
2. MANAGEMENT OF RADIATION-INDUCED HEAD AND NECK INJURY

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INTRODUCTION

During the treatment of neoplastic diseases, unavoidable toxicities to normal cells may be produced. The mucosal lining of the upper respiratory and gastrointestinal tracts is a prime target for radiotherapy-related toxicity due to its rapid cell turnover rate. The oral cavity is highly sensitive to direct and indirect toxic effects of radiation therapy (RT); this is attributable to multiple factors such as a diverse and complex microflora, trauma to oral tissues during normal oropharyngeal function, and the high mucosal cell turnover rates.

The most common oral complications related to RT are mucositis, infection, salivary gland dysfunction, taste dysfunction, and pain. These complications can lead to secondary complications such as dehydration, dysgeusia, and malnutrition.

Radiation of the head and neck (H&N) can irreversibly injure oral mucosa, vasculature, muscle, and bone. This can result in xerostomia, dental caries, trismus, soft tissue necrosis, and osteoradionecrosis (ORN). Severe oral toxicities can compromise delivery of optimal radiation-therapy protocols. For example, dose reduction or treatment schedule modifications may be necessary to allow for resolution of oral lesions. In cases of severe oral morbidity, the patient may no longer be able to continue cancer therapy; treatment is then usually discontinued. These disruptions in dosing due to oral complications can thus directly affect patient survivorship.

Management of oral complications of cancer therapy includes identification of high-risk populations, patient education, initiation of pretreatment interventions, and timely management of lesions. Assessment of oral status and stabilization of oral disease prior

Table 1. Tolerance doses (TD_{5/5}–TD_{50/5}) to whole-organ irradiation

Organ	Single dose (Gy)	Fractionated dose (Gy)
Brain	15–25	60–70
Eye (lens)	2–10	6–12
Skin	15–20	30–40
Spinal cord	15–20	50–60
VCTS	10–20	50–60
Mucosa	5–20	65–77
Peripheral nerve	15–20	65–77
Muscle	>30	>70
Bone and cartilage	>30	>70
Thyroid		30–40

VCTS = vasculoconnective tissue systems.
Modified from Rubin P. 1989. The law and order of radiation sensitivity, absolute versus relative.
In: Vaeth JM, Meyer JL, eds. Radiation Tolerance of Normal Tissues. Frontiers of Radiation Therapy and Oncology, vol 23. Basel: S. Karger, pp 7–40.

to cancer therapy are critical to overall patient care. This care should be both preventive (i.e., including careful examination of the gingival and assessment of early, treatable periodontal disease) and/or therapeutic (including the extraction of irreversibly damaged teeth) as indicated to minimize risk for oral (i.e., poor wound healing and ORN) and associated systemic complications (such as subacute bacterial endocarditis and associated complications).

Radiation doses traditionally deemed safe should be carefully reevaluated within the context of multidisciplinary management, as these doses can lead to severe late effects in different vital organs. Previously defined radiation tolerance doses¹ (TD_{5/5} and TD_{50/5}; Tables 1 and 2) remain as valuable guides by establishing reasonable dose–volume guidelines for two-dimensional radiotherapy. However, these data are being complemented by more modern analyses utilizing three-dimensional dose–volume information. These newer studies and cooperative group protocols place special emphasis on the volume of the organ irradiated, in addition to absolute dose limits, in recognition of the inhomogeneous dose distributions made possible by conformal and intensity-modulated treatment planning. As a prominent example, particular attention has been devoted to the study the dose–volume effects and quality-of-life (QOL) predictors following partial parotid gland irradiation,^{2–12} whereas the dosimetric predictors of oral mucositis and esophageal

Table 2. Normal tissue tolerance to therapeutic irradiation

Organ	TD _{5/5} volume			TD _{50/5} volume			Selected endpoint
	1/3	2/3	3/3	1/3	2/3	3/3	
Brain	60	50	45	75	65	60	Necrosis infarction
Brain stem	60	53	50	–	–	65	Necrosis infarction
Spinal cord	5 cm	10 cm	20 cm	5 cm	10 cm	20 cm	Myelitis
	50	50	47	70	70	–	Necrosis

Modified from Emami, B, J Lyman, A Brown, et al. 1991. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 21:109–122.

dysfunction post-RT are in need of further study. In addition, mathematical models such as the nominal standard dose, time-dose factor, and cumulative radiation effect have been supplanted by the linear-quadratic equation¹³ using the α/β ratio and its clinical applicability to normal tissue complication probability estimates.

Tables 1 and 2 summarize previously defined whole- and partial-organ tolerances.

A. ETIOLOGY AND PATHOGENESIS

Elimination of preexisting dental/periapical, periodontal, and mucosal infections, institution of comprehensive oral hygiene protocols during therapy, and reduction of other factors that may compromise oral mucosal integrity (e.g., physical trauma to oral tissues) can help reduce the frequency and severity of oral complications in cancer patients. Such complications can be acute (developing during therapy) or chronic (developing months to years after therapy). Radiation is not only associated with acute oral toxicities, but may also induce permanent tissue damage leading to multiple life-long risks of tooth decay, infection, and ORN among others. Multiple prospective studies have demonstrated increased acute toxicities with the addition of chemotherapy to radiation,^{14–16} particularly when administered concurrently. However, the contribution of chemotherapy to the late toxicity profile post-RT is in need of further study.

Acute effects of H&N irradiation frequently include ulcerative oral mucositis, clinically similar to that seen with high-dose chemotherapy. In addition, radiation can also induce late tissue damage that results in permanent dysfunction of vasculature, connective tissue, salivary glands, muscle, and bone.^{17,18} Loss of bone vitality occurs secondary to injuries to osteocytes, osteoblasts, and osteoclasts as well as from a relative hypoxia due to reduction in vascular supply. These changes can lead to soft tissue necrosis and ORN that result in bone exposure, secondary infection, and severe pain.

Late oral complications of RT are chiefly a result of chronic injury to vasculature, salivary glands, mucosa, connective tissue, and bone. Types and severity of these changes are directly related to radiation dosimetry, including total dose, volume irradiated, fraction size, and duration of treatment. Mucosal changes include epithelial atrophy, reduced vascularization, and submucosal fibrosis. These changes lead to an atrophic, friable barrier. Fibrosis involving muscle, dermis, and/or the temporomandibular joint (TMJ) results in compromised oral function. Salivary tissue changes include loss of acinar cells, alteration in duct epithelium, fibrosis, and fatty degeneration. Compromised vascularization and remodeling capacity of bone leads to risk for ORN.

Unlike that associated with chemotherapy, radiation damage is anatomically site-specific; toxicity is localized to irradiated tissue volumes. The degree of damage is dependent on the treatment regimen-related factors including type of radiation used, total dose administered, and field size/fractionation. Compared with chemotherapy-related effects, an important clinical feature characterizing radiation-induced tissue damage deserves mention. Irradiated tissues tend to manifest permanent damage that places the patient at continual risk for oral sequelae. The oral tissues are thus more easily damaged by subsequent toxic drug or radiation exposure, and normal physiologic repair mechanisms are compromised as a result of permanent cellular damage.

B. PATIENT EDUCATION AND DENTAL EVALUATION PRECEDING IRRADIATION

The severity of oral complications in cancer patients can be reduced significantly when an oral care plan is initiated prior to treatment. Primary preventive measures, such as appropriate nutritional intake, effective oral hygiene practices, and early detection of oral lesions are important pretreatment interventions. The involvement of a dental team experienced with oral oncology may also reduce the risk of oral complications via either direct examination of the patient or in consultation with the community-based dentist. The evaluation should be done as early as possible prior to treatment. The examination allows the dentist to determine the status of the oral cavity prior to cancer therapy, and to initiate necessary interventions that may reduce oral complications during and after that therapy.

C. PRACTICAL ASPECTS OF ACUTE AND LATE EFFECT MANAGEMENT FOLLOWING CANCER THERAPY**C1. Pain Management¹⁹**

Estimated to affect 50–80% of cancer patients and correlating with decreased QOL, pain is frequently multifactorial. Among H&N cancer patients, the etiology of pain may be treatment-related or tumor-related. Recent evidence indicates that cancer pain may be undertreated in many instances.

A number of pain management regimens have been developed. Although the particular drugs and dosing schedules used may vary among institutions, protocols should incorporate the guidelines established by the World Health Organization.²⁰ According to this system, pain should be evaluated regularly (in the case of RT, weekly or more frequently as needed), classified as mild, moderate, or severe, and treated accordingly.

Mild pain should be treated using acetaminophen-based products, moderate pain should be managed by codeine-based analgesics, and severe pain should be treated with morphine or fentanyl-based regimens.

C2. Oral Hygiene

Routine, systematic oral hygiene is important for reducing the incidence and severity of oral sequelae of cancer therapy. The patient must be informed of the rationale for the oral hygiene program as well as the potential side effects of cancer chemotherapy and RT. Effective oral hygiene is important throughout cancer treatment, with emphasis on oral hygiene beginning prior to initiation of that treatment. Considerable variation exists across institutions relative to specific non-medicated approaches to baseline oral care, given limited published evidence. Most non-medicated oral care protocols utilize topical, frequent (every 4–6 hours) rinsing with 0.9% saline. Additional interventions include dental brushing with toothpaste, dental flossing, ice chips, and sodium bicarbonate rinses. Patients utilizing removable dental prostheses or orthodontic appliances have the risk of mucosal injury or infection.

Dental brushing and flossing represent simple, cost-effective approaches to bacterial dental plaque control.

Periodontal infection causes risk for oral bleeding; healthy tissues should not bleed. Discontinuing dental brushing and flossing can increase risk for gingival bleeding, oral

infection, and bacteremia. We recommend the removal of bacterial plaque using gentle debridement via a soft or ultra-soft toothbrush during therapy in order to minimize the risk of infection. Mechanical plaque control not only promotes gingival health, but may also decrease the risk of exacerbation of oral mucositis secondary to microbial colonization of damaged mucosal surfaces.

Oral rinsing with water or saline while brushing will further aid in removal of dental plaque dislodged by brushing. Rinses containing alcohol should be avoided. Since the flavoring agents in toothpaste can irritate oral soft tissues, toothpaste with relatively neutral taste should be considered. Patients skilled in flossing without traumatizing gingival tissues may continue flossing throughout radiotherapy administration. Flossing allows the removal of dental bacterial plaque and thus promotes gingival health.

The oral cavity should be cleaned after meals. If xerostomia is present, plaque and food debris may accumulate secondary to reduced salivary function and more frequent hygiene may be necessary. In addition, it is important to prevent excessive dryness of the lips in order to reduce risk for tissue injury. Mouth breathing and/or xerostomia secondary to anticholinergic medications used for nausea management can induce the condition. Lip care products containing petroleum-based oils and waxes can be useful. Lanolin-based creams and ointments, however, may be more effective in protecting against trauma.

All patients should receive a comprehensive oral evaluation several weeks prior to the initiation of radiation. In accordance with recent studies, we recommend a minimum interval of 2 weeks prior to commencement of RT.²¹ This timing provides an appropriate interval for tissue healing in the event invasive oral procedures including dental extractions, dental scaling/polishing, and endodontic therapy are necessary. Such interventions are principally directed at reducing the risks of soft tissue necrosis and ORN.

Candidiasis is the most common clinical infection of the oropharynx in irradiated patients. Patients receiving H&N radiation are frequently colonized with *Candida*, as demonstrated by an increase in quantitative counts and rates for clinical infection. Candidiasis may exacerbate the symptoms of oropharyngeal mucositis. Treatment of oral candidiasis in the radiation patient has primarily utilized topical antifungals such as nystatin and clotrimazole. Compliance can be compromised secondary to oral mucositis, nausea, and pain and difficulty in dissolving nystatin pastilles and clotrimazole troches. The use of systemic antifungals including ketoconazole and fluconazole to treat oral candidiasis has proved effective and may have advantages over topical agents for patients experiencing mucositis. Bacterial infections may also occur early in the course of head/neck radiation and should be treated with antibiotics appropriately targeted to culture and sensitivity data. It is our recommendation to request cultures in the cases of (a) failed antimicrobial trials when a bacterial, fungal, or combined infectious process is suspected, (b) obvious constitutional symptoms (fever, elevated white count, etc.). In such cases, formal interdisciplinary evaluation (by the Head and Neck Surgery, Medical Oncology, and/or Infectious Disease services) is often sought to rule out competing sources of infection.

The risk of dental cavities increases secondary to a number of factors including shifts to a cariogenic flora, reduced concentrations of salivary antimicrobial proteins, and loss of mineralizing components. Treatment strategies must be directed to each component of the caries process. Optimal oral hygiene must be maintained. Xerostomia should be

managed whenever possible via salivary substitutes or replacements. Caries resistance can be enhanced via use of topical fluorides and/or remineralizing agents.

Increased colonization with *Streptococcus mutans* and *Lactobacillus* species increases the risk of cavity formation. Cultural data can be useful in defining the level of risk in relation to colonization patterns. Of interest, topical fluorides or chlorhexidine rinses may lead to reduced levels of *Streptococcus mutans* but not *Lactobacilli*. Due to adverse drug interactions, fluoride and chlorhexidine dosing should be separated by several hours. Remineralizing agents that are high in calcium phosphate and fluoride have demonstrated salutary in vitro and clinical effects. Delivering the drug via customized vinyl carriers may enhance the intervention. This approach extends the contact time of active drug with tooth structure, which leads to increased uptake into the enamel.

Necrosis and secondary infection of previously irradiated tissue is a serious complication for patients who have undergone radiation for H&N tumors. Acute effects typically involve oral mucosa. Chronic changes involving bone and mucosa are a result of the process of vascular inflammation and scarring that in turn result in hypovascular, hypocellular, and hypoxic changes. Infection secondary to tissue injury and ORN confounds the process.

D. STUDIES ADDRESSING SPECIFIC ISSUES REGARDING TREATMENT-RELATED TOXICITIES IN IRRADIATED H&N CANCER PATIENTS

D1. Xerostomia

Among RT sequelae following the treatment of H&N tumors, reduction in salivary flow due to salivary gland damage is of particular clinical concern. Often permanent and identified by patients as having a negative impact on QOL, xerostomia can result in serious functional impairment and patient discomfort. Clinical experience with conventional irradiation of H&N tumor subsites has demonstrated a steep and rapid reduction in salivary flow rate (FR), ranging from 18% to 50% 1 week after initiation of RT.^{22–32} Several strategies have been implemented in an attempt to minimize radiation-induced xerostomia. Randomized trials have documented the benefits of amifostine,^{33,34} pilocarpine (PC),^{35,36} and, more recently, the pre-RT surgical transfer of submandibular glands to the submental space.^{37,38} These treatment options are further described below.

As demonstrated by the prospective studies of Chao et al.³⁹ and Eisbruch and colleagues,^{8,9,40} the reduction in saliva production correlates with the clinical manifestations of xerostomia and its adverse impact on QOL. Frequent signs and symptoms of xerostomia include dryness, burning sensation of the tongue, fissures at lip commissures, atrophy of the dorsal tongue surface, difficulty in wearing dentures, and increased thirst. Saliva is necessary for the normal execution of oral functions such as taste, swallowing, and speech. Unstimulated whole salivary FRs of less than 0.1 mL/minute are considered indicative of xerostomia (normal salivary FR = 0.3–0.5 mL/minute). Xerostomia produces the following changes in the mouth, which collectively cause patient discomfort and increased risk of oral lesions:

- Salivary viscosity increases with resultant impaired lubrication of oral tissues.
- Buffering capacity is compromised with increased risk for dental caries. Oral flora become more pathogenic.

Table 3. Management of the xerostomic patient

Plaque removal	Tooth brushing Flossing
Remineralization	Other oral hygiene aids Topical high concentration fluorides Children: topical and systemic Adults: topical Remineralizing solutions
Antimicrobials	Chlorhexidine solutions (rinses) Povidone iodine oral rinses Tetracycline oral rinses
Sialogogues	Pilocarpine Bethanechol Antholettithione (Sialor TM)

Note: Prescription strength fluorides should be used, non-prescription fluoride preparations are inadequate in the face of moderate to high dental caries risk. If drinking water does not have adequate fluoride content to prevent dental decay, then oral fluoride (i.e., drops, vitamins, etc.) should be provided.

Modified from Schubert, MM, DE Peterson, and ME Lloid. 1999. Oral complications. In: Thomas ED, Blume KG, Forman SJ, eds. Hematopoietic Cell Transplantation, 2nd ed., Malden, Mass: Blackwell Science Inc., pp 751–763.

- Plaque levels accumulate due to the patient's difficulty in maintaining oral hygiene. Acid production after sugar exposure results in further demineralization of the teeth and leads to dental decay.
- Mechanical cleansing ability is affected, thereby contributing to dental caries and progressive periodontal disease. Development of dental caries also is accelerated in the presence of xerostomia due to reduction in delivery to the dentition of antimicrobial proteins normally contained in saliva.

Patients who experience xerostomia must maintain excellent oral hygiene to minimize risk for oral lesions. Periodontal disease can be accelerated and caries can become rampant unless preventive measures are instituted. Multiple preventive strategies should be considered (Table 3).

D2. Dosimetric Predictors of Xerostomia

Important predictors of the degree of dysfunction include radiation dose, technique, and volume of glandular tissue in the radiation field. The clinical implementation of image-based treatment planning, improved patient immobilization, and the introduction of 3-D conformal radiotherapy techniques have allowed significant refinement in portal design. More recently, intensity-modulated RT (IMRT) techniques now permit the concave sculpting of the dose distribution near the parotid gland borders, thereby significantly reducing the mean parotid doses while still permitting the delivery of tumoricidal doses to nearby target regions. As a result, multiple investigators have attempted to characterize the dose–response characteristics of the salivary glands following conformal irradiation.^{2,3,5,6,8–10,39,41–49} An updated analysis of a prospective trial evaluating conformal parotid-sparing irradiation conducted at Washington University⁵⁰ continues to suggest an exponential reduction in parotid FR as a function of mean dose. The mean dose threshold for stimulated saliva flow expected to result in late grade 4 xerostomia⁵¹ (defined as <25% of pretreatment level) was 26 Gy. In addition, the study revealed a

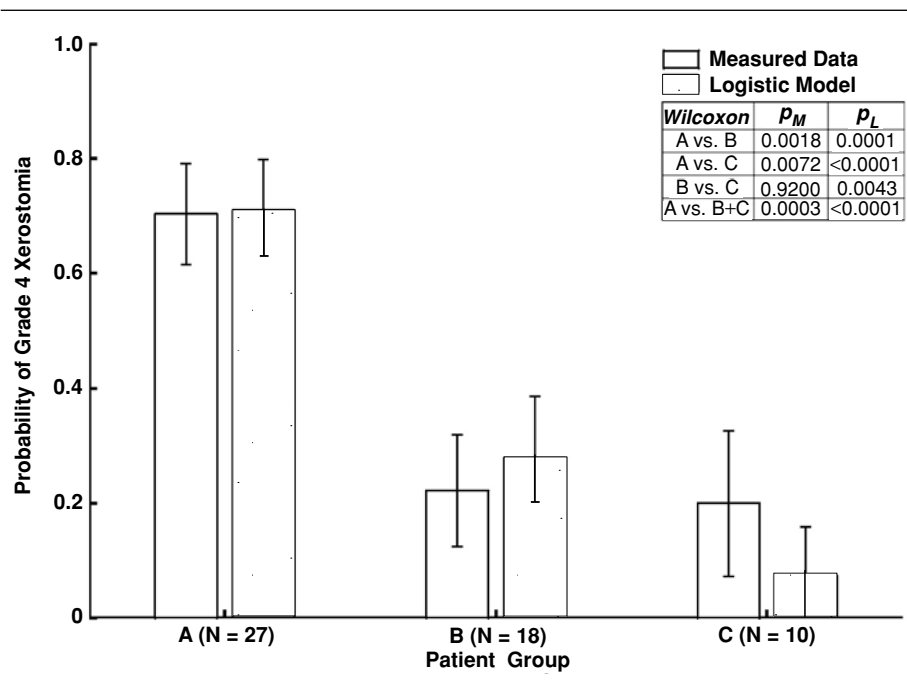


Figure 1. Probability of grade 4 xerostomia as a function of parotid gland mean dose. Patients were divided into three groups according to whether (a) both parotid glands, (b) one parotid gland, or (c) no parotid gland received a mean dose of at least 25.8 Gy. The average measured relative stimulated saliva flow at 6 months was computed for each group and used to calculate the probability of G4 xerostomia. The results were compared with the logistic model prediction for each group. Error bars represent one standard deviation. $P_{M(L)}$ = two-tailed P -values for the intergroup comparisons using saliva measurement (logistic model prediction).

70% incidence of xerostomia for patients in whom both parotid glands received a mean dose of at least 25 Gy; the risk was much smaller for patients in whom one or both parotid glands was spared (Figure 1).

A number of recent clinical publications have validated the potential for decreased late salivary toxicity with the use of conformal parotid-sparing irradiation in a number of H&N treatment subsites. The patterns of failure following parotid-sparing irradiation have also been reported and remain unchanged compared with conventional irradiation,^{47,52} suggesting no evidence of tumor protection. In an update of the University of California, San Francisco, experience with treatment of nasopharyngeal cancer, Lee et al.⁴⁴ showed excellent loco-regional progression-free and overall survival rates at 4 years of 98% and 88%, respectively, among 67 patients treated with IMRT. They also reported the time-course of post-RT xerostomia (at 12 and 24 months). Remarkably, at 24 months post-RT, less than 10% of patients experienced late RTOG grade >2 xerostomia.⁵³ Similarly, in a report of 430 patients with oropharyngeal carcinoma comparing conventional radiotherapy versus IMRT, Chao et al.² demonstrated equivalent loco-regional control rates at 2 years in comparable cohorts receiving definitive or postoperative radiotherapy. Despite the equivalent tumor control, patients treated

with IMRT had significantly lower rates of late grade 2 xerostomia (17–30%) compared with 75% among patients receiving conventional irradiation. More recently, Chao et al.⁴ analyzed treatment outcomes following definitive or postoperative IMRT among 74 patients with locally advanced oropharyngeal carcinoma. At 4 years, treatment outcomes were encouraging, with estimated loco-regional control and overall survival rates of 87%. Moreover, rates of late xerostomia were consistent with the prior findings (12% of patients had late grade 2 xerostomia).

D3. Surgical Management of Xerostomia

Jha et al.³⁷ have conducted a prospective study evaluating the efficacy of surgical transfer of one submandibular salivary gland to the submental space. Among 76 enrolled patients, the salivary gland transfer was done in 60 patients, and 43 had salivary gland transfer and postoperative RT. At a median follow-up of 14 months, 81% experienced none or minimal xerostomia, and 19% developed moderate to severe xerostomia. There were no significant postoperative complications. In response to the encouraging results from this trial, the submental transfer technique is undergoing evaluation in a prospective multicenter study (RTOG 0244).

D4. Mucositis

Oral mucositis results from radiation-induced mitotic death of the basal cells of the oral mucosal epithelium. While it represents¹⁹ an expected side effect of RT to the H&N; its severity varies from mild discomfort to severe pain. Patient-related risk factors for its development include poor nutritional status, poor dental hygiene, dental caries, poorly fitting dentures or oral prosthetics, and habits such as tobacco and alcohol use. Treatment-associated risk factors include RT dose and volume, fractionation regimen,⁵⁴ treatment site, use of concurrent chemotherapy, and surgical treatment.

The clinical course of mucositis is well described; characteristic symptoms include erythema, edema, tenderness, pain, difficulty in swallowing, and hoarseness. The typical onset of symptoms is approximately 2 weeks after initiation of RT. Symptoms may persist up to 4 weeks after completion of the therapy, or longer when concurrent chemotherapy is utilized.

Management is directed toward (1) minimizing continued exposure of the affected mucosa by chemical or mechanical irritants (such as tobacco and alcohol, or poorly fitting dentures), (2) maximizing the patients' nutritional status, (3) emphasizing oral hygiene, as discussed previously in this chapter, and (4) maintaining adequate pain management. In addition, specific medical therapy (described below) can be instituted adjunctively when necessary.

E. MEDICAL MANAGEMENT OF XEROSTOMIA AND MUCOSITIS

E1. Amifostine

Unfortunately, some patients treated with conformal parotid-sparing irradiation and the majority of patients receiving bilateral neck RT using conventional methods continue to experience debilitating xerostomia. Therefore, the potential for additional sparing

of normal tissues beyond that achievable with IMRT continues to elicit considerable research efforts. One such endeavor involves the joint utilization of IMRT and radioprotectors, chemical compounds that reduce the biological effects of irradiation in normal tissues. As the first cytoprotective drug to attain approval as a radioprotector in the United States and the European Union, WR-2721 (amifostine; Ethiol, MedImmune Pharmaceuticals) is the best studied agent to date. Originally developed by the United States Army in studies conducted at Walter Reed Hospital, amifostine was selected from a group of more than 4400 chemicals screened because of its superior radioprotective properties and safety profile.⁵⁵ Of particular relevance to H&N cancer, the drug is known to concentrate in the salivary glands, achieving an estimated dose reduction factor of 2.0 in these organs.

The effectiveness of this radioprotector was recently examined in a multi-institutional, international MedImmune Oncology phase III trial. The study included 315 patients with H&N cancer³³ treated with conventional RT with and without amifostine. Primary end points included the incidence of grade ≥ 2 acute xerostomia, grade ≥ 3 acute mucositis, and grade ≥ 2 late xerostomia and were based on the worst toxicity reported. The amifostine dose was 200 mg/m²/day intravenously 15–30 minutes before each fraction of RT. Standard fractionated RT (1.8–2.0 Gy/day for 5 days/week for 5–7 weeks, to a total dose of 50–70 Gy) was used in this study. Amifostine significantly reduced grade ≥ 2 acute xerostomia from 78% to 51% ($P < 0.0001$) and grade ≥ 2 chronic xerostomia from 57% to 34% ($P = 0.002$). Median saliva production was greater with amifostine (0.26 g vs. 0.10 g, $P = 0.04$). Amifostine did not reduce mucositis. With and without amifostine, 2-year local-regional control, disease-free survival, and overall survival were 58% versus 63%, 53% versus 57%, and 71% versus 66%, respectively. Side effects associated with amifostine included nausea, vomiting, and hypotension.

Antonadou et al.³⁴ reported the results of a prospective study designed to determine the efficacy of prophylactic administration of amifostine in protecting against acute and late toxicities from radiochemotherapy in patients with H&N cancer. Fifty patients were randomized to receive CRT (2-Gy fractions, 5 days weekly, to a total of 60–74 Gy, depending on the tumor localization and TNM classification) and carboplatin. Amifostine (300 mg/m²) was administered in the study group only 15–30 minutes before RT for 6–7.5 weeks. The primary study end point was the grading of acute and late non-hematologic toxicities (mucositis, dysphagia, and xerostomia) induced by chemoradiotherapy. Secondary end points included treatment duration, hematologic toxicity, and clinical outcome. The results showed that treatment duration was significantly shorter in the amifostine-treated group ($P = 0.013$), because treatment interruptions were more frequent in the control group. Acute toxicities (mucositis and dysphagia) were less severe in the amifostine-treated group. By week 3, all in the control group experienced grade 2 mucositis compared with only 9% in the amifostine-treated group ($P < 0.0001$). By week 5, 52.2% of the patients in the control group experienced grade 4 mucositis compared with 4.5% in the amifostine-treated group ($P = 0.0006$). Similar results were obtained for dysphagia. At 3 months of follow-up, only 27% of patients in the study group experienced grade 2 xerostomia compared with 73.9% in the control group ($P = 0.0001$). Eighteen months after therapy completion, the proportion of patients

with grade 2 xerostomia was 4.5% versus 30.4% for each respective treatment group ($P = 0.047$). Cytoprotection with amifostine did not affect the treatment outcome. This randomized trial demonstrated the efficacy of amifostine in reducing mucositis and dysphagia resulting from chemoradiotherapy in patients with H&N cancer. Furthermore, amifostine reduced the severity of late xerostomia, a side effect of RT with long-lasting consequences.

In an effort to prevent the need for daily amifostine infusions during irradiation and its associated morbidity, a randomized Phase II trial evaluated the feasibility of subcutaneous (SQ) administration of amifostine during fractionated radiotherapy.⁵⁶ Patients were randomized to receive radiotherapy or radiotherapy supported with SQ amifostine. Forty patients with pelvic malignancies, 60 with lung cancer, and 40 with H&N cancer were enrolled into the study. All H&N cancer patients had local or regional disease that justified extended-field irradiation. Overall, amifostine was interrupted in 10 patients (14.2%) for fever, rash, or severe asthenia. A significant reduction of pharyngeal, esophageal, and rectal mucositis was noted in the amifostine arm ($P < 0.04$). Among H&N cancer patients, the experimental group experienced a reduction in grade 3 or 4 mucosal toxicity compared with the control group ($P = 0.02$). Radiation-induced xerostomia was noted in 15 (75%) of 20 patients in the RT-alone arm versus 11 (58%) of 19 patients in the amifostine arm ($P = 0.32$). Response rates could not be assessed among the H&N cancer patients.

E2. Other Cytoprotective Strategies

Saliva substitutes or artificial saliva preparations (oral rinses containing hydroxyethyl-, hydroxypropyl-, or carboxymethylcellulose) are palliative agents that relieve the discomfort of xerostomia by temporarily wetting the oral mucosa.

Pilocarpine

Pilocarpine is the only drug approved by the US Food and Drug Administration for use as a sialogogue (5 mg tablets of PC hydrochloride). The role of PC, a parasympathomimetic agent, in the treatment of radiation-induced xerostomia has been studied extensively during the last two decades. Early, small randomized studies were the first to demonstrate a benefit for the post-RT use of PC. Two subsequent, large, randomized trials by Johnson et al.³⁶ and LeVeque et al.³⁵ confirmed the benefits of PC and concluded that approximately 50% of the patients experienced some relief of xerostomia symptoms. The latter study also demonstrated improvement in salivary flow. Interestingly, no correlation was observed between the improvement of salivary flow and the functional improvement demonstrated by the patients. The high response rate to placebo of approximately 25% seen in these studies, however, was not explained. In an attempt to further elucidate the mechanism of action of PC and correlate response with RT parameters, Horiot et al.⁵⁷ subsequently conducted a subsequent randomized trial. PC was administered orally at 15 mg/day with a 5 mg optional increase at 5 weeks up to a daily dose of 25 mg beyond 9 weeks. Results indicated 75% compliance; 38 patients (26%) stopped treatment before week 12 for acute intolerance (sweating, nausea, vomiting) or no response. No severe complication occurred. Ninety seven patients (67%) reported significant relief of

symptoms of xerostomia at 12 weeks. Within 12 weeks, the size of the subgroup with normal food intake almost doubled, while the size of the subgroup with (nearly) impossible solid food ingestion decreased by 38% (47 vs. 29 patients). The impact on QOL was considered important or very important by 77% of the responders. No difference was found according to dose–volume radiotherapy parameters. The authors concluded that oral PC hydrochloride acts primarily by stimulating minor salivary glands; PC can be of benefit to patients suffering of severe xerostomia regardless of radiotherapy dose–volume parameters; and all responders are identified by 12 weeks post-RT.

The treatment is initiated at 5 mg orally, 3 times daily; the dose is then titrated to achieve optimal clinical response and minimize adverse effects. Some patients may experience increased benefit at higher daily doses; however, incidence of adverse effects increases proportionally with dose. The patient's evening dose may be increased to 10 mg within 1 week after starting PC. Subsequently, morning and afternoon doses may also be increased to a maximum 10 mg/dose (30 mg/day). Patient tolerance is confirmed by allowing 7 days between the increments. The most common adverse effect at clinically useful doses of PC is hyperhidrosis (excessive sweating); its incidence and severity are proportional to dosage. Nausea, chills, rhinorrhea, vasodilation, increased lacrimation, bladder pressure (urinary urgency and frequency), dizziness, asthenia, headache, diarrhea, and dyspepsia are also reported, typically at dosages greater than 5 mg, 3 times daily. Pilocarpine usually increases salivary flow within 30 minutes after ingestion. Maximal response, however, may occur only after continual use. Pilocarpine may exert a radioprotective effect on salivary glands if given during RT to the H&N.

Biafine

Biafine is a hypotonic oil and water emulsion thought to stimulate skin healing mechanisms through the selective recruitment of macrophages and the stimulation of granulation tissue. Biafine products have been used in patients undergoing RT in France for over 25 years. The potential benefit of Biafine may be clinically significant in the H&N patient population because of the proportion of grades 2 and 3 toxicities experienced. RTOG 99-13 is a recently completed study designed to compare Biafine with usual institutional practices and to evaluate its use as a prophylactic agent in reducing skin toxicity. Patients were randomized into one of the three arms: Arm 1, using a pre-declared institutional preference regimen not to include Biafine; Arm 2, with tid application of Biafine at the initiation of therapy; and Arm 3, with tid application of Biafine after the initiation of skin symptoms. Results are pending.

Vitamin E and Pentoxifylline

Vitamin E (VE) is a fat-soluble vitamin existing in a variety of forms in many foods. The most common form of VE in a Western diet is known as alpha-tocopherol. VE is considered to have antioxidant properties and VE supplements have been tested in a number of conditions including: malabsorption disorders, hematologic disorders, cardiovascular disease, and cancer. VE has been proposed as a potential radioprotector. A prospective, double-blind randomized trial in H&N cancer patients treated with RT was designed

to test the hypothesis that VE provides oral mucosal protection. An oil solution of either VE (400 mg) or placebo was rinsed twice a day over the oral cavity. Radiation doses ranged from 50 to 70 Gy per 5 to 7 weeks in conventional fractionation. The density of the incidence of severe mucositis was evaluated in both the arms. Results indicated that severe mucositis was more frequent in the placebo group (54 events/161 patients-week = 33.5%) than in the VE group (36 events/167 patients-week = 21.6%, $P = 0.038$). VE reduced the risk of severe mucositis by 36%. The investigators concluded that VE is efficacious in reducing the incidence of severe radiotherapy-induced mucositis in patients with H&N tumors treated with RT.

Pentoxifylline is a xantine derivative that acts by decreasing blood viscosity. Its use is well established in patients with chronic peripheral arterial disease and other cardiovascular conditions. Recent studies have demonstrated a reduction in chronic radiation-induced fibrosis (RIF) among breast and H&N cancer patients⁵⁸ receiving pentoxifylline and vitamin E. Pentoxifylline may also have a role in the treatment of chronic trismus.⁵⁹ Further studies should be performed to confirm these findings; at present, it is reasonable to consider the use of pentoxifylline and VE in the treatment of RIF.

E3. Skin Toxicity

Analogous to oral mucositis,¹⁹ skin toxicity is an expected, usually temporary side effect of RT to the H&N. Risk factors predictive of its development include poor nutritional status, fair complexion, history of extensive sun exposure, diabetes mellitus, and certain collagen vascular diseases (i.e., scleroderma or lupus). Treatment-associated risk factors include the use of large irradiation fields, treatment with tangential fields, electron beam therapy, altered fractionation regimens, and use of concurrent chemotherapy and surgical treatment.

The clinical course of skin toxicity is also well-characterized; in order of severity, manifestations include erythema, hyperpigmentation, and dry and moist desquamation. The typical onset of symptoms is approximately 2 weeks after initiation of RT; these may persist up to 4 weeks after completion of the therapy.

Management emphasizes (1) careful cleansing of the skin, (2) moisturizing treated skin using a hydrophilic moisturizer (Aquaphor, Eucerin crème, or aloe vera gels), (3) preventing mechanical or chemical irritation of treated skin (such as resulting from tight clothing or perfumes), and (4) maintaining adequate pain management. In the cases of moist desquamation, extra precautions should be taken to minimize the possibility of skin infection and associated treatment delays.

E4. Osteoradionecrosis

The unilateral vascular supply to each half of the mandible results in ORN, most frequently involving mandible versus maxilla. Presenting clinical features include pain, diminished or complete loss of sensation, fistula, and infection. ORN typically occurs within the first 3 years post-diagnosis, although it is thought that patients remain at indefinite risk. The diagnosis of ORN relies on the clinical examination of chronically exposed bone. Radiographic findings include decreased bone density and pathologic

fractures. Pathologic fractures can occur, as the compromised bone is unable to appropriately undergo repair at the involved sites. Risk for tissue necrosis is in part related to trauma or oral infection; however, idiopathic cases can also occur.

The incidence of ORN is somewhat difficult to estimate from the retrospective series, as it depends on the primary site and volume irradiated, and degree of comorbidities in the studied patient population. Indeed, review of the literature reveals widely ranging incidence rates from 0.4% to 56%.⁶⁰ A recent report by Reuther et al.⁶¹ evaluated the incidence of ORN in a large cohort of 830 patients and showed an overall incidence of 8.2%. The most common location was the body of the mandible. Unfavorable prognostic factors included male gender, advanced stage, segmental mandibular resections, and tooth extractions (found responsible for up to 50% of cases).

Management of Osteoradionecrosis

Patients who develop ORN should be comprehensively managed, including elimination of trauma, avoidance of removable dental prosthesis if the denture bearing area is within the necrosis field, assuring adequate nutritional intake, and discontinuation of tobacco and alcohol use. Topical antibiotics (e.g., tetracycline) or antiseptics (e.g., chlorhexidine) may contribute to wound resolution. Wherever possible, coverage of the exposed bone with mucosa should be achieved. Analgesics for pain control are often effective. Local resection of bone sequestrae may be possible.

Hyperbaric oxygen therapy (HBO)^{62–64} is generally recommended for the management of ORN, in that it increases oxygenation of irradiated tissue, promotes angiogenesis, and enhances osteoblast repopulation and fibroblast function. HBO is usually prescribed as 20–30 dives at 100% oxygen and 2–2.5 atm of pressure. If surgery is needed, 10 dives of postsurgical HBO are recommended. Unfortunately, HBO technology is not always accessible to patients who might otherwise benefit.

Partial mandibulectomy may be necessary in severe cases of ORN. The mandible can be reconstructed to provide continuity for aesthetics and function. In a report of 29 cases, Chang et al.⁶⁵ reviewed the M.D. Anderson Hospital experience with treatment of advanced mandibular ORN with free flap reconstruction. At a mean follow-up of 33 months, they reported a 21% complication rate and a 14% flap loss rate. A multidisciplinary cancer team including oncologists, oncology nurses, maxillofacial prosthodontists, general dentists, hygienists, and physical therapists is appropriate for management of these patients.

E5. Trismus

Musculoskeletal syndromes may develop secondary to radiation and surgery. Lesions include soft tissue fibrosis, surgically induced mandibular discontinuity, and parafunctional habits associated with emotional stress caused by cancer and its treatment. Patients can be instructed in physical therapy interventions including mandibular stretching exercises as well as use of prosthetic aids designed to reduce severity of fibrosis. It is important that these approaches be instituted prior to the development of trismus. If clinically significant changes develop, several approaches including stabilization of occlusion, trigger

point injection and other pain management strategies, muscle relaxants, and/or tricyclic medications can be considered.

E6. Dysphagia and Esophageal Toxicity

Dysphagia can be a prominent symptom in chemotherapy or head/neck radiation patients. Etiology is likely associated with several factors including direct neurotoxicity to taste buds, xerostomia, infection, and psychologic conditioning.

A total fractionated radiation dose of more than 3000 Gy reduces acuity of sweet, sour, bitter, and salt tastes. Damage to the microvilli and outer surface of the taste cells has been proposed as the principal mechanism for the loss of the sense of taste. In many cases, taste acuity returns 2–3 months after completion of RT. However, many other patients develop permanent hypogeusia.

Zinc supplementation (zinc sulfate 220 mg, twice a day) has been considered on a therapeutic basis in view of known antioxidant properties. A recently reported randomized trial⁶⁶ showed that the use of zinc supplementation produced a significant reduction in the severity of radiation-induced mucositis and oral discomfort (taste was not evaluated as a primary endpoint). These data are in need of further validation; however, it is reasonable to consider the use of zinc supplementation until such evidence becomes available.

Recent publications have attempted to quantitate the degree of pharyngeal transport dysfunction following chemoradiotherapy.¹⁵ In a series of 15 patients with locally advanced H&N cancer receiving concomitant hydroxyurea and hyperfractionated irradiation, Kotz et al. performed post-RT videofluoroscopic swallow function studies and observed posterior pharyngeal dysfunction characterized by impaired pharyngeal constrictor motility in 12 patients (80%). All patients exhibited pharyngeal abnormalities limiting bolus transport and clearance. In a series of 29 patients with unresectable H&N cancer, Eisbruch et al.⁶⁷ performed serial (pretherapy at 1–3 months post-RT and at 6–12 months post-RT) swallowing studies with videofluoroscopy and esophagograms. Posttreatment changes included reduced inversion of the cricopharyngeal muscle and laryngeal closure, promoting aspiration. The rate of aspiration increased significantly in the early and late post-RT studies.

Loss of appetite can also occur in cancer patients concurrent with mucositis, xerostomia, taste loss, dysphagia, nausea, and vomiting. QOL is compromised as eating becomes more problematic. Oral pain upon eating may lead to selection of foods that do not aggravate the oral tissues, often at the expense of adequate nutrition. Modifying the texture and consistency of the diet, adding between-meal snacks to increase protein and caloric intake, and administering vitamin, mineral, and caloric supplements can minimize nutritional deficiencies.

Nutritional counseling may be required during and following the therapy; maintenance of appropriate caloric and nutrient intake should be emphasized. Nasogastric feeding tubes or percutaneous esophageal gastrostomy may be required when swallowing is significantly impaired. Total parenteral nutrition represents a means to provide adequate nutrition but is generally reserved for patients who cannot eat due to mucositis or nausea, as opposed to dysgeusia alone.

When cancer therapy-associated mucositis has resolved, nutritional counseling must consider long-term complications including xerostomia, increased caries risk, altered ability to masticate, and dysphagia. Consideration must thus be given to taste, texture, moisture, calories, and nutrient content.

Cancer patients undergoing high-dose chemotherapy and/or radiation can experience fatigue related to either disease or its treatment. These processes can produce sleep deprivation or metabolic disorders, which collectively contribute to compromised oral status. For example, the fatigued patient will likely have impaired compliance with mouth care protocols designed to otherwise minimize risk of mucosal ulceration, infection, and pain. In addition, biochemical abnormalities are likely involved in many patients. The psychosocial component can also play a major role, with depression contributing to the overall status.

F. SUMMARY

- Toxicity from H&N cancer irradiation is complex and multifactorial. The nature and severity of the side effect profile for a given patient result from the interplay of patient-related, tumor-related, and treatment-factors.
- Among the side effects studied, skin toxicity and mucositis represent the most common acute effects of irradiation. Supportive care is essential to prevent superimposed infection and other complications that might lead to treatment breaks or, in extreme cases, discontinuation of therapy.
- Technological advances with conformal radiotherapy techniques have allowed for increasing salivary gland sparing. Further protection may be achieved with existing and future medical therapies.
- Swallowing dysfunction following chemoradiation for laryngeal cancer is significant and may persist for 1–2 years. Efforts should be made to ensure proper patient education and reassurance in this regard.

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