPIII [39–42].

Between these particles, UPIII is a main subunit of urothelial plaques that play a key role in urothelial structure [43].

The urothelium also contains a luminal negatively charged glycosaminoglycan (GAG) called a mucous layer that covers the umbrella cells on top of the apical membrane [44].

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GAGs can be in a non-sulfated form like hyaluronic acid (HA) or a sulfated form like heparan sulfate and heparin, chondroitin sulfate (CS), dermatan sulfate, and keratan sulfate [45].

Tight junctions between umbrella cells, the urothelial plaques, and the glycosaminoglycan (GAG) layer make an efficient barrier against electrolyte and nonelectrolyte urine concentrations in bladder mucosa [46, 47].

Data on underlying mechanisms of acute radiation effects in the urinary bladder are limited. The urothelium barrier of the bladder is affected by radiation. Decrease in the number of umbrella cells [48], loss of the superficial UPIII layer [48], and GAG layer damage [49, 50] have been reported in patients with radiation cystitis. However, due to slow cell turnover rate of bladder epithelium (in the range of 42–350 days) [46, 51], gross tissue breakdown does not occur in early radiation cystitis [48].

Following the urothelium barrier impairment, urine substances infiltrate the bladder wall and produce more injuries by induction of the inflammatory response, mast cell proliferation, activation, degranulation and histamine release, vasodilatation, and also erythematous swelling [48]. Urine ion content, histamine, and other inflammatory substances irritate nerve terminals within the bladder wall [52]. This damaged barrier is also susceptible to secondary infection that could produce more injury [53].

Molecular responses including increased synthesis of intercellular adhesion molecules (ICAM1) [54] and prostaglandin [55] resulted in increased inflammatory reactions and detrusor muscle edema and decreased the bladder capacity. All these events finally produce overactive bladder symptoms.

16.2 Timing

The first symptoms of early radiation effects on the urinary bladder usually occur 4–6 weeks after treatment begins. They are usually mild and transient. It has been found that grade 2 or higher acute bladder toxicity may take an average of 6 weeks (range 2–21 weeks) after the completion of treatment to improve [55, 56], but 5–20% of patients may develop persistent late bladder damage from 6 months to 10 years after treatment [57]. The risk of late bladder damage depends on pre-radiation therapy genitourinary morbidity [4], smoking history (≥1 pack per day) [58], body mass index(>30 kg/m^2) [58], any kind of procedure before radiation therapy [59], and a high dose per fraction [60] that go beyond the scope of this book.

16.3 Risk Factors

The risk of acute bladder damage increases with pre-radiation therapy genitourinary morbidity score [4, 61].

Chemotherapy administered concurrently with radiation therapy has not been shown to significantly increase the risk of acute bladder complications [12, 34, 62],

whereas use of hormonal therapy in prostate cancer has been associated with more acute genitourinary complications [4, 61].

Radiation total dose, maximum bladder dose, and higher volume of bladder exposed to radiation are associated with a higher risk of acute toxicity [29, 63, 64]. The treatment time and dose per fraction have not been reported to be related with acute bladder injury [56, 65].

Other clinical factors such as age, transurethral resection of the prostate before radiation therapy, diabetes mellitus, and smoking have not been reported to be associated with acute bladder toxicity [4, 56], although some of them as previously mentioned are related to late toxicity.

16.4 Symptoms and Diagnosis

Radiation cystitis symptoms during the early reaction phase include frequency, nocturia, urgency, dysuria, and hematuria [66].

Urgency: Sudden and compelling desire to pass urine, which is difficult to defer
Incontinence: Involuntary leakage of urine with the feeling of urgency
Frequency: Voiding more than eight times during the day
Nocturia: Need to wake up more than once at night to void

Bacterial infection may complicate the clinical picture.

Direct examination of the urothelium demonstrates mucosal edema, hyperemia, and inflammation.

16.5 Scoring

Radiation Therapy Oncology Group (RTOG) radiation induced bladder morbidity scoring criteria presented in Table 16.1 [67].

Table 16.1 RTOG bladder morbidity scoring

Grade 1	Frequency of urination or nocturia twice pretreatment habit/dysuria, urgency not requiring medication
Grade 2	Frequency of urination or nocturia that is less frequent than every hour. Dysuria, urgency, and bladder spasm requiring local anesthetic (e.g., Pyridium)
Grade 3	Frequency with urgency and nocturia hourly or more frequency/dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic/gross hematuria with/without clot passage
Grade 4	Hematuria requiring transfusion/acute bladder obstruction not secondary to clot passage, ulceration, or necrosis

16.6 Prevention

Acute symptoms of radiation injury to the bladder are usually self-limited and manageable [68], but prevention of these symptoms is important because they are associated with a marked impact on quality of life and increased occurrence of late toxicities [56].

16.6.1 Bladder Sparing

With the introduction of novel radiation therapy techniques like intensity-modulated radiation therapy (IMRT) or image-guided radiotherapy (IGRT), treatment conformity and normal tissue sparing improve, which minimize the risk of treatment-related toxicity. A significant reduction in acute bladder toxicity in prostate, cervical, and rectal cancer patients treated with this highly conformal treatment versus 3D conformal radiotherapy (3DCRT) has been found [69–73].

Different dose-volume parameters have been proposed to predict acute genitourinary toxicities. For example, maximum dose (Dmax) of bladder in prostate cancer study [29] and volume of bladder receiving 35 Gy or more in rectal cancer [36] have been reported to have significant correlations with the risk of acute bladder toxicity.

16.6.2 Intravesical Instillation

Intravesical GAG instillations including hyaluronic acid [73] and chondroitin sulfate [74] in patients undergoing radiation therapy may reduce overactive bladder symptoms due to covering of the bladder urothelium and preventing of cellular damage by urinary irritants.

The proposed treatment scheme of chondroitin sulfate is weekly instillations of 40 mL of 0.2% solution of chondroitin sulfate during radiation therapy in outpatient clinic after a course of radiation therapy (at least 2 days after chemotherapy). A single-use catheter is usually used to empty the bladder and then fill it with the 40 mL solution. Patients are asked not to void at least 2 h after the instillation [74].

The proposed treatment scheme of intravesical hyaluronic acid prescription is instillations of 40 mg/50 mL intravesical hyaluronic acid. Instillations should begin 1 week before starting radiation therapy and then weekly instillations until 4 weeks after completion of radiation therapy [73].

16.7 Management

Generally, all patients with acute radiation cystitis symptoms should be encouraged to increase fluid intake. It can result in urine irritant dilution and prevent urinary tract infections [75].

Acute radiation cystitis often responds to symptomatic therapy. Anticholinergics have been the mainstay of management for storage symptoms such as frequency. Other treatment options include analgesics like phenazopyridine and alpha-1 blocker [66].

16.7.1 Anticholinergics

Anticholinergic agents block acetylcholine effects at muscarinic receptors and suppress bladder muscle contractions [76]. These agents improve bladder storage and alleviate symptoms.

Oxybutynin and tolterodine are widely used for overactive bladder symptoms. They are nonspecific muscarinic receptor blocker and can cause side effects by acting on other parts of the body (e.g., dry mouth or eyes, constipation, or nausea). Oxybutynin and tolterodine appear to have similar effects on patients' symptom improvement but have a lower risk of withdrawals and dry mouth [76, 77]. Extended release preparations of these drugs are available and are associated with similar efficacy and less risk of dry mouth [76, 77]. Hyoscyamine is another anticholinergic agent that is used to treat cystitis. Data for comparing hyoscyamine to other anticholinergic drugs are lacking.

Oxybutynin chloride:
Immediate release: 5 mg PO two to three times daily; not to exceed 5 mg PO four times daily [78]
Extended release: 5–10 mg PO daily; may be increased by 5 mg/day at weekly intervals, not to exceed 30 mg/day [78]

Tolterodine:
Immediate release: 2 mg PO q12h [79]
Extended release: 2–4 mg PO once daily [79]

Oxybutynin chloride and tolterodine are contraindicated in patients with gastric or urinary obstruction or retention, paralytic ileus, severe ulcerative colitis, and uncontrolled narrow-angle glaucoma [78, 79].

16.7.2 Alpha-1 Blocker

Tamsulosin is an α-1A-specific blocker that induces selective relaxation of the detrusor muscle and improved bladder compliance [80]. Tamsulosin may be the preferred drug to prescribe over other apha-1 blockers like prazosin because of its more acceptable side effect profile and greater patient satisfaction [81].

Usage: 0.4 mg PO once daily, 30 min after same meal each day [82];

it should be used with caution in patients with coronary artery disease [82].

16.7.3 Analgesics

Phenazopyridine is a urinary analgesic that is excreted into the urine and induces a local analgesic effect.

Usage: 100–200 mg PO after meals three times daily [83].

Phenazopyridine is *contraindicated* in hypersensitivity to drug, severe hepatitis, and renal impairment (CrCl <50 mL/min) [83].

16.7.4 Intravesical GAG

Damage to the GAG layer has been found in radiation cystitis mechanism. Intravesical GAG could be bound to the damaged bladder surface and reduce radiation cystitis symptoms. The glycosaminoglycan molecule is not absorbed into the body and doesn't penetrate the bladder and remain on the mucosal surface [84].

Extensive clinical experience has been gained with formulations containing either chondroitin sulfate, hyaluronic acid, or a combination of chondroitin sulfate and hyaluronic acid in late radiation cystitis [50]. More trials are needed to determine the benefit of these agents in acute radiation cystitis.

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Radiation Proctitis

17

The rectum is the most affected organ during pelvic radiation therapy because of its fixed position in the central part of pelvic cavity [1]. Acute radiation proctitis occurs in more than 75% of the patients during pelvic radiation therapy [2]. Treatment interruption due to severe acute radiation proctitis has been reported in 10–20% of patients undergoing pelvic radiation therapy [3, 4].

17.1 Mechanism

Radiation-induced acute colorectal injury involves all mucosal compartments including the epithelium, goblet cells, and lamina propria.

Mitotic arrest occurs in rapidly proliferating epithelial stem cells in mucosal crypts and leads to cell depletion; shortening, narrowing, and loss of crypts; eroded surface of epithelium; and mucosal break down. Inflammatory cell infiltration of the epithelium by neutrophilic and eosinophilic cells occurs. Cryptitis due to neutrophil infiltration through the crypt wall and crypt abscesses by eosinophil accumulation develop. The number of goblet cells is reduced, and glandular atrophy occurs. Significant inflammation of the lamina propria with vessel congestion occurs and leads to hyperemia, edema, and ulceration [5–7].

Inflammatory mediators including eicosanoids are induced in the rectum as an early response to direct radiation injury or secondary to mucosal damage and lead to an increase in inflammatory cell infiltration and activation, capillary permeability, and proctitis severity [8].

17.2 Risk Factors

Several patient-related factors have been reported to be associated with acute radiation proctitis like patients with younger age (less than 60 years) [9], presence of hemorrhoids, diabetes [10], and inflammatory bowel diseases [11] (see Chap. 15).

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Treatment-related factors including multiple radiation dosimetric factors (like the percent volume of rectum receiving more than 30, 35, and 60 Gy, mean rectal dose, the percent volume of anal canal receiving 15 Gy, the rectal length irradiated to doses of 5 Gy, and more) [9, 10, 12] and concurrent chemotherapy are proposed as factors related to probability of acute radiation proctitis [13].

17.3 Timing

Early symptoms can develop during the first or second week of radiation therapy [14] and increase in frequency and severity throughout the radiation therapy course [5]. Symptoms including anorectal dysfunction usually resolve within 2–3 months after treatment completion [4].

17.4 Symptoms

Acute radiation proctitis manifests by increased frequency and urgency of defecation, rectal pain, tenesmus, mucous discharge, and less commonly bleeding and fecal incontinence [3, 15]. Fecal urgency and incontinence are associated with alterations in sphincter function and reduction in the minimum basal and mean squeeze pressures in anorectal manometry [3]. Preexisting patient symptoms or medical conditions may be worsened during radiation therapy. Preexisting hemorrhoids may be inflamed and exacerbate patient symptoms.

Perianal skin reactions occur in patients with this area present in radiation portals that presents with the skin changes that are discussed in Chap. 1.

Edematous mucosa with visible and friable vascular pattern is the most common morphologic change that is seen endoscopically in its maximal score in the acute phase of radiation proctitis [5]. Infrequently, spontaneous hemorrhage or visible ulcers may be seen [14].

17.5 Scoring

Radiation Therapy Oncology Group (RTOG) and European Organization for Research and Treatment of Cancer (EORTC) radiation toxicity grading classify all symptoms related to the lower gastrointestinal tract in a single scoring category (Table 17.1) [16].

Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 classifies proctitis (either acute or chronic) into five grades (Table 17.2) [17]:

Table 17.1 RTOG/EORTC radiation toxicity grading for lower gastrointestinal tract

	Definition
Grade 1	Increased frequency or change in quality of bowel habits not requiring medication/rectal discomfort not requiring analgesics
Grade 2	Diarrhea requiring parasympatholytic drugs (e.g., Lomotil)/mucous discharge not necessitating sanitary pads/rectal or abdominal pain requiring analgesics
Grade 3	Diarrhea requiring parenteral support/severe mucous or bloody discharge necessitating sanitary pads/abdominal distention (flat plate radiograph demonstrates distended bowel loops)
Grade 4	Acute or subacute obstruction, fistula, or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion

Table 17.2 CTCAE v4 proctitis grading

	Definition
Grade 1	Rectal discomfort, intervention not indicated
Grade 2	Symptoms (e.g., rectal discomfort, passing blood or mucus); medical intervention indicated; limiting instrumental ADL
Grade 3	Severe symptoms; fecal urgency or stool incontinence; limiting self-care and ADLs
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

17.6 Prevention

Intensity-modulated radiation therapy (IMRT) can reduce the irradiated volume of the rectum and improve acute radiation-induced proctitis compared to 3D conformal radiation therapy (3DCRT). However, dose-volume parameters do not significantly change in rectal cancer treated with IMRT because of large volume of rectum included in target volume of treatment fields [18–25].

Amifostine can reduce acute radiation-induced proctitis in patients receiving pelvic radiation therapy and is recommended at a dose of ≥340 mg/m^2 intravenously to prevent radiation proctitis [26, 27]. Intrarectal and subcutaneous application of amifostine also have been reported to be effective alternative routes to the intravenous amifostine in protection against acute radiation-induced rectal damage [28–30].

Investigational methods including injecting hyaluronic acid [31, 32] and human collagen [33] in the perirectal fat as well as insertion of an inflatable balloon applicator into the rectum [33, 34] have been proposed in prostate cancer radiation therapy to increase the distance between rectum and prostate and consequently decrease the radiation dose of the anterior rectal wall and proctitis.

Sucralfate is a nonabsorbable basic aluminum salt of sucrose sulfate that has been proposed in prevention of radiation-induced proctitis due to its cytoprotective

properties, angiogenesis and epithelial proliferation improvement, protection of denuded mucosa, and binding bile acids; however, several studies did not find substantial benefit of oral or rectal sucralfate in the reduction of acute radiation proctitis symptoms [35, 36].

Rectal misoprostol, a prostaglandin E1 analog, is another agent that is evaluated as a radioprotection of acute proctitis and provides mixed results in related studies [37, 38]. It has been shown that rectal hyaluronic acid (HA), a major mucopolysaccharide, can reduce epithelial cell death and provide a positive effect on radiation proctitis [39].

Aminosalicylate compounds including prodrugs (sulfasalazine and balsalazide) or active (mesalazine) agents have anti-inflammatory properties due to their ability in inhibition of inflammatory mediators and cells. Balsalazide converts to active form by colonic bacteria after oral administration with minimal systemic absorption and has more efficacy in patients with more distal colon disease due to a high concentration of active drug to the distal compared to other oral agents like mesalazine [40]. It has been suggested that oral balsalazide is able to prevent or reduce symptoms of radiation proctitis in patients undergoing irradiation for prostate cancer [41]. Rectal mesalazine did not show any prophylactic effect on radiation-induced proctitis during radiation therapy for prostatic carcinoma [42].

Nonsystemic glucocorticosteroids, such as beclomethasone dipropionate (BDP), have been suggested as efficient agents for the prevention of radiation-induced proctitis due to their anti-inflammatory properties and safer pharmacokinetic profile compared with systemic agents. Further studies are needed to confirm these primary promising results [43].

Clinical use of prophylactic sucralfate, misoprostol, HA, balsalazide, mesalamine, or BDP for radiation proctitis protection cannot be recommended based on current results.

Butyrate enemas have not shown any benefit given for the prevention of acute radiation proctitis [44].

Fecal calprotectin and lactoferrin are two indicative markers of intestinal inflammation that are released by migrated intestinal neutrophils [45, 46]. It has been shown that the fecal levels of calprotectin and lactoferrin increase during pelvic radiation therapy and are associated with acute radiation proctitis in non-colorectal cancers [47–49]. Increased fecal calprotectin and lactoferrin levels in colorectal cancer limit their use as a diagnostic marker in this setting [50, 51]. Another marker proposed in this regard is human DNA concentration that is excreted in feces due to epithelial cell damage [51]. These factors are promising tools that allow monitoring mucosal damage and treatment modification with the aim of acute injury prevention.

17.7 Management

Acute proctitis can be treated with dietary modification, topical agents, and/or cessation of treatment in severe cases.

Fecal urgency or incontinence can be improved by dietary modification. Patients should be encouraged to have adequate soluble fiber (e.g., fruits without skins, oat, bran, barley) in their regulatory diet. Dietary fiber increases stool bulk and enhances stool consistency and viscosity [52]. Treatment of concomitant diarrhea may help to control fecal urgency or incontinence. All dietary modification and medications that are discussed for treatment of diarrhea in radiation-induced enteritis (Chap. 15) could be effective in improvement of these patients' symptoms. Loperamide is particularly useful in this setting due its positive effect on anal sphincter pressure that helps in stool continence [3, 53, 54].

Current data support using of butyrate as an effective medical treatment of acute radiation proctitis. Butyrate enema (80 mL once per day or enemas of 40 mL twice daily) can improve patient symptoms. Butyrate, a distinct form of short-chain fatty acid, is the major energy source for colonocytes and provides a trophic effect on colonic mucosa by enhancing epithelial cell proliferation and differentiation [55–57].

Other medical agents such as rectal sucralfate and rectal steroid enema plus oral sulfasalazine may be effective [58], but there is no recommendation for using of them in treatment of radiation proctitis. Due to high incidence of radiation proctitis, there is substantial need for further studies to evaluate several topical agents alone or in combination with oral medications as well as in combination with different topical agents with different actions in treatment of radiation proctitis.

Patients with perianal skin reaction should be informed to have good hygiene and use a sitz bath several times daily. Topical agents could be used based on severity of reaction (see Chap. 1).

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Fatigue

18

Radiotherapy-induced fatigue is a common early and long-lasting side effect of radiation therapy, which, despite its negative effect on patient quality of life, is often underestimated and undertreated in daily practice. Patients usually do not consider fatigue as a treatment side effect. Indeed only in one-fourth of cases are any intervention proposed to the patient, and only about 50% of patients discuss it with a physician [1].

Hickok et al. reported on the radiation-induced fatigue incidence in 372 patients with various types of cancer who had received radiation therapy without concurrent chemotherapy. They found that of the 160 patients who did not have any fatigue at the start of irradiation, 70% (112 patients) developed the symptoms during radiation therapy, and approximately 84% of patients that reported fatigue at the initiation of therapy also reported fatigue over the course of treatment [2].

18.1 Mechanism

Several conditions can induce fatigue in cancer patients including anemia, mood, and sleep disorders; patient's symptoms such as pain, nausea and vomiting, diarrhea and electrolyte disturbances, cardiopulmonary, hepatic renal or endocrine dysfunction, infection, and poor nutritional status; and the side effects of drugs such as opioid analgesics or anticonvulsants [3].

Some of these variables may be produced by the tumor itself or treatment with radiation or chemotherapy.

It has been proposed that anemia induced by radiation can cause fatigue due to decreased oxygen delivery to tissue and a negative energy balance [3–5]. Irradiation of different parts of the body may induce fatigue by different mechanisms. Severe diarrhea during pelvic radiation therapy [6], hypothyroidism as a consequence of neck radiation therapy [7], psychological effect in women receiving radiation therapy for early breast cancer [8], direct effects on normal brain parenchyma related to cranial radiation therapy [9], or a decline in neuromuscular efficiency in prostate

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cancer radiation therapy [10] may be related to fatigue etiology in patients treated with radiation therapy.

Available data suggest that activation of the pro-inflammatory cytokine network and inflammatory response may be responsible for radiation-induced fatigue. In particular, increased levels of the interleukin-6 (IL-6), IL-1 receptor antagonist (IL-1ra), and C-reactive protein (CRP) are associated with a higher frequency and severity of fatigue [11–15]. Excessive nuclear factor (NF)-κB pathway activation has been seen in fatigued patients who have a key role in controlling expression of pro-inflammatory genes [16, 17].

Pro-inflammatory cytokines can also be produced in the central nervous system in response to radiation and generate fatigue [11, 12, 18].

Persistent posttreatment fatigue is associated with elevated markers of pro-inflammatory cytokine activity and alterations in the cellular immune system along with subtle dysregulation in hypothalamic-pituitary-adrenal axis function [11, 19–21].

Some investigators have not validated these relationships, so further evaluation is needed [22].

Other mechanism proposed for radiation-induced fatigue is mitochondrial dysfunction. A defect in mitochondrial oxidative phosphorylation is induced by radiation and causes genetic instability and cellular damage. Mitochondrial synthesis of ATP is disrupted and fatigue develops [23].

18.2 Timing

Fatigue may be developed or increased from baseline levels during radiation therapy. Fatigue usually begins during the second or third week of radiation therapy. Symptoms of fatigue become more severe over the course of treatment (cumulative fatigue) [24]. More than three-fourths of fatigue occurs by the third to fifth weeks of treatment. Fatigue is usually reduced gradually after treatment completion to the pretreatment levels within 4–8 weeks following the completion of treatment [25] but in some patients is protracted over many weeks (may last from 3–4 weeks to 2–3 months after treatment stops) [20, 26–31].

It has been observed that the radiation therapy-free weekends are associated with a lesser fatigue [32].

18.3 Risk Factors

There are inconsistent data across studies evaluating fatigue-related factors, and additional research is warranted to determinate the predictor factors of radiation-induced fatigue. We discuss some of these factors here.

One of the uniformly reported predictive factors for fatigue during radiation therapy is higher than the baseline fatigue level. The presence of fatigue at the

initiation of irradiation is associated with more fatigue experienced by patients during radiation therapy [33, 34].

Both fatigue and psychological disorders (like anxiety and mood disorders) are prevalent in cancer patients and have overlapping symptoms that produce some ambiguity for conclusion. There are conflicting data regarding to relationship between fatigue severity and psychological distress [7, 22, 35, 36]. Some have reported no significant relationship [37], and others have shown predictability of mood disorders for fatigue [36].

Some researchers have found differences in fatigue levels by radiation therapy sites. High frequency of radiation-induced fatigue was seen in breast cancer patients receiving radiation therapy rather than other common cancers including lung or prostate cancer [38–44], although some reported that patients with lung, gastrointestinal, and head and neck cancers experience more severe fatigue and that their fatigue increases more intensely over the course of radiation than does that of patients with breast cancer [45].

There are sparse data about the treatment parameter for radiation-induced fatigue. Radiation field sizes seem to be positively associated with maximum radiation-induced fatigue [46, 47]. Total dose might also be expected to influence the severity of fatigue although linear increase in fatigue with cumulative radiation dose over time is not seen [48].

Correlation between immune serum markers and fatigued patients has been proposed [49]. An analysis of different variables showed that higher baseline neutrophil counts have more consistent relation with fatigue than circulating cytokines, coagulation factors, peripheral blood indices, and biochemical factors [33]; however, more studies are needed to assess the relation of different immune markers and fatigue level.

Data about the role of chemotherapy as a predictor of radiation therapy-induced fatigue is also inconclusive. Some studies have shown that pretreatment with chemotherapy may increase fatigue severity, although others have reported that fatigue severity scores are not associated with chemotherapy [50, 51].

Other clinical variables including disease stage, previous surgery, weight [51, 52], and demographic variables such as race, gender, age, marital status, personality characteristics, and employment status [2, 3, 48, 53, 54] have not been consistently reported to be related with fatigue induced during radiation therapy.

18.4 Symptoms

Cancer-related fatigue is defined as a sensation of tiredness or lack of energy that is associated with functional limitations and impaired quality of life [34, 53, 55–60]. Unlike simple tiredness, it is more debilitating and not relieved by sleep or rest. It interferes with activities of daily living like preparing food or cleaning the house and leads to withdrawal from enjoyable activities like social activities with friends and family and even discontinuation of cancer treatment [26, 61]. Objective

physical function (performance status) [62–64] and psychological status (mental/emotional aspects) [65–67] are also affected by fatigue.

There is a diurnal variation in radiation-induced fatigue, with increasing levels in the evening, which is consistent with the diurnal pattern of fatigue in the general population [68–71]. The severity of both evening and morning fatigue increases during radiation therapy and then decreases following the completion of radiation therapy [72].

18.5 Diagnosis and Scoring

Fatigue is a sensation with multidimensional components including sensory, cognitive, affective, behavioral, and physiologic aspects.

Based on NCCN guidelines "Cancer-related fatigue is defined as a 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 that significantly interferes with usual functioning" [73].

Numerous assessment measures (including unidimensional and multidimensional scales) have been developed for screening and diagnosis of cancer-related fatigue. Most of them are based on patient self-report; however, there is no consensus about the best method for assessment.

Multidimensional measures examine several domains of sensory, cognitive, affective, behavioral, and physiologic function that is affected by cancer-related fatigue. Therefore, a multidimensional measurement may seem to be a more specific and refined diagnostic tool but may be too long to complete and not be suitable for screening or scoring in practice [9, 74].

Unidimensional measures (single-item or multi-item) are often single-question scales that are rapid and sensitive and can be applied efficiently for screening of the occurrence and measuring the severity of cancer-related fatigue but may lose the multiple dimensions of fatigue [3, 75]. Moreover, some argue that the extent of overlap between fatigue and depression is reduced with using a single item than a multi-item measure for fatigue [76].

Consideration of the measurement properties, strengths, and limitations of these instruments, including reliability, validity, specificity, sensitivity, recall period, respondent burden, translation in multiple languages, and the availability of normed values to aid interpretation, should be used to guide decisions about the utility of a measure for specific clinical or research purposes [3].

Specific diagnostic criteria have been proposed for defining cancer-related fatigue as an independent entity in the International Classification of Diseases, 10th revision (ICD-10) [77–79].

Some of the other multidimensional scales for cancer-related fatigue have been proposed including the Multidimensional Fatigue Inventory [80, 81], the Functional Assessment of Cancer Therapy-Fatigue Scale [82], the Piper Fatigue Scale [83], the Fatigue Symptom Inventory [84, 85], the Lee Fatigue Scale [86, 87], the revised Schwartz Cancer Fatigue Scale [88], and the Cancer Fatigue Scale [89].

The Lee Fatigue Scale has established internal consistency reliability in a variety of populations including cancer patients [86, 87, 90, 91]. In this scale, fatigue

severity is measured using 13 items. Each item has a 0–10 numeric rating scale with higher scores indicating higher levels of fatigue severity. Respondents are asked to rate each item based on how they felt "right now," within 30 min of awakening (i.e., morning fatigue), and before going to bed (i.e., evening fatigue) for two consecutive days and nights. The fatigue scale score is calculated as the mean of the 13 fatigue items. It has established that cutoff scores for clinically significant levels of fatigue (i.e., ≥3.2 for morning fatigue, ≥5.6 for evening fatigue) [86, 91].

There are several unidimensional single-item scales such as the Symptom Distress Scale [92], the Rotterdam Symptoms Checklist [93], the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 quality-of-life measure [94], the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) [95], the MD Anderson Symptoms Inventory [96], the Zung Self-Rating Depression Scale [97], the Visual Analog Fatigue Scale [98], or multi-item scales such as the Brief Fatigue Inventory [99].

Based on National Comprehensive Cancer Network (NCCN) guidelines, fatigue should be assessed quantitatively on a 0–l0 scale (where 0 means no fatigue and 10 means the worst fatigue imaginable, how would you rate your fatigue at its worst over the past 7 days?); A score of 0 indicates an absence of fatigue, a score of 1–3 indicates the presence of mild fatigue that does not require clinical intervention, and scores of 4–6 and 7–10 indicate moderate and severe fatigue, respectively, which require further evaluation and clinical intervention [73].

Proposed (1998 draft) ICD-10 criteria for cancer-related fatigue is shown in Table 18.1.

Table 18.1 Proposed (1998 draft) ICD-10 criteria for cancer-related fatigue

Six (or more) of the following symptoms have been present every day or nearly every day during the same 2-week period in the past month, and at least one of the symptoms is (A1) significant fatigue (A1)
A1. Significant fatigue, diminished energy, or increased need to rest, disproportionate to any recent change in activity level
A2. Complaints of generalized weakness or limb heaviness
A3. Diminished concentration or attention
A4. Decreased motivation or interest to engage in usual activities
A5. Insomnia or hypersomnia
A6. Experience of sleep as unrefreshing or nonrestorative
A7. Perceived need to struggle to overcome inactivity
A8. Marked emotional reactivity (e.g., sadness, frustration, or irritability) to feeling fatigued
A9. Difficulty completing daily tasks attributed to feeling fatigued
A10. Perceived problems with short-term memory
A11. Post-exertional malaise lasting several hours
B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
C. There is evidence from the history, physical examination, or laboratory findings that the symptoms are a consequence of cancer or cancer therapy
D. The symptoms are not primarily a consequence of comorbid psychiatric disorders such as major depression, somatization disorder, somatoform disorder, or delirium

18.6 Management

All cancer patients should be screened by a certain fatigue scale at their initial and follow-up visits.

Patients with significant fatigue scale should be further evaluated by history and physical examination. Cutoff for significant fatigue varies based on different fatigue scale tools (see Sect. 18.5).

Based on NCCN guidelines, primary patient evaluation includes:

History and physical examination (disease status and treatment, review of systems, social support status/availability of caregivers, economic status, onset, pattern, duration change over time) [73]

Assessment of: Treatable contributing factors (pain, anemia, nutritional deficits/imbalance, sleep disturbance/poor sleep hygiene, decreased functional status, emotional distress, drug induced sedation comorbidities (alcohol/substance abuse, cardiac dysfunction, hot flashes, hypothyroidism, hypogonadism, adrenal insufficiency, gastrointestinal dysfunction, hepatic dysfunction, infection, neurologic dysfunction, pulmonary dysfunction, renal dysfunction) [73]

In context with medical assessment of treatable factors, laboratory tests may be ordered as clinically indicated including complete blood count (CBC), electrolyte profile (sodium, potassium, chloride, bicarbonate), chemistry panel (creatinine, blood urea nitrogen, glucose, magnesium, calcium, phosphorus, bilirubin, serum transaminases, alkaline phosphatase, lactate dehydrogenase, albumin, total protein), transferrin, total iron-binding capacity, ferritin, iron levels, folic acid, B12 level, and thyroid function tests [100].

After primary patient evaluation, if there are any treatable contributing factors, it should be managed, and if fatigue persists with clinical management of these conditions, additional therapeutic modalities may be required [101].

There are both pharmacologic interventions and integrative non-pharmacologic behavioral interventions to alleviate fatigue symptoms that physicians can consider in the setting of no specific causal factors. Patients should be managed by multidisciplinary teams (oncologist, psychologist, physical therapist, exercise specialist, oncologist nurse, and nutritionist) for the best treatment approach.

18.6.1 Non-pharmacologic Interventions

There are various non-pharmacologic interventions including exercises (e.g., home-based exercise, supervised exercise), education and counseling, sleep therapy, and complementary therapy. These non-pharmacologic interventions alone or in combination with pharmacologic approaches may be implemented for the effective management of cancer-related fatigue [102].

18.6.2 Exercise

Exercise can be helpful for individuals with cancer-related fatigue during and post-cancer therapy [103–108]. Exercise improves patient function during radiation therapy, which is attributed to reduce radiation fatigue and the improvement of quality of life [109–111]. The proposed mechanism of exercise in reducing cancer-related fatigue is balancing in energy resources, attenuation of the progressive muscle wasting, and disruptions in muscle metabolism that occur with cancer and prescribed treatments [112].

Both home-based exercise and supervised exercise can improve fatigue. Home-based exercise program is a potentially effective, low-cost, and safe intervention [108], and supervised exercise allows individualizing the exercise regimen to the specific condition of the patient and type of cancer by professional therapists and offers greater motivation. Therefore, supervised exercise might be more effective than home-based exercise in improvement in physical and psychological functioning especially in patients that have cancer or treatment-related morbidity [110, 113–116].

Exercise contraindications (such as extensive lytic bone metastases, extreme thrombocytopenia) should be regarded. Neutropenic patients must avoid environments where the risk of exposure to infectious agents is high (e.g., public swimming pools) [117]).

Home-based physical activity interventions usually consist of at least 10–30 min per day for at least 2–5 days per week [102].

Supervised exercise interventions consist of combined aerobic, resistance, and stretching exercises [118].

18.6.3 Counseling and Education

Education and counseling about cancer-related fatigue, its adverse effects, and strategies to deal with it by telephone or online support programs, comprehensive coping strategy programs or other programs, or organizations have been reported to greatly benefit cancer-related fatigue management [119, 120].

Efforts to educate should be directed at patient's educational level. Open communication between patient, family, and caregiving team can facilitate discussions about the experience of fatigue and its effects on daily life.

18.6.4 Optimize Sleep Quality

One approach of non-pharmacologic supportive interventions to optimize sleep quality and also decrease cancer-related fatigue is cognitive behavioral therapy, which is a form of psychotherapy that treats problems and boosts happiness by modifying dysfunctional emotions, behaviors, and thoughts.

Cognitive behavioral therapy for insomnia (stimulus control instructions, sleep restriction therapy, and sleep hygiene counseling) seems to improve cancer-related fatigue [120–122].

Due to some inconsistent results, additional research is needed to explore the impact of this intervention on patients with different degrees of insomnia and fatigue.

The aim of stimulus control is to limit the amount of time that patients spend awake in bed. The recommendations consist of going to bed at the same time each night or when sleepy, waking up at the same time every morning, and leaving the bed after 20 min if unable to fall sleep [102].

The aim of sleep restriction is to limit the amount of time that patients spend in bed to the amount of actual total sleep time to increase sleep consolidation. The protocol includes avoiding afternoon naps and limiting total time in bed [102].

The sleep hygiene principle consists of a variety of behaviors and environmental factors; it can be implemented by educating patients to avoid heavy meal closest to bed time, avoiding caffeine in the afternoon, and establishing an environment that can promote sleep, such as preparing a dark, quiet, and comfortable bedroom [102].

18.6.5 Complementary Therapies

Energy conservation such as tai chi (energy arts from China) [122, 123], polarity therapy (energy therapy) [124], pranayama (control of breath) [125], and yoga [126, 127] may be effective interventions for managing cancer-related fatigue. Further confirmatory studies are warranted.

The general consideration of energy conservation should be provided to patients like balancing activities with rest, pacing slowly and steadily, selecting the tasks based on priority and eliminating unnecessary tasks, and avoiding poor body posture [128].

There are some positive results about use of back massage [100] and acupuncture [129] in cancer-related fatigue. Further research is required to investigate their mechanism and efficacy in this era.

18.6.6 Other Psychosocial Interventions

Cognitive behavior therapy has a clinically relevant effect in reducing fatigue and functional impairments in cancer survivors [130]. Although a variety of cognitive behavioral and psychosocial interventions can be beneficial, discovering what patients benefit from what type of psychosocial intervention is an unresolved issue [131].

Whether all patients require formal cognitive behavioral therapy by a psychologist or psychiatrist in addition of general counseling is unclear [131].

Group therapy (approximately six patients per group) may be effective in both emotional and physical symptoms and enhance quality of life for cancer patients undergoing radiation therapy [117].

The results suggest that relaxation training [132] and hypnosis [133] may improve several psychological parameters such as fatigue in ambulatory patients who are undergoing radiation therapy [132].

Mindfulness-based stress reduction may be a useful therapeutic intervention for improving cancer-related fatigue, although the evidence is preliminary [134].

18.6.7 Nutrition Counseling

Patients should be encouraged to have adequate intake of fluid* (e.g., 8–12 cups of fluid throughout the day) and adequate nutrition (e.g., high-protein diet) [128].

Caution should be taken in patients with comorbidities that affect fluid balance (e.g., congestive heart failure).

18.6.8 Pharmacologic Intervention

Methylphenidate (Ritalin®) is a central nervous system (CNS) stimulant that is structurally related to amphetamines with a short half-life and a rapid onset of action.

The results suggest that methylphenidate could be considered in patients with severe cancer-related fatigue [135–138].

Prescribing strategy: start methylphenidate at 5 mg in the morning and 5 mg at noon, titrating as necessary. The maximal dose with the potential for benefit in cancer-related fatigue is 40 mg daily [117].

Contraindications: hypersensitivity, glaucoma, family history of Tourette's syndrome or motor tics, marked anxiety, tension, agitation, taking MAOIs within 2 weeks, and risk of severe hypertensive reaction.

Modafinil, a non-amphetamine wake-promoting agent, is used for the treatment of narcolepsy. As compared with other psychostimulants such as methylphenidate, it has a relatively selective site of action in the brain, with resultant fewer adverse effects and lower potential for abuse.

There is insufficient evidence to prescribe modafinil for patients with cancer-related fatigue outside of a clinical trial context [139, 140].

Steroids (e.g., dexamethasone [141], methylprednisolone [142], megestrol acetate [143]) may be effective in cancer-related fatigue in patients with advanced cancer [144, 145]. The possibility of steroid-induced secondary fatigue in terminally ill cancer patients should be taken into consideration [146].

Antidepressants (e.g., paroxetine) have failed to demonstrate any improvements in fatigue [145, 147]. There are some positive results about bupropion sustained-release efficacy in cancer-related fatigue. Further studies would be necessary to establish the efficacy of this intervention [147, 148].

Guarana (*Paullinia cupana*) is a plant native to the Amazon basin. Guarana was shown to be effective for fatigue in breast cancer patients receiving systemic chemotherapy. Further studies are needed to confirm its efficacy and its use in radiation therapy-related fatigue [149].

High doses of American ginseng (*Panax quinquefolius*) have been shown to be an effective and safe natural supplement for helping manage the fatigue associated with cancer treatment. While data seem promising, additional studies are needed to confirm these findings before ginseng can be recommended as a treatment for cancer-related fatigue [150].

Multivitamins do not improve radiation-related fatigue [151].

IV vitamin C administration appears to reduce cancer-related fatigue. Additional well-designed placebo-controlled studies investigating the effects of IV vitamin C on cancer-related fatigue appear warranted [152].

Donepezil is an inhibitor of acetylcholinesterase used for Alzheimer's, and dementia was not significantly superior to placebo in the treatment of cancer-related fatigue [153].

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Hematological Side Effects

19

Profound hematologic toxicity, prominently leukopenia, frequently develops following radiation therapy that includes a large volume of bone marrow in the radiation field [1–8]. The percentage of patients with radiation-induced leukopenia has been reported in up to 50% and 90% of patients treated with pelvic field irradiation alone and with concurrent chemotherapy, respectively [1, 6]. These values are lower for thrombocytopenia (1% and 30% of patients treated with pelvic field irradiation alone and with concurrent chemotherapy, respectively) and anemia (30% and 50% of patients treated with pelvic field irradiation alone and with concurrent chemotherapy, respectively) [1, 10].

19.1 Mechanism

The bone marrow is a cellular stroma consisting of the vascular system with nutritive vessels and a very complex sinusoidal system [11]. At birth, virtually all marrow is hematopoietic. Conversion of red marrow to yellow marrow with advancing age begins in the distal bones, and the distribution of active red marrow in the adult is in the skull (13.1%), clavicle (1.5%), scapula (4.8%), sternum (2.3%), ribs (7.9%), vertebrae (28.4%), pelvis (36.2%), and proximal extremities (5.7%). There is a gradual reduction in the percentage of cellularity of red marrow with age and its replacement by fatty yellow marrow [12].

The cellular stroma of bone marrow houses active blood-cell-forming stem cells [13]. The peripheral blood also contains hematopoietic stem and progenitor cells. Due to the dynamic equilibrium between the hemopoietic cell populations in the bone marrow and peripheral blood, the peripheral blood cell populations could be sensitive indicators of radiation-induced damage to hematopoietic tissues [14].

The hematopoietic stem and progenitor cells are highly sensitive to radiation [15]; however, nondividing mature cells (e.g., granulocytes, red cells, or platelets) tolerate higher radiation doses. After exposures at doses as low as 4 Gy, the cellularity of the irradiated bone marrow progressively declines [16–18]. It has been found

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that an exposure dose of 30–47 Gy delivered in a period of 3–4 weeks to the sternal area results in severe depression of the sternal marrow [19].

Breakdown of the sinusoidal system results in erythrocytes spreading throughout the parenchyma, and a hemorrhagic bone marrow develops with radiation [16].

The most sensitive indication of acute radiation effect on peripheral blood counts is a reduction in number of circulating lymphocytes, together with the appearance of abnormal lymphocyte figures [17]. If the limited volume of marrow receives radiation (less than 3% of the total active adult marrow), the peripheral blood counts may be within normal limits despite marrow hypoplasia [17].

It has been demonstrated that irradiated bone marrow sites can be recovered early by the stem cell migration of the protected bone marrow sites or peripheral blood [13, 20, 21]. Proliferation and release of stem cells increase in non-irradiated bone marrow after radiation therapy. The depletion of stem cells in the protected bone marrow at the beginning of radiotherapy seems to be due to such migration [16, 22]. Another reason for this diminution could be the result of an increased rate of differentiation.

After stem cell transplantation, the times to "rebuild" for the granulocytic, erythropoietic, and megakaryocytic cell lines are 10–12, 5–7, and 10 days, respectively [11].

Although blood count recovery occurs a few months after completion of therapy in 90% of patients, bone marrow regeneration and recovery require a much longer time. The potential of regeneration appears to depend on the dose received. It has been shown that a dosage of 30 Gy or more of bone marrow radiation needs an extended time to recover and may permanently depress the marrow [19, 23]. This could be due to permanent damage to the precursor cells of the marrow elements or to a physiological alteration of the blood vessels and supporting syncytium. These factors could be responsible for the prevention of growth of the regenerating cells and/or the repopulation of cells from marrow in other parts of the body [17]. Permanent loss of hematopoietic activity in the irradiated areas is compensated by increased activity in the non-irradiated areas [24, 25].

19.2 Timing

In patients undergoing conventional fractionated radiation therapy, occurrence, degree, and timing of blood count suppression are dependent on the proportion of active marrow volume in the radiation fields. The field size is the most important determining factor for the adverse hematologic effects on severity and timing. For example, it is estimated that the proportion of active marrow included in the periaortic, mantle, and pelvic fields is about 10%, 25%, and 40%, respectively, and nadir levels of the cell counts occur at different times for these fields [26].

The number of peripheral blood cells decreases according to their radiation sensitivity and life expectancy. The total white cell count declines during radiation therapy. Lymphocytes are the most sensitive, and monocytes are the most refractory leukocytes to change. The lymphocyte count drops first and by the greatest amount,

the neutrophils less, and the monocytes only exhibit a transient, early, modest dip. After the nadir, counts for white cells levels maintain a plateau [27].

The platelet count declines gradually with radiation therapy to a nadir and thereafter is maintained its level [27].

The hemoglobin very gradually decreases during radiation therapy and reaches its lowest value at the end of radiation therapy, which could be related to the long red blood cell life expectancy compared to leukocytes and platelets [27].

Complete peripheral blood count recovery is observed at 1–3 months following therapy, although it may still be below the pre-therapy levels, and lymphocyte count recovers fastest [27]. Peripheral blood counts are an unreliable indicator for assessing the true status of bone marrow reserve, and bone marrow suppression may sustain for months to years despite normalized peripheral blood counts [28, 29]. Patients may have normal peripheral blood counts with a marked suppression of bone marrow secondary to increasing proliferation of unexposed bone marrow [28].

19.3 Risk Factors

Radiation-related factors such as larger radiation field and higher radiation dose are the most important factors affecting bone marrow injury and degree of depression in the peripheral blood counts [19, 30].

Chemotherapy is another factor affecting hematologic toxicity of radiation therapy. Patients with previous and concomitant chemotherapy have increased risk for radiation-induced neutropenia [31].

19.4 Symptoms

Depression of each hematopoietic cell lineage translates into potential problems for the patient. The Radiation Therapy Oncology Group has defined a scoring system for acute hematologic toxicity of radiotherapy (Table 19.1) [9].

Table 19.1 RTOG acute radiation hematologic effects scoring

	Grade 1	Grade 2	Grade 3	Grade 4
White blood cells/ml	3000 to <4000	2000 to <3000	1000 to <2000	<1000
Platelet/ml	75,000 to <100,000	50,000 to <75,000	25,000 to <50,000	<25,000 or spontaneous bleeding
Neutrophils/ml	1500 to <1900	1000 to <1500	500 to <1000	<500 or sepsis
Hgb (g/dl)/Hct(%)	9.5 to <11/28 to <32	7.5 to <9.5/ <28	5 to <7.5 (pack cell transfusion required)	–

Patients with isolated neutropenia may not have any specific symptoms. Neutropenia may place the patient at substantial risk for infection, and a fever may be the first sign.

Thrombocytopenia is generally not associated with any symptoms and is self-limited, but manifestations of bruising, petechiae, and mucosal bleeding infrequently occur. Intracranial hemorrhage is the most dangerous manifestation of thrombocytopenia, though it is particularly rare, and most episodes occur at platelet counts less than 5000/mL.

Symptoms related to significant anemia are easy fatigue, low compliance for activity, rapid heart rate, and shortness of breath.

19.5 Prevention

There is correlation between radiation technique parameters regarding bone marrow and hematologic toxicity. These parameters could be modifiable with intensity-modulated radiation therapy (IMRT) and more advanced techniques. New techniques can reduce radiation dose to bone marrow and decrease acute hematologic toxicity [32–35].

One problem with standard IMRT planning is the large volume of bone marrow that needs to be avoided. By considering only red (active) marrow in marrow contouring, the planning process could be improved [36]. The distribution of marrow containing red (active) and yellow (inactive) marrow is different among individuals [37]. Active red marrow can be visualized poorly in computed tomography (CT) scanning. Functional bone marrow imaging like 2-deoxy-2-[F-18]fluoro-D-glucose (FDG)-positron emission tomography (FDG-PET) [38] or single-photon emission computed tomography (SPECT) [18] can provide information about functional normal bone marrow and its physiologic distribution. Incorporation of these modalities into the IMRT planning process avoids the unnecessary contouring of inactive yellow marrow for calculation of dose constraints. Structural imaging techniques such as magnetic resonance imaging (MRI) in place of functional imaging may be useful in this regard [18, 37, 38].

The potential for cytokines in prevention of the hematopoietic system radiation injury has been studied in lethally irradiated animals, and observations suggest that some cytokines such as G-CSF [39, 40], interleukin-1 (IL-1) [41, 42], tumor necrosis factor (TNF)-alpha [43], and Fms-related tyrosine kinase 3 ligand (FLT3LG) [44–46] may mediate radioprotective effects to the hematopoietic progenitor cell and stem cell compartments. It has also been shown that meloxicam, a selective inhibitor of cyclooxygenase 2, can modulate hematopoiesis and elevate numbers of granulocytic precursor cells in bone marrow and granulocyte counts in peripheral blood by increasing endogenous G-CSF production [47]. Currently, there is no recommendation for the prophylactic use of these factors.

19.6 Treatment

19.6.1 Neutropenia

The proliferation and differentiation of hematopoietic cells are regulated by a family of cytokines including colony-stimulating factors (CSFs) and interleukins, which are specific to each cell lineage [48]. Granulocyte colony-stimulating factor (G-CSF) controls the production, differentiation, and function of neutrophilic granulocytes. Single classes of high-affinity receptor for G-CSF are present on the precursor and mature cells of neutrophilic granulocytes [48].

The mature human G-CSF is a 19.6 kDa glycoprotein containing 174 amino acids [49], and its molecular cloning has been well described [50].

It is well known that *E. coli* is a useful host for the production of recombinant human G-CSF [51], but there are also various products that are derived from different tissues (e.g., yeast, transgenic plants, and mammalian cells) [52].

There are lots of controversies about using of colony-stimulating factors during radiation therapy regarding acute and late side effects.

G-CSF treatment is well tolerated during continuous fractionated radiation therapy and can be used clinically to alleviate severe and threatening neutropenia caused by radiation therapy or by combined radio-chemotherapy [53, 54].

The number of G-CSF receptors on bone marrow cells increases with radiation [55], and administration of recombinant human G-CSF can accelerate the recovery of radiation-induced neutropenia [56–58] and reduce its severity and duration [59–62].

After administration of recombinant human G-CSF, the level of circulating neutrophils increases by accelerating production, inhibition of neutrophil apoptosis, reduction of transit time from stem cell to mature neutrophil, and accelerating neutrophil entry into the blood, and neutrophil function is enhanced. An increase in neutrophil progenitors in the marrow and hematopoietic stem cell mobilization can be seen in G-CSF administration [63–65].

Clinical application of recombinant human G-CSF is hampered in some situations by various side effects. G-CSFs should not be included in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum based on the results of GM-CSF or G-CSF morbidity in mediastinal chemoradiotherapy. More severe thrombocytopenia was seen in patients with CSF administration [66–68]. Further studies will be required to determine if chemoradiotherapy for other sites of disease will provoke similar problems.

Possible reason for thrombocytopenia observed in this site of irradiation is that the CSF mobilizes progenitor cells into the peripheral blood and new precursor cells are destroyed during migration into the irradiation volume because large numbers of these cells may be irradiated as they pass through the heart [67].

Outside of clinical trials, in patients receiving concomitant chemotherapy and radiation therapy, treatment is suspended for severe neutropenia and is resumed when the toxicity decreases to lower grade.

There is a concern about the reduction in the capacity of bone marrow recovery with simultaneous treatment of G-CSF during radiation therapy in the postradiation phase. Mechanisms like enhanced production of inhibitory cytokines, a decrease in endogenous production of the growth factors due to the exogenously induced pharmacological levels, downregulation of growth factor receptors on target cells [69], and decreased sensitivity of bone marrow to radiation during G-CSF application are proposed for this phenomenon [70]. Further investigations are needed to determine the late bone marrow effect of G-CSF administration during radiation therapy and the timing, duration, and dosage of G-CSF application for successful treatment and a favorable outcome.

The American Society of Clinical Oncology (ASCO) guidelines recommend that "CSFs should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum. In the absence of chemotherapy, therapeutic use of CSFs may be considered in patients receiving radiation therapy alone if prolonged delays secondary to neutropenia are expected."

European Society of Clinical Oncology (ESMO) guidelines also recommend that "primary prophylaxis with G-CSF is not indicated during chemoradiotherapy to the chest due to increased rate of bone marrow suppression associated with an increased risk of complications and death" [71].

Three clinically available forms of G-CSF are [72]:

*A glycosylated form (lenograstim), which is produced by using the expression in mammalian cells, and a *non-glycosylated form (filgrastim), which is produced by using expression in *E. coli* [73]
*A pegylated form of non-glycosylated Hu G-CSF (pegfilgrastim)

Pegfilgrastim is developed to produce a long-acting filgrastim requiring less frequent dosing than its parent drug [74]. A single dose of PEG-rhG-CSF has a similar clinical safety to rhG-CSF and significant advantageous effects [75].

The recommended dose for G-CSF is 5 g/kg/day and for Pegfilgrastim is as a single dose of either 100 mcg/kg (individualized) or of a total dose of 6 mg (general approach) [71, 76]. Both are injected subcutaneously. A single subcutaneous injection of rhG-CSF results in an increase in circulating granulocytes within 2 h; the granulocyte concentration peaks by 12 h and remains elevated for the next 36 h before decreasing slowly back to baseline [77]. The median time to reach the peak concentration is 2.5–5 days for pegfilgrastim, and neutrophilic level remains above baseline for around 9–10 days [74].

Patients should be monitored with serial CBCs. Administration should be continued until the absolute neutrophil count reaches to upper level or normal [78].

The G-CSF receptors are expressed not only on myeloid cells but also on other hematopoietic cells including monocytes, platelets, and possibly certain lymphocyte subsets [79]. No significant changes in lymphocyte or monocyte counts have been observed during the course of rhG-CSF treatment.

Data on the effects of G-CSF on platelet function are limited. It seems that G-CSF enhances platelet aggregation and activation in humans [80].

Radiation-induced thrombocytopenia may be worsened by G-CSF administration, possibly due to a decrease in the number of megakaryocytes in the bone marrow and an increase in the trapping of megakaryocytes in the spleen [72, 81]. G-CSF-induced thrombocytopenia seems to be a transient event and may improve spontaneously despite continual G-CSF treatment [82].

Common side effects observed during G-CSF treatment consist of mild musculoskeletal pain, papular skin rash, and some laboratory abnormalities like elevated alkaline phosphates [54, 61, 82].

The exact effects of G-CSF administration on cancer cells remain controversial. G-CSF administration increases the production of neutrophils, and cytotoxic mediators produced by neutrophils could kill the cancer cells [83, 84]. On the other hand, G-CSF has been shown to promote tumor angiogenesis by upregulating VEGF [85], which is released by neutrophils and reduces radiation-induced vascular damage [86].

It has been shown that prophylactic G-CSF administration for treatment of advanced unresectable head and neck cancers resulted in an unexpected reduced local control [87, 88]. The effects of G-CSF on tumor growth, especially during radiation therapy, are controversial and require further investigation [84].

Furthermore G-CSF can stimulate the clonal growth of some non-hematopoietic tumor cells like bladder [89] or colon [90] cancers, and the remote effect of G-CSF on the growth of tumor cells lying outside radiation treatment portals is proposed by some [91].

It has been suggested that the simultaneous or sequential administration of two or more complementary cytokines has resulted in better patterns of hematologic recovery. The capacity of multiple cytokine combinations (like GM-CSF and IL-3 [92–94], TPO with IL-4 or IL-11 [95], IL-3 receptor agonist and rhG-CSF [96], and rhG-CSF and pegylated megakaryocyte growth and development factor [97]) to accelerate hematologic recovery and ensure multi-lineage protection following severe radiation-induced myelosuppression has been assessed in animal studies with promising results [92–98]. Further investigations in this field will clearly be necessary before drawing any conclusions.

19.6.2 Thrombocytopenia

There is no threshold for platelet counts that for counts below which prophylactic transfusion should be prescribed to all patients with radiation-induced thrombocytopenia. Several studies support a threshold of 10,000 platelets/mL or less for initiating transfusions to patients with solid tumors and a higher threshold; perhaps 20,000/mL has been proposed for patients with tumor with the presence of necrotic sites (e.g., gynecologic, colorectal, melanoma, or bladder tumors) [23, 99].

Thrombopoietin, a lineage-specific growth factor specific for platelets, regulates platelet production via the stimulation of its receptor on megakaryocytes and platelets leading to proliferation and differentiation. Two variant forms of human thrombopoietin have been developed including first-generation agents, recombinant

human thrombopoietin (rHuTPO) and pegylated recombinant human megakaryocyte growth and development factor (PEG rHuMGDF), and second-generation agents—the TPO peptide mimetics, TPO non-peptide mimetics, and TPO agonist antibodies [100–102].

Clinical trials with recombinant TPO [100] and recently romiplostim (a TPO peptide mimetic) [103] have shown that these agents can improve platelet counts in patients receiving chemotherapy. Further studies need to be performed for use of these agents in radiation-induced thrombocytopenia.

Platelet factor 4 (PF4) is released from radiation-damaged megakaryocytes and inversely affects platelet count recovery after radiation. Anti-PF4 strategy can improve outcomes of radiation-induced thrombocytopenia and needs to be explored [104].

Interleukin 11 (IL-11) is a stromal cell-derived cytokine that enhances the growth of early progenitors and promotes megakaryocytopoiesis and erythropoiesis [105]. Given recombinant human interleukin-11 (rHuIL-11) activity in chemotherapy-induced thrombocytopenia, it needs to be studied as one possible therapeutic option in radiation-induced thrombocytopenia [106–108].

19.6.3 Anemia

Radiation is more effective on tumor cells with higher oxygenation. Anemia is associated with poor tumor oxygenation, relative tumor radioresistance, and decreases the effectiveness of radiation therapy, with subsequent reductions in treatment outcomes including locoregional control and overall survival of cancer patients [10, 109]. Correcting the radiation-induced anemia and maintaining normal hemoglobin levels in patients undergoing radiation therapy have a significant importance due to decrease in tumor hypoxia, improve treatment outcomes, and have a determinant impact on quality of life [109–112]. Both blood transfusion and use of erythropoiesis-stimulating agents (e.g., darbepoetin, erythropoietin) can increase the hemoglobin levels during radiation therapy, but the effects of medications used for correction of radiation-induced anemia on locoregional control and overall survival are questionable [113–117].

Many radiation oncologists have not given ample attention to treating mild to moderate anemia during radiation therapy unless symptoms of severe anemia are present or the hemoglobin falls below a threshold of 9–10 g/dL. However, managing mild to moderate anemia is important for radiation therapy outcome improvement and quality of life preservation [109, 118].

Radiation-induced anemia is usually mild and readily correctable. It has been reported that for most patients with uterine and cervical cancer, the severity of anemia during radiation therapy was modest (59% of anemic patients with hemoglobin levels between 10 g/dL and 11.9 g/dL and 11% with hemoglobin levels between 9 g/dL and 9.9 g/dL). Only a few patients had levels below 8.9 g/dL. Data on colorectal, prostate, lung, and breast cancers yielded similar results [109].

Blood transfusion and recombinant human erythropoietin (rHuEPO) administration can significantly improve radiation-induced anemia [111, 113, 119–122]. There are no randomized studies comparing blood transfusion and rHuEPO efficacy and safety in patients undergoing radiation therapy.

A number of studies have shown an effect of perioperative transfusion on cancer recurrence rates [123–128]. The mechanism of how blood transfusion affects tumor viability is related to some types of immunosuppression [129]. Therefore, some have proposed that rHuEPO administration in patients undergoing radiation therapy may have some benefits over transfusion due to its potential to correct anemia without the risks associated with transfusion [130].

Several studies using transfusion to correct radiation-induced anemia have shown improvement in local control, but there is no study comparing transfusion with rHuEPO, and no definitive conclusion can be drawn about transfusion or rHuEPO safety during radiation therapy.

It has been demonstrated that erythropoietin receptors are expressed in several human cancer cells and may modulate the cellular effects of recombinant human erythropoietin on cancer cells, leading to increased cell survival and growth [131, 132]. Belenkov et al. reported that the addition of exogenous recombinant human erythropoietin induces cancer cells to become more resistant to ionizing radiation and to cisplatin [133]. These data indicate that the administration of rHuEPO to cancer patients undergoing radiation therapy should proceed with caution, especially when the cancer type has been shown to be positive for erythropoietin receptor.

There is no guideline for erythropoietin use during radiation therapy. Based on these findings, we recommend that erythropoietin should not be administered during radiation therapy outside of the experimental setting.

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Radiation-Induced Nausea and Vomiting (RINV)

20

Radiation-induced nausea and vomiting (RINV) is generally less frequent and less severe than the nausea and vomiting encountered in patients receiving chemotherapy. This problem is often underestimated and undertreated by radiation oncologists in clinical practice; however, it can be very distressing and may cause delay or even interruption of radiotherapy [1–3]. The incidence of RINV was studied in two prospective observational studies. The Italian Group for Antiemetic Research in Radiotherapy (IGARR) analyzed the incidence of RINV in 1020 patients receiving various kinds of radiation therapy without concurrent chemotherapy. Vomiting and nausea occurred in 11% and 27.1% of patients, respectively, and 27.9% of patients had both vomiting and nausea [1]. Nausea was twice as frequent as vomiting (27.1% vs. 11%) and lasted longer (median duration 10 vs. 3 days). The RINV incidence rates based on anatomical sites were 28% for breast, 39% for pelvis, 40.4% for head and neck, 48.8% for thorax, 40.4% for brain, and 71.4% for upper abdominal sites.

In a second study of 368 patients receiving radiation therapy again without concurrent chemotherapy, the overall incidence rates for nausea and vomiting were 39% and 7%, respectively, with 63% in abdominal or pelvic fields and by 48% in head/neck/brain fields [4].

20.1 Mechanism

The mechanism of RINV differs depending on radiation site. RINV is primarily due to a serotonin (5-hydroxytryptamine)-mediated pathway [5]. Damage to the enterochromaffin cells of the gastrointestinal mucosa by radiation leads to release of serotonin, which may initiate the emetogenic response through activation of serotonin receptors, visceral afferent fibers, and the chemoreceptor trigger zone (CTZ) in the brain stem [6].

If the gastrointestinal tract is included in the field of radiation, direct effects are likely with stimulation of afferent pathways in the upper gastrointestinal tract.

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RINV also can be mediated by activation of CTZ through release of humoral factors from tissue injury [7].

Increased intracranial pressure due to radiation-induced edema and inflammatory processes associated with radiation injury may also play a role in RINV [7].

20.2 Timing

Acute RINV is seen most frequently with radiation therapy. The latent period ranges from 30 min to 4 h in single-fraction study [6], and it generally begins 3–4 days after fractionated radiation therapy [1, 4, 8]. Delayed emesis is not observed with radiation therapy, unlike with chemotherapy, and anticipatory emesis is extremely rare with radiation therapy [6].

20.3 Risk Factors

The risk of developing RINV depends on several patient and treatment-related risk factors.

The most significant radiotherapy-related risk factors include the site (upper abdomen) and radiation field size (>400 cm) [1, 9]. Other factors like single and total dose, fractionation schedule, and treatment techniques are also important [6]. A single high dose and larger dose per fraction have a greater risk of inducing RINV [10].

Gagnon and Kuettel demonstrated diurnal variation in the gastrointestinal tract with more sensitivity to radiation-induced damage in the late morning than in the afternoon. This study was limited to prostate cancer patients [11].

Patient-related risk factors include age, gender, general health status, alcohol consumption, concurrent or previous chemotherapy, and previous experience of emesis [6]. The risk of RINV is higher in female patients, those younger than 50 years, and patients with a previous history of poorly controlled emesis. Conversely, the risk is decreased in those with a high alcohol intake [6].

It has been reported that the incidence of RINV may have some correlation with ABO blood group and it seems that patients with type A blood groups are the most vulnerable individuals to these side effects [12].

20.4 Symptoms

Patients with RINV experience lower well-being and quality of life, lower satisfaction with aspects of daily living, and more frequent fatigue, anxiety, and depression [4]. Prolonged vomiting can cause dehydration, electrolyte imbalances, and malnutrition.

20.5 Prevention and Management

Radiation therapy sites are classified base on their potential risk for developing RINV in ASCO and MASCC/ESMO guidelines (Table 20.1) [13, 14]. The National Comprehensive Cancer Network (NCCN) [15], Multinational Association for Supportive Care in Cancer (MASCC)/European Society for Medical Oncology (ESMO) [14], and American Society of Clinical Oncology (ASCO) [13] have released guidelines for the management of RINV based on risk category (Table 20.2).

The NCCN guidelines stratify patients into two categories of total-body irradiation and upper abdomen/localized sites [15]. Localized sites have not been determined, but recommendations for both are nearly the same (Table 20.2).

In the setting of concurrent chemoradiotherapy, antiemetic strategies consistent with chemotherapy agents being used should be offered based on each of the three guidelines.

Neurokinin-1 (NK-1) receptor inhibitors in combination with a 5-HT3 receptor antagonist and dexamethasone improve control of acute and delayed chemotherapy-induced nausea and vomiting after highly and moderately emetogenic chemotherapy. The role of these agents in the management of RINV is not well studied. Dennis et al. have suggested that the combination of aprepitant and granisetron may have a protective effect against RINV after both single- and multiple-fraction moderately emetogenic radiation therapy for thoracolumbar irradiation, which is more than historical control data from patients receiving prophylaxis with a 5-HT3 receptor antagonists alone [16]. Further evaluation of this combination in patients receiving concurrent chemoradiotherapy is ongoing.

The optimal duration of antiemetic therapies for the prevention of RINV is not clear. The MASCC/ESMO guidelines have no recommendation for the duration of 5-HT3 antagonist treatment, and the ASCO and NCCN guidelines recommend 5-HT3 antagonist administration prior to each radiation fraction for high- and moderate-risk radiation therapies. Some argued that RINV episodes occur significantly during the first and second week of treatment, and prophylactic antiemetics may not be necessary for a full course of radiation therapy. This issue needs to be further evaluated in future studies to demonstrate the optimal duration of administration [8, 17].

Table 20.1 Risk classification for RINV

	Definition
High risk	Total body irradiation and total nodal irradiation
Moderate risk	Upper abdomen, half-body irradiation, upper-body irradiation
Low risk	Cranium, craniospinal, head and neck, lower thorax region, pelvis
Minimal risk	Breast, extremity

Table 20.2 Recommendations for RINV

	MASCC/ESMO	ASCO	NCCN
High risk	A 5-HT3 receptor antagonist + dexamethasone	A 5-HT3 receptor antagonist before each fraction and for at least 24 h after completion or radiotherapy + a 5-day course of dexamethasone during fraction 1–5	Total-body irradiation: Granisetron 2 mg PO daily or ondansetron 8 mg PO twice daily ± dexamethasone 4 mg PO daily prior to each day of radiotherapy
Moderate risk	A 5-HT3 receptor antagonist; a short course of dexamethasone is optional	A 5-HT3 receptor antagonist before each fraction and for at least 24 h after completion or radiotherapy + a short course of dexamethasone during fraction 1–5 may be offered	
Low risk	A 5-HT3 receptor antagonist as either prophylaxis or rescue	A 5-HT3 receptor antagonist alone as either prophylaxis or rescue. For patients suffering from RINV while receiving rescue therapy only, prophylactic treatment should continue until radiotherapy is completed	
Minimal risk	A dopamine receptor antagonist or a 5-HT3 receptor antagonist rescue	A dopamine receptor antagonist or a 5-HT3 receptor antagonist rescue. Antiemetic prophylaxis should continue throughout radiation treatment if a patient experiences RINV while receiving rescue therapy	

There are five different 5-HT3 receptor antagonist agents. Granisetron and ondansetron are commonly employed for the treatment of RINV. In general, these agents are considered to be equally effective; however, pharmacologic differences do exist between these two agents [17–19].

Granisetron binds irreversibly to 5-HT3 receptors with antiemetic activity up to 48 h following administration, and ondansetron binds reversibly to the receptor, losing antagonist activity by 24 h following administration of commonly employed doses. Higher doses or multiple-daily dosing of ondansetron may be required to maintain antiemetic efficacy; however, granisetron is effective as a once-daily dose [19]:

Granisetron: 2 mg orally, 1 mg or 0.01 mg/kg IV
Ondansetron: 8 mg orally 2–3 times daily, 8 mg or 0.15 mg/kg IV

Side effects include headache, constipation, diarrhea, asthenia, and dizziness. 5-HT3 receptor antagonists have been reported to produce some dose-dependent, nonclinically asymptomatic changes in electrocardiographic parameters like increased PR interval, QT interval, or QRS complex duration. Intravenous granisetron has been shown to be associated with fewer effects on the electrocardiogram than intravenous ondansetron [20]. In patients at risk for QT prolongation, 5-HT3 receptor antagonists should be used with caution (e.g., patients with electrolyte abnormalities, congestive heart failure, brady-arrhythmias, in combination with other medications that cause QT prolongation) [21].

Two dopamine agonist receptors are more commonly used [18]:

Metoclopramide: 20 mg orally
Prochlorperazine: 10 mg orally or IV

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