

# Symptom Control Issues and Supportive Care of Patients With Head and Neck Cancers

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**Abstract:** Combined-modality treatment of head and neck cancers, though linked to improved outcomes over earlier treatment methods, can be associated with acute and late adverse effects. These toxicities may lead to significant morbidity, increased mortality, and decreased quality of life. It is necessary to provide patients with adequate supportive-care measures in order to lessen suffering while maintaining the ability to deliver necessary doses of anticancer agents. The current review describes the pathology, assessment, and treatment options for cases of mucositis, impaired swallowing, nutritional and metabolic changes, xerostomia, radiation dermatitis, lymphedema, taste alterations, and pain, all of which may be associated with treatment of patients with head and neck cancers. Additionally, the pretreatment and during-treatment evaluation of dental health, as well as posttreatment dental care, are described.

Head and neck cancers are located within and adjacent to functionally critical structures. Surgical resection or the use of radiation therapy to eradicate cancers can provide a cure, however, treatment may be associated with acute and late effects. Over the past decade there has been a marked increase in the use of combined-modality therapy as studies have demonstrated improved outcomes with this approach.<sup>1</sup> Combined-modality therapy is now a standard treatment option for patients who, for example, wish to undergo radiation-based function preservation therapy, patients with unresectable disease, patients with locally advanced nasopharyngeal primaries, and high-risk postoperative patients. Unfortunately, improved outcomes are obtained at the expense of increased acute and late effects. These toxicities may result in significant morbidity, increased mortality, and decreased quality of life. In addition to the physical toxicities associated with head and neck cancer treatment, patients are faced with a host of psychological and social problems associated with cancer diagnosis, treatment, and survivorship.<sup>2</sup>

## Keywords

Head and neck cancer, supportive care, mucositis, dermatitis, lymphedema, xerostomia

## The Impact of Side Effects, Symptoms, and Functional Loss

Clearly, the acute toxicities of therapy have a dramatic impact on patients and their families. Whether dealing with wound-healing issues in a patient who has undergone surgical resection, mucositis in a patient undergoing radiation, or chemotherapy-induced vomiting in a patient receiving palliative therapy for metastatic disease, it is apparent to patients, caregivers, and medical staff that the acute side effects of therapy must be addressed aggressively. Failure to provide adequate supportive measures may: 1) compromise the delivery of curative therapy, 2) result in significant morbidity and mortality, and 3) cause undue suffering and diminished quality of life for both patient and caregiver.

The late effects of therapy are often less overt and may be overlooked or marginalized. The question arises as to why efforts should be directed at identifying and studying the late effects of treatment. The obvious answer is that late effects may diminish quality of life and functional capacity; however, there may be broader implications.<sup>3,4</sup> Patients treated for head and neck cancer have higher mortality due to nonmalignant causes than comparable patients without a cancer history. In a study by Hall and colleagues, the death rate for cancer patients “cured” of their disease was 18% higher than for age- and comorbidity-matched controls.<sup>5</sup> There are several potential reasons for this discrepancy. First, physicians often treat comorbid disease in cancer patients in a less aggressive manner than they would in patients without cancer; thus, cancer patients may have a higher death rate from comorbid disease. A second possibility is that cancer treatment or treatment-related side effects may directly affect a patient’s long-term health.<sup>6,7</sup> Therefore, studying late effects has profound implications for patient quality—and, potentially, duration—of life.

When assessing late effects of therapy, it is critical to have a framework on which to judge manifestations. Surgery, radiation, and chemotherapy are associated with alterations in normal tissue function. The alterations in function may be subclinical and without any evident adverse effect<sup>8</sup>; alternatively, treatment may result in altered function that requires patients to use adaptive strategies and coping mechanisms. Patients may adapt easily to some functional abnormalities. For example, a patient who requires dental extraction prior to chemoradiation may be able to obtain dentures that allow near normal mastication and a healthy diet. Other functional effects may result in significant handicaps.<sup>9-11</sup> For example, a patient who works as a salesperson and undergoes total laryngectomy may find it difficult or impossible to continue to work in the same capacity as he or she did

prior to surgery. It is critical that we assess the clinical and subclinical effects of treatment on function as well as the way in which functional deficits result in disability and handicap.

## Mucositis

Mucositis is a complex biological process that results from chemotherapy or radiation damage to the mucous membranes and underlying soft tissue. The normal maturation of mucosal cells from basal to surface layers requires approximately 14 days, corresponding to the onset of clinical mucositis and associated symptoms after initiation of radiation. Mucositis can occur in the mouth, pharynx, esophagus, and, at times, the entire gastrointestinal (GI) tract.<sup>12</sup> Oral and pharyngeal mucositis is a serious and currently inevitable acute complication of radiotherapy in head and neck cancer patients. Mucositis impairs eating, swallowing, and speech, resulting in a significant decline in quality of life. If severe, mucositis can result in life-threatening sepsis or inanition requiring hospitalization and treatment interruptions.

### *Pathobiology*

Sonis and associates have developed a five-stage model that depicts the biological processes and pathways that are involved in the development of mucositis.<sup>13,14</sup> Stage 1, “initiation,” is that of beginning tissue damage. Radiation and/or chemotherapy cause breakage of basal epithelial and submucosa strands and generation of cell, tissue-, and vessel-damaging reactive oxygen species (ROS). In stage 2, “primary damage response,” cumulative damage to DNA and non-DNA components leads to a series of biological changes accelerating epithelial and mucosa cell damage. DNA activation of nuclear factor- $\kappa$ B (NF- $\kappa$ B) can upregulate nearly 200 genes that influence mucosal integrity, thereby disturbing the delicate proapoptotic and antiapoptotic actions in normal tissue. Specifically, NF- $\kappa$ B upregulates genes responsible for the production and release of proinflammatory cytokines. Proinflammatory cytokines stimulate connective tissue disintegration and decrease oxygen in epithelial cells, causing both cell damage and cell death. Non-DNA mechanisms such as radiation- and chemotherapy-induced activation of sphingomyelinase or ceramide synthase also occur during stage 2 and damage the cell membrane. During stage 3, “signal amplification,” gene upregulation started in stage 2 continues and positive feedback loops such as the interaction between NF- $\kappa$ B and tumor necrosis factor- $\alpha$  and interleukin-1 $\beta$  arise, increasing the initial damage. Through these first three stages, mucosal erythema may be the only sign visible upon physical examination. During stage 4, “ulceration,” extraordinarily painful lesions

are clearly visible. Superficial bacterial colonization may be present in the oral cavity, and cell-wall products from these colonizations can invade the submucosa. This invasion stimulates mononuclear cells to produce and release additional proinflammatory cytokines. It is thought that these proinflammatory cytokines further increase tissue injury by promoting expression of proapoptotic genes.<sup>13</sup> The abilities to taste and eat food may be significantly impaired and the patient may report a significant decline in overall quality of life. At this point, patients are at risk for infection because mucosal breaks allow systemic entry of microorganisms that are normally confined to the mouth. The fifth and final stage, "healing," will begin only when radiation and chemotherapy end and the triggers for these series of complex biological events are removed.

### ***Assessment and Examination***

Ongoing assessment of the mucosa during treatment and after treatment is essential. Physical examination of the oral cavity in the early phases of mucositis may reveal only mild erythema. This is followed by the development of patches of white discoloration of the mucosa. Confluent deep erythema and pseudomembrane formation may follow. The most severe manifestation of confluent mucositis is frank ulceration of the mucosa with spontaneous bleeding. This sequence is reflected in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0 mucositis grading system. Despite having a standardized system for grading oral mucositis, several assessment issues must be noted. First, it is impractical to routinely visualize all potentially involved mucosa to assess for lesions; thus, the degree of mucositis may be underreported. Second, mucositis-related symptoms and function loss may not always correlate with mucosal appearance. For example, some patients may experience severe pain or swallowing difficulty with few or no visible lesions. Finally, frank ulceration may resolve while other manifestations such as mucosal edema and pain persist, leaving long-term unrecognized sequelae. In order to address these concerns, the effect of mucositis on function has been incorporated into CTCAE v3.0. Therefore, functional deficits should be assessed in order to give a broader and more accurate perspective of the ramifications of mucositis.

### ***Prevention and Treatment***

Numerous preventive and treatment measures for oropharyngeal mucositis have been reported, but rarely have these been substantiated or corroborated by rigorous well-controlled studies. Two groups have undertaken to review the mucositis literature: the Cochrane Collaborative<sup>15</sup> and the Multinational Association for Supportive

Care in Cancer (MASCC).<sup>16</sup> The Cochrane Collaborative reviewed intervention trials aimed at preventing oral mucositis. MASCC assessed both preventive and treatment measures. The Cochrane review indicated the following agents provided some evidence of benefit in more than one study:

- Amifostine showed minimal benefit in moderate or severe mucositis (relative risk [RR]=0.84; 95% confidence interval [CI], 0.75–0.95 and RR=0.60; 95% CI, 0.37–0.97, respectively)
- Antibiotic paste demonstrated moderate benefit (RR=0.87; 95% CI, 0.79–0.97)
- Hydrolytic enzymes reduced moderate and severe mucositis with RR=0.52 (95% CI, 0.36–0.74) and RR=0.17 (95% CI, 0.06–0.52), respectively

The MASCC guidelines recommend multidisciplinary development and evaluation of oral care protocols and patient and staff education in the use of such protocols to reduce the severity of oral mucositis from chemotherapy and/or radiation therapy. As part of the protocols, the panel suggests the use of a soft toothbrush that is replaced on a regular basis. Elements of good clinical practice should include the use of validated tools to regularly assess oral pain and oral-cavity health. The inclusion of dental professionals is vital throughout the treatment and follow-up phases. The MASCC guidelines further recommend:

- patient-controlled analgesia with morphine as the treatment of choice for oral mucositis pain in patients undergoing hematopoietic stem-cell transplantation; regular oral pain assessment using validated instruments for self-reporting is essential
- that sucralfate not be used for the prevention of radiation-induced oral mucositis
- that antimicrobial lozenges not be used for the prevention of radiation-induced oral mucositis
- the use of midline radiation blocks and three-dimensional radiation treatments to reduce mucosal injury
- benzydamine for prevention of radiation-induced mucositis in patients with head and neck cancer receiving moderate-dose radiation therapy.

A variety of newer agents are entering phase III trials with the promise of minimizing mucositis and, therefore, improving quality of life and treatment compliance. This is particularly important when more aggressive combined-modality regimens are being utilized. However, any future remedy must show consistent results and be easily administered before it gains universal acceptance in head and neck cancer treatment.

## Swallowing

Swallowing is a complicated, multiphase process. During the oral phase, the oral cavity acts as a receptacle where the food is masticated and a bolus is formed. The oral tongue aids in pushing the food bolus posteriorly towards the pharynx. As the food bolus passes the faucial arches, the pharyngeal peristaltic reflex initiates a smooth wave of muscular contraction that results in rapid propulsion of the food bolus down the alimentary tract. The soft palate elevates upward and in a posterior direction to prevent the food bolus from entering the nasopharynx. The tongue base moves posteriorly, while the larynx is pulled up and forward. When we think of swallowing function, we normally consider the physiologic and anatomic abnormalities that affect outcome,<sup>15</sup> for example tissue loss postoperatively or edema from radiation therapy. However, swallowing dysfunction should be viewed as a global construct that incorporates all factors that may contribute to a patient's perception of altered function. This includes xerostomia, dentition, taste, mucosal sensitivity, and altered mucosal sensation.

Swallowing may be evaluated by several methods. The modified barium swallow is usually considered the gold standard. Alternatively, swallowing may be assessed through a flexible endoscopic evaluation of swallowing (FEES) study. FEES is a videoendoscopic procedure that allows visualization of swallowing and is helpful for assessing residuals, laryngeal penetration, and aspiration. It does not assess the oral phase, pharyngeal stripping, transit through the upper esophageal sphincter, or the extent of aspiration.

The bulk of patients do not have clinically significant swallowing deficits at presentation. However, swallowing deficits may develop as a result of therapy. Unfortunately, clinical trials rarely report functional outcome in a clear and consistent manner. Rosenthal and colleagues reviewed dysphagia outcome in eight clinical trials.<sup>18</sup> Results varied depending on the treatment regimen, with 1-year feeding tube rates as low as 3% and as high as 41%. Other factors that may affect swallow outcome include the availability of aggressive swallow therapy.

Dysphagia is associated with significant consequences. First, patients with dysphagia may aspirate and develop aspiration pneumonia. Chronic aspiration may result in pulmonary compromise. In addition, dysphagia can cause decreased or altered oral intake leading to nutritional deficiencies (see below). Patients with significant reduction in caloric intake may require feeding tube placement or total parenteral nutrition. Finally, dysphagia is associated with a marked decrease in quality of life.<sup>19</sup>

## Dietary Adaptations

Many patients with dysphagia must adapt their diet to food consistencies they can swallow. Dietary adaptations can be either beneficial or detrimental. Adaptive dietary changes include the use of supplements. Maladaptive changes can include the limitation or elimination of specific food groups. Investigators at Vanderbilt-Ingram Cancer Center conducted a 24-hour diet recall using state-of-the-art diet software in patients who completed chemoradiation 1, 6, and 12 months prior to study entry.<sup>20</sup> Results demonstrated that 80%, 50%, and 20% of patients, respectively, were using dietary supplements. As late as 12 months after chemoradiation, patients had diets low in antioxidants, high in fat, and low in fiber. Many patients indicated dentition and xerostomia contributed to diet adaptations. Beecken and Calman reported similar results in 24 long-term survivors of head and neck cancer treatment.<sup>21</sup> All patients had completed therapy at least one year prior to study entry (average: 3 years 5 months, range: 18 months to 7 years). Seventy-two percent of patients reported dietary modifications: 12 patients ate no dry food and 5 ate only soft-food consistencies. Increasing dietary modifications were associated with decreased energy and protein intake.

## Nutrition and Metabolic Changes

### Nutritional Assessment, Weight Loss, and Intervention

Adequate nutrition requires a balance between nutrient intake and demand. Because cancers of the head and neck often involve portions of the alimentary system, oral intake is frequently limited, leading to malnutrition. Overall, the incidence of malnutrition in head and neck cancer patients is between 30% and 50%.<sup>7,22</sup> Patients with advanced-stage disease are more likely to present with or develop malnutrition during therapy than patients with early-stage disease.<sup>23,24</sup> Numerous studies have been conducted to determine whether nutritional status at the time of presentation predicts for various outcomes. Although the data in head and neck cancer patients are both limited and flawed, malnutrition does appear to have adverse associations: it is associated with a decrease in quality of life (although results are conflicting),<sup>25</sup> an increase in surgical complications,<sup>7</sup> a decrease in immune function,<sup>7</sup> and, most importantly, a decrease in survival.<sup>22,23</sup> In one study of 114 patients, the 2-year survival rate was 37.7% in well-nourished patients versus 7.5% in malnourished patients.<sup>22</sup> Similar data regarding survival have been noted by others.<sup>25</sup> Whether decreased survival in malnourished patients is due to the physiologic effects of malnutrition or whether it is an epiphenomenon reflecting associated generalized weakness and deconditioning, more advanced

**Table 1.** Definition of Critical Weight Loss

Cumulative Weight Loss and Time Course		
Time Course	Significant Weight Loss	Severe Weight Loss
1 week	≤2%	>2%
1 month	≤5%	>5%
3 months	≤7.5%	>7.5%
6 months	≤10%	>10%

disease, or lower socioeconomic status is unclear. Nonetheless, the importance of nutritional support cannot be overemphasized.

Nutritional deficiencies can be due to cancer or its treatment. Chemotherapy, radiation therapy, and surgery all adversely impact on energy balance; therefore, all head and neck cancer patients, regardless of the treatment plan, should undergo a complete evaluation at baseline to determine whether nutritional deficiencies exist. If nutritional deficiencies are identified, the severity of those deficiencies and the underlying cause should be ascertained. Based on the assessment, a risk status should be determined. Table 1 provides a definition of critical weight loss as a function of time. Patients with a critical weight loss should be seen quickly by a dietician to formulate an aggressive intervention strategy. Based on the findings of the nutritional assessment, a support plan should be developed. Nutritional assessments should continue on a frequent basis throughout the treatment phase and periodically during recovery to ensure adequate nutritional intake. This generally requires the expertise of a dietician versed in the issues facing patients with head and neck cancer.

In order to develop an optimal intervention strategy, it is important to understand the factors that contribute to weight loss and dietary inadequacies. Issues that must be considered include: 1) alimentary tract obstruction or dysfunction related to tumor or treatment; 2) tumor-related symptoms such as pain; 3) toxicities of radiation therapy such as mucositis, mucous production, and tissue edema; 4) toxicities of chemotherapy such as nausea and vomiting; 5) problems secondary to substance abuse; and 6) socioeconomic factors such as lack of support or finances. In addition, patients may present with cancer cachexia-like syndrome. Although some patients have a single cause of malnutrition, for most head and neck cancer patients, nutritional deficits are multifactorial.

Intervention strategies are based on the identified factors contributing to malnutrition. Patients should be made aware of their caloric and protein requirements. Dietary intake diaries aid patients and staff in determin-

ing whether patients are achieving their nutritional goals and can help identify issues that need to be addressed. For patients with mild or moderate nutritional deficiencies, the use of supplements and appetite stimulants may be sufficient to achieve weight maintenance. More aggressive intervention may be required for some postoperative patients and patients undergoing chemoradiation for locally advanced disease.

### **Enteral Feeding**

It is critical for medical staff who treat head and neck cancer patients to be familiar with the indications for and care of feeding tubes.<sup>23,26</sup> Most patients who undergo surgery will have a nasogastric (NG) feeding tube placed. For those who are likely to recover swallowing function quickly, this is a reasonable choice, as complications are usually minor. For patients who are likely to have prolonged difficulty swallowing, gastrostomy placement should be considered. Gibson and Wenig conducted a retrospective chart review of 89 head and neck cancer patients who underwent surgical resection: 43 received a preoperative percutaneous endoscopic gastrostomy (PEG) and 46 were provided nutrition via an NG tube.<sup>27</sup> Hospital stay was reduced in PEG patients with laryngeal, tongue base, and tonsil primaries. The benefit was limited to stage 3 and 4 tumors. Schweinfurth and associates conducted a retrospective chart review of head and neck cancer patients to identify prognostic factors for prolonged enteral feeding requirements.<sup>28</sup> Of 142 patients, 38 (27%) required long-term enteral feeding; 9 of 38 eventually had their tubes removed. Predictors for long-term enteral feeding included heavy alcohol use, tongue-base involvement, pharyngectomy, composite resection, myocutaneous flap reconstruction, and radiation. The authors recommended gastrostomy placement at the time of surgery for these high-risk patients.

Enteral feeding may also be required by patients undergoing radiation-based treatment. The painful ulcerations, edema, and mucous production that accompany mucositis can cause a marked decrease in oral intake; a weight loss of 10% or more during therapy is common.<sup>29</sup> A high percentage of patients who undergo chemoradiation require feeding-tube placement in order to provide adequate caloric intake. Studies of tube-feeding in patients receiving chemoradiation have demonstrated that patients who have feeding tubes placed prophylactically have decreased weight loss compared to those who do not.<sup>30,31</sup> Recently, the practice of prophylactic feeding tube placement has been questioned because it may lead to higher rates of long-term tube dependence due to muscular atrophy.<sup>18</sup> Therefore, patients who have feeding tubes placed should be encouraged to continue swallowing exercises as directed by a speech and swallowing pathologist.

Once a feeding tube is placed, the patient must work with the dietician and treating physician to develop a nutritional plan. Feedings may be given by 24-hour continuous infusion, bolus feedings, or a combination. Most patients use bolus feedings for the sake of convenience. Basal energy expenditure (BEE) can be calculated using the Harris-Benedict equation,<sup>32</sup> which takes weight, height, and age into consideration:

**Men:**  $BEE = 66.5 + (13.75 \times \text{kg}) + (5.003 \times \text{cm}) - (6.775 \times \text{age})$

**Women:**  $BEE = 655.1 + (9.563 \times \text{kg}) + (1.850 \times \text{cm}) - (4.676 \times \text{age})$

Because head and neck cancer patients undergoing aggressive combined modality therapy are stressed, they should receive 1.5–2.0 g of protein per kg body weight. Additionally, fluid requirements are increased due to insensible losses from radiation mucositis and dermatitis.

Most head and neck cancer patients who require prolonged enteral feeding will undergo PEG placement. Complications of PEG placement are uncommon and generally minor. In one report of 136 PEGs placed in 126 head and neck cancer patients, 97% of tubes were placed successfully.<sup>33</sup> Only 7 complications were noted: prolonged ileus (1%), skin infection (1%), and tube dislodgement (4%). Three patients (2%) required laparotomy. Alternatives include placement by interventional radiologists or surgically placed tubes. In a survey of outcomes among 83 patients with a broad array of medical problems who required a surgical gastrostomy, 41 patients experienced a complication; 14% were major and 86% were minor.<sup>34</sup> Major complications included wound infection, ileus, fistula, and tube obstruction requiring re-placement. Absolute contraindications to feeding-tube placement include inability to bring the anterior wall in apposition to the abdominal wall, obstruction of the pharynx or esophagus, and uncorrectable coagulopathy.<sup>35</sup>

It must be noted however, that the placement of a feeding tube does not guarantee adequate caloric intake. Patients who undergo feeding-tube placement are often ill and debilitated by treatment. They usually require assistance from caregivers in order to master the many complicated tasks required for tube-feeding. Silver and colleagues reported the results of a study assessing the ability of caregivers to assist elderly (>60 years) head and neck cancer patients who had undergone feeding-tube placement.<sup>36</sup> Thirty patient/caregiver pairs were evaluated between 1 and 3 months post-feeding tube placement. Caregivers reported an average of 62 hours of direct patient care per week. Overall, caregivers did not feel that they had been adequately trained. Lack of training was

one of the factors that contributed to inadequate caloric and fluid intake by patients.

GI dysmotility is a common problem in patients undergoing aggressive chemoradiation and enteric feedings. Contributing factors include medications (such as opioids), electrolyte imbalance, decrease in activity level, dehydration, and a physiologic stress response. GI dysmotility results in decreased feeding capacity due to early satiety, bloating, and nausea. It may cause reflux of stomach contents, which can exacerbate mucositis, and also increase the risk for aspiration. The use of prokinetic agents such as metoclopramide can increase gastric motility. Proton pump inhibitors can decrease reflux.

### *Metabolic Changes Associated With Cancer Cachexia*

Cancer cachexia is a term that is used to describe a metabolic state noted in patients with advanced cancer.<sup>37</sup> This syndrome is characterized by anorexia, fatigue, weight loss, weakness, muscle and fat wasting, and anemia. Cancer cachexia is caused by the production of proinflammatory mediators. Anorexia is a common complaint in patients with cancer. Considerable work has been done in rats to elucidate the underlying mechanism of anorexia. In the rat model, appetite is regulated by central and peripheral mechanisms.<sup>38</sup> Orexigenic and anorexigenic hormonal and neuropeptide signals contribute to balancing the system. Unfortunately, our understanding of anorexia in humans is limited, and the scant data available are in conflict with the rat data. Thus, treatment of anorexia is based on clinical trials, the quality of which is variable at best.

The French National Federation of Cancer Centers recommended the use of three agents—megestrol acetate, corticosteroids, and medroxyprogesterone—for treatment of cachexia.<sup>39</sup> The data to support the use of other pharmacologic therapy was weak and failed to provide convincing evidence of efficacy. The use of corticosteroids is associated with well-established acute and long-term side effects. Megestrol, a semisynthetic progestin, has become one of the most commonly used agents to treat weight loss in patients with cancer cachexia and HIV-associated wasting syndrome. Two small randomized trials have been conducted in head and neck cancer patients undergoing chemoradiation to determine whether megestrol is effective in improving appetite and decreasing weight loss.<sup>40,41</sup> The larger of the two trials randomized 129 patients to one of three arms: control, megestrol 40 mg 4 times daily, or cisapride. Cisapride was no better than placebo. Patients receiving megestrol had an increase in appetite score ( $P=.0001$ ) and less weight loss at 2, 4, 6, and 8 weeks ( $P$  values significant at each time point).

## Dental Care

Dental care remains a critical component of the multidisciplinary approach to the head and neck cancer patient. Dental oncology represents a combination of several aspects of dentistry, including general dentistry, maxillofacial prosthetics, oral medicine, oral surgery, and oral pathology.<sup>42</sup> Although a formal dental oncology practice is not available in all communities, good basic dental care is required in order to achieve maximal functional outcomes after radiation therapy. In order to understand why dental care plays an important role in disease management, it is imperative to understand the effects of radiation therapy and chemotherapy on the normal tissues of the oral cavity.

The tissues of the oral cavity demonstrate differing sensitivities to the ionizing effects of radiation and to chemotherapy, both of which target rapidly dividing cells. The higher the cellular turnover rates, the more sensitive the tissues are to the effects of chemotherapy and radiation. Thus, because nonkeratinized mucosal epithelial cells display one of the most rapid cellular turnover rates, these cells within the oral cavity are particularly sensitive to the acute effects of chemotherapy and radiation. Late radiation effects can involve all tissues but particularly those that proliferate slowly and stem from radiation-induced microvascular damage.<sup>43,44</sup>

Importantly, the damaging effects of radiation-based therapies are not limited to the oral mucosa. All tissues (dentition, bone, periodontium, masticatory musculature, salivary glands) are at risk for both acute and late toxicities. Although few firm evidence-based guidelines for dental care in head and neck cancer have been published, a full dental program is a well-recognized component of successful head and neck care.<sup>45,46</sup> In order to minimize acute and late dental complications of radiation or chemoradiation, the dental care program should encompass at least three time points: pretreatment evaluation, evaluation during treatment, and posttreatment care.

### *Pretreatment Evaluation*

Prior to therapy for head and neck cancer, a dental evaluation must be undertaken. A complete dental examination should include several key components. First, a history and physical examination of the oral cavity and extraoral tissues (eg, lymph nodes) should be performed. Panorax radiography with bite wing and periapical views should be obtained. Consultation with the treating medical or radiation oncologist is necessary in order to determine several key therapeutic components, including tumor localization, stage, radiation treatment fields, planned dose of radiation, and fractionation.<sup>42,47-49</sup> The goal of the pre-

therapy dental examination is to identify areas of mucosal inflammation or infection; determine tumor involvement of bone; evaluate root structure; and assess for the presence of dental caries, cysts, abscesses, impacted teeth, incomplete tooth eruption, and tooth decay. In general, the pretherapy dental examination should identify areas that are considered to be at high risk for complications, with particular attention paid to nonrestorable dental conditions and factors that may further compromise mucosal integrity or promote osteoradionecrosis.<sup>47-49</sup> Patients who have not undergone full dental prophylaxis within three months prior to therapy should undergo this procedure prior to initiation of radiation or chemoradiation.<sup>42</sup>

Because of the high risk of complications, dental extractions should be strongly considered for advanced caries; periapical disease; moderate to severe periodontal disease; partially impacted third molars with evidence of pericoronitis; and teeth with advanced bone loss, mobility, or excessive bleeding on inspection.<sup>42,44,50,51</sup> However, the timing of extractions proves important as 14–21 days of healing is required prior to initiation of radiation-based therapy. Failure to allow adequate healing increases the risk of osteoradionecrosis.<sup>42,48-50</sup> Restorative dental care should also be performed on salvageable tissues prior to the initiation of radiation.

Daily fluoride treatments represent an important component of dental care and prophylaxis. Caries are common in postirradiated patients, especially in those with xerostomia. A review of multiple studies demonstrates that fluoride varnishes are effective in caries prevention in both nonirradiated and irradiated patient populations. Commonly, standard dental impressions are used to create a fluoride tray; a nightly fluoride treatment (5% sodium fluoride for 5–10 minutes) is recommended.<sup>42,50-52</sup> This plan for daily fluoride treatments should be reviewed with the patient as compliance at this juncture is critical for maximal dental outcomes. Epstein and colleagues demonstrated that only 43% of irradiated patients reported using the recommended fluoride treatment regularly.<sup>53</sup> Significant differences in the mean caries incidence between compliant and noncompliant patients were noted. If noncompliance is related to difficulties with the fluoride tray, a 1.1% fluoride paste can be used.<sup>49,53,54</sup>

### *Evaluation During Treatment*

Although no firm guidelines exist for the frequency of oral evaluations during radiation or chemoradiation, a medical caregiver should inspect the patient's oral cavity on a weekly basis during therapy. The goals of this evaluation include reinforcement of good oral hygiene and assessment of acute toxicities—such as xerostomia, mucositis, or microbial overgrowth—as aggressive management

of acute toxicities may prevent further mucosal damage and complications. Patients with baseline trismus must be monitored closely for any worsening of this condition.<sup>44,48,49,51,55,56</sup>

Frequent oral evaluations allow reinforcement of patient education and promotion of compliance. The following on-treatment strategies have been advocated for dental health. Brushing should be performed 2–4 times per day using a soft-bristled toothbrush, which is cleaned frequently with chlorhexidine. If the gums are too sore to use a toothbrush, the teeth can be cleaned with a finger wrapped in gauze and dipped in sodium bicarbonate, 0.9% normal saline, or water, if toothpaste is not tolerated. Daily oral fluoride treatments remain crucial. A mild mouth rinse (eg, 0.9% normal saline or a sodium bicarbonate solution) can be used at least 4 times per day. Waxed or taped dental floss should be used once per day in patients with platelet counts greater than 50,000/mm<sup>3</sup>. Patients must be counseled to avoid wearing removable dentures and partials during therapy. If the patient must wear these appliances, then the appliances should be brushed after every meal or at least twice per day and removed at night. The appliance must be soaked overnight in commercial cleanser or water. At the first sign of irritation, appliance-wearing should be discontinued.<sup>44,48,49,51,55,57</sup>

### **Posttreatment Care**

At the completion of therapy, dental care in the early period after treatment (first 3 months) encompasses several goals, including the identification of nonhealing mucosa or areas of continued irritation and assessment of areas of infection, xerostomia, and swallowing dysfunction, which may impact on nutrition. In general, healing of visible mucositis usually occurs 2–3 months after the completion of therapy. However, inflammation may persist. Thus, an oral cavity examination should be performed routinely until ulcers heal. Once patients have recovered sufficiently from the acute toxicities of treatment, they should be placed on 3-month dental visits.<sup>48,49,51</sup>

The long-term post-therapy goals of the dental team should include continued assessment for development of trismus and complications from xerostomia (caries, candidiasis, tooth loss, tooth demineralization, denture intolerance, sialadenitis, and periodontal disease) and identification of osteoradionecrosis. Moreover, the dental team proves critical in the early identification of tumor relapse or in the identification of new primary tumors. It should be remembered that patients with a history of squamous cell head and neck cancer develop second primary tumors of the aerodigestive tract at a rate of 2–3% per year.<sup>44,48,49,51,56</sup> Locoregional recurrence also remains a serious concern for the first 3 years post-therapy, and the best chance for successful treatment of a recur-

rence or new primary tumor requires early identification and management.

### **Xerostomia**

The major salivary glands (parotid, submandibular, and sublingual) produce about 90% of salivary secretions<sup>58</sup>; minor salivary glands lining the upper aerodigestive mucosa provide the remainder. The parotid glands contribute the greatest portion of salivary flow. The saliva produced by the parotid glands is predominantly serous. The volume of secretion by the submandibular and sublingual glands is comparatively less and is predominantly mucinous. As we age, we rely relatively less on parotid salivary volume and more on the submandibular glands.

Saliva is a complex solution containing proteins, electrolytes, and nonelectrolyte-nonprotein compounds. Major components include amylase to aid in starch digestion, mucin to aid in lubrication, and bicarbonate to act as a buffer for acids that may damage dentition. Saliva has numerous functions. It aids in the maintenance of mucous-membrane integrity and provides protection from desiccation and environmental toxins. Lysozymes, lactoferrin, and peroxidases found within saliva have antibacterial, antifungal, and antiviral effects. Saliva aids in food bolus formation and the perception of taste. It is also necessary for normal vocalization. Most importantly, saliva is critical for dental integrity.

Xerostomia is defined as the sensation of dryness of the mouth. Assessment of xerostomia is usually based on either patient report or measurement of salivary flow. Patient report measures vary from simple grading systems such as the Radiation Therapy Oncology Group Acute Radiation-Induced Salivary Gland Morbidity Score (Table 2) to questionnaires designed to assess various aspects of xerostomia and its effect on function. Unfortunately, patient reporting does not correlate well with objective measures; thus, direct measurement of salivary flow is being used with increased frequency to assess and grade xerostomia. Direct measurement of salivary flow includes both unstimulated and stimulated salivary flow rates. Unstimulated flow rates are obtained by having a patient spit into a plastic container for a specified period of time (usually 2–5 minutes). The normal unstimulated salivary flow is 0.3–0.5 mL/min. To obtain stimulated flow rates, patients are asked to chew paraffin or sugar-free gum while saliva is collected. Alternatively, salivary flow can be measured after applying 4% citric acid every 20 seconds for 2 minutes. The normal stimulated flow rates are 1–2 mL/min.

Xerostomia may be caused by a variety of factors, including the normal aging process, medical conditions such as Sjogren disease, drugs such as chemotherapeutic

**Table 2.** Xerostomia Grading Systems

<p><b>RTOG Acute Radiation-Induced Salivary Gland Morbidity Score</b></p> <ul style="list-style-type: none"> <li>• <b>Grade 1:</b> <ul style="list-style-type: none"> <li>– Mild dryness; slightly thickened saliva; slightly altered or metallic taste</li> </ul> </li> <li>• <b>Grade 2:</b> <ul style="list-style-type: none"> <li>– Moderate to complete dryness; thick, sticky saliva; markedly altered taste</li> </ul> </li> <li>• <b>Grade 3:</b> <ul style="list-style-type: none"> <li>– Not defined for acute xerostomia</li> </ul> </li> <li>• <b>Grade 4:</b> <ul style="list-style-type: none"> <li>– Acute salivary-gland necrosis</li> </ul> </li> </ul> <p><b>CTCAE version 3.0 Criteria for Xerostomia</b></p> <ul style="list-style-type: none"> <li>• <b>Grade 1:</b> <ul style="list-style-type: none"> <li>– Symptomatic (dry or thick saliva) without significant dietary alterations</li> <li>– Unstimulated flow rate &gt;0.2 mL/min</li> </ul> </li> <li>• <b>Grade 2:</b> <ul style="list-style-type: none"> <li>– Symptomatic and significant oral intake alterations (eg, copious water, other lubricants; diet limited to purees and/or soft, moist foods)</li> <li>– Unstimulated flow rate 0.1–0.2 mL/min</li> </ul> </li> <li>• <b>Grade 3:</b> <ul style="list-style-type: none"> <li>– Symptoms lead to inability to adequately aliment orally, IV fluids, tube feedings, or TPN-indicated</li> <li>– Unstimulated flow rate &lt;0.1 mL/min</li> </ul> </li> </ul>
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CTCAE=Common Terminology Criteria for Adverse Events; IV=intravenous; RTOG= Radiation Therapy Oncology Group; TPN=total parenteral nutrition.

agents, and mood disorders such as anxiety and depression. Of note, xerostomia is a clinically significant acute and late effect of radiotherapy to the salivary glands. When the major salivary glands are in the radiation port, there is a greater than 50% decrease in unstimulated flow after the first week of therapy. The salivary flow reaches less than 10% within two weeks. Permanent xerostomia begins to occur above 25 Gy.<sup>59,60</sup>

Xerostomia results in a wide variety of symptoms and functional impairment. First, xerostomia has been demonstrated to correlate negatively with quality of life measures.<sup>61–63</sup> Second, xerostomia results in dental decay, which can be rapidly progressive and may result in loss of dentition. Dental extraction in patients who have had radiation therapy to the oral cavity is associated with an increased risk of osteoradionecrosis, a dreaded and difficult-to-manage complication of head and neck cancer therapy.<sup>64</sup> Third, saliva is necessary to maintain normal oral intake and adequate nutritional balance. Hamlet and

coworkers compared swallowing function in 15 head and neck cancer patients with xerostomia to 20 controls.<sup>65</sup> Subjects underwent a videofluoroscopic modified barium swallow and a scintigraphic swallow study. Results demonstrated that there was no significant difference in swallow function between patients and controls for liquids and pastes. However, for dry material, there was a marked increase in the time required for chewing and oral manipulation. No difference in pharyngeal function was noted in this study. Scintigraphy demonstrated an increase in oral and pharyngeal residue in patients. Of note, patients with xerostomia perceive difficulty with swallowing.<sup>66</sup>

Alterations in mastication and swallowing result in dietary adaptations.<sup>20,67</sup> In a pilot study conducted by investigators at Vanderbilt University, dietary recalls were conducted in head and neck cancer patients at three different phases of recovery: early (1–2 months post-treatment), mid (4–6 months post-treatment), and late (8–14 months post-treatment). Results demonstrated that even at 12 months post-treatment, patients reported a marked decrease in intake of dry or crumbly foods.<sup>20</sup> In the qualitative component of the study, two of the most commonly reported causes of dietary adaptation were xerostomia and altered dentition. Similarly, Bäckström and colleagues reported the results of a dietary study comparing 35 patients with xerostomia due to radiation therapy and 24 controls.<sup>67</sup> The average energy intake was 300 kcal less per day in patients with xerostomia compared to controls. In both of these studies, dietary alterations led to nutrient deficiencies.

In a study by Rhodus and coworkers, patients with xerostomia due to Sjogren disease, systemic lupus erythematosus, and irradiation therapy for head and neck cancer and a matched control group were assessed for speech performance. Salivary flow rates were statistically significantly lower for patients with salivary-gland dysfunction regardless of cause. Patients were asked to complete a series of diadochokinetic speech-performance tests with and without the assistance of water. For both dry and water-assisted tasks, patients with xerostomia had a significantly lower mean number of completed tasks when compared to controls.<sup>68,69</sup>

All patients with xerostomia should receive preventive measures, including a low-sucrose diet, daily concentrated fluoride dental treatment, and routine dental care. If no salivary function is present, care should center around comfort with the use of mouthwashes and salivary substitutes. Caphosol, an electrolyte solution which is supersaturated with calcium and phosphate, was developed to replace the normal ionic pH balance in the oral cavity. Caphosol is indicated for dryness of the mouth or throat (hyposalivation, xerostomia). In addition, a number of topical agents are available over the counter. An exten-

sive listing of these agents may be found in *Oral Health in Cancer Therapy: A Guide for Health Care Professionals* (<http://www.doep.org/OHCT2monographrevised.pdf>).

For patients with residual salivary function, mechanical, gustatory, and pharmacologic stimulants should be used. Pharmacologic stimulants, although only modestly effective overall, should be tried as individual patients may derive significant benefit. Oral pilocarpine has been shown in randomized trials to reduce grade 3 xerostomia in some patients<sup>70,71</sup>; however, chronic use of this cholinergic agent may result in sequelae and quality of life may not be improved.<sup>72,73</sup> Cevimeline hydrochloride, a long-acting selective agonist of muscarinic receptors, has been shown to be helpful for Sjogren patients,<sup>74</sup> but results from a large randomized trial in radiotherapy patients are still unreported in manuscript form.

Amifostine is approved by the US Food and Drug Administration for reducing radiation-induced xerostomia. Daily administration schedule, nausea, hypotension, and cost have limited its widespread acceptance.<sup>75</sup> A meta-analysis was performed to assess the efficacy of amifostine in reducing the side effects of radiotherapy. Results demonstrated that amifostine was able to decrease acute xerostomia (odds ratio [OR] 0.24; 95% CI, 0.15–0.36;  $P < .00001$ ) and late xerostomia (OR 0.33; 95% CI, 0.21–0.51;  $P < .00001$ ). Intramuscular administration may decrease its side-effect profile. Surgical transfer of the contralateral submandibular gland to the submental triangle before radiation has demonstrated efficacy in preliminary studies.<sup>76</sup> Intensity-modulated radiation therapy (IMRT) technology is becoming available at more centers, allowing improved sparing (mean dose  $\leq 26$  Gy) of the parotids without compromising tumor control. Measurements of stimulated and unstimulated salivary flow after IMRT show considerable decreases in xerostomia and improved quality of life compared to patients treated with standard three-dimensional conformal irradiation techniques.<sup>61</sup> The question of whether IMRT in combination with amifostine can further reduce radiation xerostomia is under clinical investigation.<sup>77</sup>

## Radiation Dermatitis

The basal layer of the epidermis, hair follicles, and sebaceous glands contain rapidly dividing progenitor cells that are radiosensitive. As progenitor cells die during fractionated irradiation, few cells are left in the germinal layer to replenish the upper epithelium that is normally desquamated. This results in sloughing of the epidermis, exposing the underlying dermal tissue. Megavoltage radiation, used in modern treatment facilities, provides relative skin-sparing ability; damage to the skin was once a dose-limiting toxicity. However, with the increased use of



**Figure 1.** Confluent radiation dermatitis with moist desquamation.

concomitant chemotherapy, skin reactions are enhanced as a result of cytotoxicity and interference with DNA repair. Chemotherapeutic agents such as doxorubicin, actinomycin D, bleomycin, hydroxyurea, 5-fluorouracil, methotrexate, and taxanes can potentiate the severity of radiation dermatitis. Reactions are also worse in skin folds and areas of decreased tissue thickness, such as around the pinna of the ear or at the laryngeal prominence. The use of tissue compensators or wedges in the lateral radiation fields can minimize this effect. Other factors that affect the degree of dermatitis include pretreatment condition of the patient's skin, age, nutritional status, diabetes, areas of skin friction or moisture, and medication.<sup>78,79</sup>

Rubin and Cassarett divided radiation dermatitis into chronological categories: the acute, subacute, and late clinical periods.<sup>80</sup> The acute period of skin damage is of greatest interest to the oncologist because the symptoms are often dose-limiting and preclude aggressive treatment. Early effects include skin erythema, hyperpigmentation, hair loss, dry desquamation, and moist desquamation. Erythema can be seen as early as 24 hours after treatment; however, this is usually only a transient inflammatory response mediated by vascular flow. Generally, acute erythema occurs beginning the second week of treatment and is confined to the radiation portal. An increase in melanin and the number of melanocytes to protect the basal epithelial layer results in hyperpigmentation, and the skin becomes dry and flaky as sebaceous glands are lost. Moist desquamation occurs during the fourth and fifth weeks as basal cell layers are lost, exposing the underlying dermal tissue (Figure 1).

**Table 3.** Characteristics and Treatment of Various Stages of Radiation Dermatitis.

Sign/Symptom	Pathology	Time of Onset and Duration	Treatment Options
Early erythema/skin reddening and swelling	Capillary dilatation from histamine-like substances	Onset: within hours of treatment. Duration: hours to days	<ul style="list-style-type: none"> <li>• Rarely needed</li> <li>• Antihistamines when necessary</li> </ul>
Erythema/dryness/pain	Degeneration of basal epithelium and reduced flow of sebaceous glands	Onset: 1 to 2 weeks Duration: 7 to 10 days	<ul style="list-style-type: none"> <li>• 1% hydrocortisone cream</li> <li>• Calamine and tannic acid</li> <li>• Pure aloe vera gel</li> </ul>
Hyperpigmentation	Darkening of existing melanin, increased synthesis of melanin	Onset: fourth week Duration: months	<ul style="list-style-type: none"> <li>• Rarely needed</li> </ul>
Dry desquamation/pruritus	Focal destruction of basal epithelium, degeneration of sebaceous glands	Onset: 2 to 3 weeks Duration: 1 week	<ul style="list-style-type: none"> <li>• Anhydrous lanolin</li> <li>• Aquaphor (Beiersdorf)</li> <li>• Eucerin (Beiersdorf)</li> <li>• Lubriderm (Warner Lambert)</li> <li>• A &amp; D Ointment (Schering)</li> <li>• Natural Care Gel (Bard)</li> <li>• 1% hydrocortisone cream</li> <li>• Pure aloe vera gel</li> </ul>
Moist desquamation/serous exudates	Global destruction of germinal layer, with exposure of underlying dermis and leakage of serum; permanent epilation	Onset: fourth to fifth week Duration: 2 to 4 weeks	<ul style="list-style-type: none"> <li>• Gentle cleansing ¼ H<sub>2</sub>O<sub>2</sub></li> <li>• Tagaderm (3M)</li> <li>• Op-Site (Smith and Nephew)</li> <li>• Bioclusive (Johnson &amp; Johnson)</li> <li>• Duoderm (Squibb)</li> <li>• Domeboro (Miles)</li> <li>• Moisture-vapor permeable dressings</li> </ul>
Tissue necrosis/nonhealing ulcer	Complete destruction of epidermis, superficial capillaries, and connective tissue; overlying infection normal	Onset: 6 to 8 weeks Duration: indeterminate	<ul style="list-style-type: none"> <li>• Pentoxifylline</li> <li>• Hyperbaric oxygen</li> <li>• Surgical debridement and flap reconstruction</li> </ul>

Epilation occurs during the third week, and permanent hair loss occurs after 5500 cGy. Following treatment, moist desquamation heals as the basal epithelium at the edges of the exposed area migrates centrally to close the injured area. Late effects from severe dermatitis arise from vascular changes within the dermis. These include thinning and atrophy of the skin, hypo- or hyperpigmentation, telangiectasia, fibrosis, and, rarely, tissue necrosis.<sup>81</sup> Many approaches exist to managing radiation-induced skin reactions, yet few are scientifically based (Table 3). Procedures for skin management are therefore highly variable among institutions and practitioners. Patient education should include methods of minimizing skin trauma and irritation, promotion of healing, preventing infection, and reducing discomfort (Table 4).

## Lymphedema

Surgical disruption of lymphatic structures, radiation-induced tissue damage, and direct invasion of lymphatics by tumors or blockage of surrounding tissue by tumor bulk place head and neck cancer patients at risk for developing edema and/or lymphedema. Lymphedema results from an imbalance in capillary filtration and lymph drainage that leads to collection of fluid and protein in the extravascular and interstitial spaces of the affected area.<sup>82</sup> Head and neck and breast cancer patients are believed to experience lymphedema more than any other cancer groups. One report estimates that 6–30% of head and neck cancer patients develop edema/lymphedema<sup>83</sup>; however, patients with locally advanced disease treated with

**Table 4.** Daily Patient Instructions to Minimize Dermatitis During Radiation Therapy

- Protect the treated area from direct sun exposure more than 15 minutes each day. Avoid sunburn.
- Wash affected area with warm water and mild, nonperfumed soap. Use hands instead of washcloth. Avoid hot water. Air-dry with hair dryer on cool setting or blot with soft towel.
- Do not use aftershave or perfumes on treated area. If shaving is necessary, use only electric razor.
- Keep skin folds dry by exposing to air as much as possible.
- Avoid skin friction and rubbing by wearing loose-fitting cotton clothes. Avoid collared shirts, if possible.
- Avoid heating pads, hot water bottles, or ice packs on the treated area.
- Avoid creams, ointments, or powders unless authorized by the doctor or nurse.
- If dressings are used, avoid applying tape over the irradiated area.

combined-modality therapy may experience lymphedema more frequently.

Unfortunately, there are no adequate contemporary epidemiologic studies of lymphedema in the head and neck population; however, clinical experience indicates that patients usually develop lymphedema 2–6 months post-treatment. Lymphedema may manifest itself in a variety of ways. Most commonly, patients will notice the development of submental or facial swelling. Swelling is often positional—patients will note that it is worse in the morning after being recumbent at night and resolves when they are upright. Lymphedema of the soft tissues may become severe enough to limit range of motion and function in the jaw, neck, and shoulders. Other less well recognized manifestations of lymphedema include alterations in voice quality, swallowing dysfunction, chronic middle-ear pain, and nasal congestion. Lymphedema may resolve spontaneously over time or it may lead to progressive fibrosis and loss of function.

Assessment of lymphedema should begin with a careful history and physical (Table 5). When conducting a history and physical examination of a patient with possible edema and/or lymphedema, keep in mind that comorbid processes, such as myxedema, lipedema, deep vein thrombosis, cellulitis, or other infections may contribute to swelling.<sup>82</sup> It is critically important to distinguish lymphedema from recurrent cancer. If, after completion of the history and physical examination, additional information is needed to make a differential diagnosis and/or to determine type of treatment, additional diagnostic test-

**Table 5.** Medical History and Physical Examination for Lymphedema

#### Medical history should include:

- Review of cancer therapy treatment to determine likelihood that symptoms are related to treatment
- Review of all current and prior medical diagnoses that may contribute to soft-tissue swelling or reaction, including any recent infections
- Documentation of course of lymphedema, including onset of swelling, location of swelling, and exacerbation and remission of symptoms
- Symptom and function review: heaviness or other sensations in affected area, skin crease depth in neck, perceived swelling, pain, decrease or difficulty in mobility, swallowing dysfunction, voice alterations

#### Physical examination should include:

- Visual inspection of the skin and soft tissues of the head and neck region
- Palpation of skin and soft tissues, observing for pitting edema, firmness and induration of the skin, erythema, and warmth
- Determination of range of motion in the neck, jaw, and shoulders
- Evaluation of oral cavity to assess for edema
- Endoscopic evaluation to assess pharyngeal and laryngeal edema

ing such as CT scan,<sup>84</sup> ultrasound,<sup>85</sup> transnasal fiberoptic endoscopy,<sup>86</sup> and lymphoscintigraphy can be useful.<sup>87-89</sup>

A combination of manual lymphatic drainage and the use of compression garments are the mainstay of treatment. Treatment may improve appearance, movement, and discomfort/pain. Manual lymphatic drainage should be undertaken by lymphedema therapists trained in head and neck drainage techniques.<sup>83</sup> Patients should also be educated about factors that alleviate and worsen symptoms. In particular, it is important that patients with significant lymphedema use postural techniques at night to minimize fluid build-up. Microorganisms penetrating the skin may trigger infections among patients with lymphedema. If infection is present, aggressive treatment with antibiotics such as penicillin or erythromycin is indicated.<sup>90</sup> Consultation with a physical therapist may be beneficial to prevent loss of range of motion in the neck and shoulders.

## Taste Alterations

When we eat, we hope to enjoy the flavor of our food. Numerous components contribute to flavor, including taste buds; sense of smell; and mucosal sensory nerves that

allow us to detect texture, temperature, and irritants such as chili or pepper.<sup>91</sup> Taste buds are located predominantly on the dorsal surface of the tongue, but may also be found on the palate, pharynx, and epiglottis.<sup>64</sup> Each taste bud is composed of 50–100 taste-receptor and support cells. Taste buds are exposed to the epithelial surface through pores. Originally it was thought that there were specialized taste buds for each of the four primary taste sensations (sweet, salt, sour, and bitter); currently, it is thought that all taste buds are able to detect all types of taste.

Hypogeusia (decreases in taste sensation), ageusia (absence of taste sensation), and dysgeusia (altered taste sensation) are common complaints in patients with head and neck cancer. Cancer patients may experience taste alterations due to the neoplastic process itself, and this may contribute to the weight loss noted in patients with cancer cachexia.<sup>92</sup> In addition, taste alterations may occur as a side effect of treatment, such as radiation or chemotherapy.<sup>93–95</sup> Patients complaining of these symptoms are unable to taste and smell the aroma of food normally.<sup>96</sup> This may result in dietary adaptations, decreased oral intake, weight loss, nausea and vomiting, and decrease in quality of life.

There are no known treatments for loss of taste or taste alterations; although small preliminary studies and anecdotal reports have indicated that zinc may prevent or treat taste alterations in cancer patients. Based on these reports, investigators at the North Central Cancer Treatment Group conducted a placebo-controlled trial to determine the efficacy of zinc in preventing taste alterations in head and neck cancer patients undergoing radiation therapy or chemoradiation.<sup>97</sup> One hundred sixty-nine patients were randomized to receive zinc 45 mg orally 3 times daily or placebo throughout radiation therapy and for 1 month after the completion of therapy. Eighty-one percent of patients experienced taste alterations—61% in the zinc arm and 71% in the placebo arm. Most patients could not fully characterize their taste change. The following changes in taste were noted via questionnaire data: absence of taste (16%), absence of taste with or without exacerbation of bitter taste (8%), salty taste (5%), sweet taste (5%), and metallic taste (10%). Time to taste alteration was 2.3 weeks with zinc versus 1.6 weeks with placebo. The difference was not statistically significant; thus, it was concluded zinc was not effective in preventing taste alterations in patients being treated with radiation therapy for head and neck cancer.

## Pain

Pain is a common symptom experienced by patients with head and neck cancer. It may result from tumor or treatment. The incidence, severity, and clinical course of pain depend on numerous factors, including: 1) the site and

stage of disease; 2) the primary treatment modality; and 3) the time point in the trajectory of the disease process. Unfortunately, there are relatively few epidemiologic studies about pain in the head and neck population. The available data indicate that patients frequently present with pain, that treatment itself results in pain, that a significant percentage of patients experience chronic pain as a late effect of treatment, and that pain may be a harbinger of recurrent disease.

Chaplin and Morton reported the results of a prospective, longitudinal study of pain in 201 head and neck cancer patients.<sup>98</sup> The cohort included 93 patients who were alive without disease 2 years post-treatment. Patients were treated with surgery, radiation, or a combination of both. Forty-eight percent of patients had pain at the time of diagnosis, of which 8% rated their pain as severe. At 12 and 24 months post-treatment, pain was reported in 25% and 26% of patients, respectively. Pain was rated as severe by less than 5% of patients at both time points. Shoulder and arm pain was reported by 14% of patients at diagnosis. The incidence of shoulder pain increased to 37% at 1 year and 26% at 2 years. Neck dissection was associated with increased pain at 12 and 24 months.

Treatment-related pain is ubiquitous. Pain is an expected sequelae of surgery, thus perioperative pain control has traditionally been an important goal of the treatment team. As concurrent chemoradiation is being used with increasing frequency, the severity and impact of pain secondary to radiation mucositis is beginning to be recognized. In a recent prospective, longitudinal, multicenter study, investigators assessed mucositis-related pain in patients receiving radiation with or without chemotherapy for head and neck cancer.<sup>99</sup> Seventy-five patients were enrolled, 67% of whom received concurrent chemoradiation therapy. Pain was assessed using the Oral Mucositis Daily Questionnaire (OMDQ), a measure of mucositis-related pain and resulting function loss.<sup>100</sup> Seventy-six percent of patients reported severe mouth and throat soreness at some point over the course of treatment. Pain was severe despite the fact that the vast majority of patients (85%) were taking opioids. In addition, mucositis-related pain resulted in impairment in swallowing, eating, drinking, talking, and sleeping in the majority of patients. Similarly, the MASCC initiated a prospective study to characterize the clinical and economic effects of mucositis injury. All patients had squamous cell carcinoma and were planned for full-course radiation with either IMRT or conventional fractionation with or without concurrent chemotherapy. Patients completed the OMDQ daily throughout treatment. Results for the first 61 patients demonstrated that a high percentage of patients experienced significant mouth and throat soreness.<sup>101</sup> Patients with increased levels of pain required increased use of healthcare resources. Unfortunately,

initial reports from the Longitudinal Oncology Registry of Head and Neck Carcinoma (LORHAN) indicate that mucositis-related pain may be undertreated, particularly in the community setting.<sup>102</sup> The LORHAN cancer registry examines patterns of care for head and neck cancer patients. Eligible patients must be over 18 years of age, newly diagnosed for head and neck cancer, and scheduled to receive radiation or drug therapy. In a report of the first 509 patients, it was noted that there was a significant difference in the use of supportive care between community and academic centers. Of note, patients treated at community sites were prescribed opioids less frequently than patients being treated at academic sites (44% versus 81%;  $P < .0001$ ).

It is important to note that pain may be the presenting symptom for recurrent disease. Smit and colleagues conducted a retrospective chart review of 813 patients who were treated with curative intent.<sup>103</sup> They identified 95 head and neck cancer patients who were without evidence of cancer after completing therapy and subsequently developed recurrent disease. Patients with neck recurrence that could be surgically salvaged were excluded. A control group of 95 head and neck cancer patients whose disease did not recur was also identified. Forty-six percent of these patients with recurrent disease indicated that localized pain was the first symptom of recurrent disease; an additional 23% of patients had referred pain. Thus, pain preceded the diagnosis of recurrent disease in 70% of patients. Of note, only 2% of patients without recurrent disease reported pain; however, the low rate of pain reported by the control group may be due to issues with documentation.

## Survivorship

As increasing numbers of patients are cured of their cancers, it is evident that survivors have distinct physical, emotional, and social issues that need to be addressed. The area of survivorship, which has been neglected, is gaining attention both in the clinical and research arenas. Because of the nature of the disease and its treatment, head and neck cancer patients and their families experience significant post-treatment sequelae from their disease. It is important to understand the primary concerns of patients as they enter the post-treatment phase of their disease trajectory in order to adequately address their concerns. Dwyer and associates<sup>104</sup> conducted a qualitative study to assess the day-to-day impact of cancer on head and neck cancer patients and their caregivers. Patients were asked to participate in either focus groups or individual interviews. The following questions were used as an interview guide:

- What kinds of changes have you experienced? What things are you no longer able to do? How important were those things to you?
- What are the most troublesome symptoms you have experienced? What makes the symptoms troublesome?
- We are interested how your cancer has affected relationships with your family and friends. What has changed?
- What advice would you offer to others who are facing what you have gone through?

In addition, the patients completed several questionnaires, including the NEO Five-Factor Inventory (which assesses 5 domains of personality: neuroticism, extroversion, openness to new experience, agreeableness, and conscientiousness); the EORTC-HN 35 (a checklist assessing the prevalence of symptoms); and the Vanderbilt Multidimensional Cancer Coping Inventory. Upon completion of the interview, a thematic analysis of the transcripts was undertaken. Eleven patients (64% male, mean age: 53 years [range: 43–76 years], 64% completed treatment in the past 3 months) and 6 caregivers participated in the study. Several important themes were identified: fear of recurrence, role transitions in family and work, dealing with lingering side effects, and mood disorders. Some of these issues are not usually addressed by physicians during routine follow-up. It is critical that physicians are aware of the breadth of issues facing cancer survivors and provide patients with the support services needed to address them.

## Conclusions

Head and neck cancer patients experience a wide array of tumor- and treatment-related symptoms, ranging from physical issues such as dysphasia, pain, and lymphedema to psychosocial issues such as depression and anxiety. These biopsychosocial sequelae profoundly affect patient quality of life. Thus, physicians and staff who care for head and neck cancer patients must recognize that a considerable amount of time and effort needs to be spent on supportive-care issues. In order to optimally care for patients, evidence-based treatment protocols, algorithms, and pathways are needed. Whereas investigators are making progress to more clearly define the supportive care needs of head and neck cancer patients, evidence-based strategies to ameliorate acute and late effects of therapy are woefully inadequate. Considerable resources need to be spent identifying and testing strategies that will decrease symptom burden, enhance coping skills, and limit the effect of cancer on patients and their community of family, friends, and coworkers. Without such efforts, treatment of acute and late effects will remain experiential.

## References

- Murphy BA, Cmelak A. The role of chemoradiation for oral cavity cancers. *Oral Maxillofac Surg Clin N Am*. 2006;18:605-614.
- Murphy BA, Cmelak A, Bayles S, Dowling E, Billante C. Symptom management: head and neck cancer. In Doyle D, Hanks G, Cherny NI, Calman K, eds. *Oxford Textbook of Palliative Medicine*. Oxford: Oxford; 2003.
- Lopez MJ, Robinson P, Madden T, et al. Nutritional support and prognosis in patients with head and neck cancer. *J Surg Oncol*. 1994;55:33-36.
- Mandel DD. The role of saliva in maintaining oral homeostasis. *J Am Dent Assoc*. 1989;119:298-304.
- Hall SF, Groome PA, Rothwell, D. The impact of comorbidity on the survival of patients with squamous cell carcinoma of the head and neck. *Head Neck*. 2000;22:317-322.
- Chang V. The value of symptoms in prognosis of cancer patients. In: Portenoy RK, Bruera EA, eds. *Topics in Palliative Care*. Oxford, UK: Oxford; 2000:23-53.
- van Bokhorst-De van der Schuer MA, von Blomberg-van der Flier BM, Riezebos RK, et al. Differences in immune status between well-nourished and malnourished head and neck cancer patients. *Clin Nutr*. 1998;17:107-111.
- Bentzen SM, Dorr W, Anscher ME, et al. Normal tissue effects: reporting and analysis. *Semin Radiat Oncol*. 2003;13:189-202.
- Perry A, Shaw M. Evaluation of functional outcomes (speech, swallowing and voice) in patients attending speech pathology after head and neck cancer treatment(s): development of a multi-centre database. *J Laryngol Otol*. 2000;114:605-615.
- Jones R. Impairment, disability and handicap - old fashioned concepts? *J Med Ethics*. 2001;27:377-379.
- Cardol M, Brandsma JW, deGroot IJM, et al. Handicap questionnaires: what do they assess? *Disabil Rehabil*. 1999;21:97-105.
- Dodd M. The pathogenesis and characterization of oral mucositis associated with cancer therapy. *Oncol Nurs Forum*. 2004;31:5-11.
- Sonis ST. The pathobiology of mucositis. *Nat Rev Cancer*. 2004;4:277-284.
- Sonis ST, Elting LS, Keefe D, et al. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. *Cancer*. 2004;100(9 suppl):1995-2025.
- Worthington HV, Clarkson JE, Eden OB. Interventions for preventing oral mucositis for patients with cancer receiving treatment. *Cochrane Database System Rev* 2006;2. Arr. No.: CD000978. DOI: 10.1002/14651858.CD000978.pub2.
- Mucositis Guidelines; 2006. Available at: <http://www.mascc.org/>. Accessed October 1, 2007.
- Marchetta F. Function and appearance following surgery for intraoral cancer. *Clin Plastic Surg*. 1976;3:471-479.
- Rosenthal DI, Lewin JS, Eisbruch A. Prevention and treatment of dysphagia and aspiration after chemoradiation for head and neck cancer. *J Clin Oncol*. 2006;24:2636-2643.
- Epstein JB, Emerton S, Kolbinson DA, et al. Quality of life and oral function following radiotherapy for head and neck cancer. *Head Neck*. 1999;21:1-11.
- Murphy BA, Friedman J, Dowling E, Cheatham R, Cmelak A. Dietary intake and adaptations in head and neck cancer patients treated with chemoradiation. *Proc Am Soc Clin Oncol*. 2002;21:Abstract 932.
- Beecken L, Calman F. A return to "normal eating" after curative treatment for oral cancer. *Eur J Cancer B Oral Oncol*. 1994;30B:387-392.
- Brookes GB. Nutritional status-a prognostic indicator in head and neck cancer. *Otolaryngol Head Neck Surg*. 1985;93:69-74.
- van Bokhorst-De van der Schuer MA. The impact of nutritional status on the prognoses of patients with advanced head and neck cancer. *Cancer*. 1999;86:519-527.
- Newman LA, Vieira F, Schwiezer V, et al. Eating and weight changes following chemoradiation therapy for advanced head and neck cancer. *Arch Otolaryngol Head Neck Surg*. 1998;124:589-592.
- Hammerlid E, Wirblad B, Snadin C, et al. Malnutrition and food in take in relation to quality of life in head and neck cancer patients. *Head Neck*. 1998;20:540-548.
- Colasanto JM, Prasad P, Nash MA, Decker RH, Wilson LD. Nutritional support of patients undergoing radiation therapy for head and neck cancer. *Oncology (Williston Park)*. 2005;19:371-387.
- Gibson S, Wenig BL. Percutaneous endoscopic gastrostomy in the management of head and neck carcinoma. *Laryngoscope*. 1992;102:977-981.
- Schweinfurth JM, Boger GN, Feustel PJ. Preoperative risk assessment for gastrostomy tube placement in head and neck cancer patients. *Head Neck*. 2001;23:376-382.
- Lin A, Jabbari S, Worden FP, et al. Metabolic abnormalities associated with weight loss during chemoradiation of head and neck cancer. *Int J Radiat Biol Phys*. 2005;63:1413-1418.
- Daly JM, Hearne B, Dunaj J, et al. Nutritional rehabilitation in patients with advanced head and neck cancer receiving radiation therapy. *Am J Surg*. 1984;148:514-520.
- Lee JH, Machtay M, Unger LD, et al. Prophylactic gastrostomy tubes in patients undergoing intensive irradiation for cancer of the head and neck. *Arch Otolaryngol Head Neck Surg*. 1998;124:871-875.
- Harris J, Benedict R. A biometric study of basal metabolism in man. Carnegie Institution publication. 279;1919:40-44.
- Saunders JR, Brown MS, Hirata RM, Jaques DA. Percutaneous endoscopic gastrostomy in patients with head and neck malignancies. *Am J Surg*. 1991;162:381-383.
- Bergstrom LR, Larson D, Zinsmeister AR, Sarr MG, Silverstein MD. Utilization and outcomes of surgical gastrostomies and jejunostomies in an era of percutaneous endoscopic gastrostomy: a population-based study. *Mayo Clin Proc*. 1995;70:829-836.
- Eisen GM, Baron TH, Dominitz JA, et al. Role of endoscopy in enteral feeding. *Gastrointest Endosc*. 2002;55:794-797.
- Silver HJ, Wellman NS, Arnold DJ, Livingstone AS, Byers PM. Older adults on home enteral nutrition: enteral regimen, provider involvement, and health care outcomes. *J Parenter Enteral Nutr*. 2004;28:92-98.
- Tisdale M. Metabolic alterations in cachexia and anorexia. *Nutrition*. 2000;16:1013-1014.
- Davis MP, Dreicer R, Walsh D, Lagman R, LeGrand SB. Appetite and cancer-associated anorexia: a review. *J Clin Oncol*. 2004;22:1510-1517.
- Desport JD, Gory-Delabaere G, Blanc-Vincent MP, et al. Standards, options and recommendations for the use of appetite stimulants in oncology 2000. *Br J Cancer*. 2003;89(suppl 1):S98-S100.
- Fietkau R, Riepl M, Kettner H, Hinke A, Sauer R. Supportive use of megestrol acetate in patients with head and neck cancer during radio(chemo)therapy. *Eur J Cancer*. 1997;33:75-79.
- Chen H. Effect of megestrol acetate and propulsid on nutritional improvement in patients with head and neck cancers undergoing radiotherapy. *Radiother Oncol*. 1997;43:75-79.
- Sullivan M. The expanding role of dental oncology in head and neck surgery. *Surg Oncol Clin N Am*. 2004;13:37-46.
- Sonis ST, Fey EG. Oral complications of cancer therapy. *Oncology (Williston Park)*. 2002;16:680-686; discussion 686,691-692, 695.
- Vissnik A, Jansma J, Spijkervet FK, Burlage FR, Coppes RP. Oral sequelae of head and neck radiotherapy. *Crit Rev Oral Biol Med*. 2003;14:199-212.
- Bruins HH, Jolly D, Koole R. Preradiation dental extraction decisions in patients with head and neck cancer. *Oral Surg Oral Med Oral Pathol*. 1999;88:406-412.
- Bruins HH, Koole R, Jolly DE. Pretherapy dental decisions in patients with head and neck cancer: a proposed model for dental decision support. *Oral Surg Oral Med Oral Pathol*. 1998;86:256-267.
- Tong AC, Leung AC, Cheng JC, Sham J. Incidence of complicated healing and osteoradionecrosis following tooth extraction in patients receiving radiotherapy for treatment of nasopharyngeal carcinoma. *Aust Dent J*. 1999;44:187-194.
- Hancock PJ, Epstein JB, Sadler GR. Oral and dental management related to radiation therapy for head and neck cancer. *J Can Dent Assoc*. 2003;69:585-590.
- Rankin KV, Conklin C, Flaitz CM, Haveman CW, Mobley CC, Redding SW. *Oral Health in Cancer Therapy*. 1999, Austin Texas: Texas Dental Association/Texas Cancer Council.
- Meraw SJ, Reeve CM. Dental considerations and treatment of the oncology patient receiving radiation therapy. *J Am Dent Assoc*. 1998;129:201-205.
- National Cancer Institute. Oral Complications of Chemotherapy and Head/Neck Radiation. June 2007. Available online: [www.cancer.gov](http://www.cancer.gov).
- Beltran-Aguilar ED, Goldstein JW, Lockwood SA. Fluoride varnishes: a review of their clinical use, cariostatic mechanism, efficacy and safety. *J Am Dent Assoc*. 2000;131:589-596.
- Epstein JB, van der Meij EH, Emerton SM, et al. Compliance with fluoride gel use in irradiated patients. *Spec Care Dentist*. 1995;15:218-222.
- Epstein JB, van der Meij EH, Lunn R, Stevenson-Moore P. Effects of compliance with fluoride gel application on caries and caries risk in patients after radiation therapy for head and neck cancer. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1996;82:268-275.
- Foote RL, Loprinzi CL, Frank AR, et al. Randomized trial of a chlorhexidine mouthwash for the alleviation of radiation induced mucositis. *J Clin Oncol*. 1994;12:2630-2633.

56. Scully C, Felix DH. Oral medicine—update for the dental practitioner: dry mouth and disorders of salivation. *Br Dent J*. 2005;199:423-427.
57. Dodd MJ, Larson PJ, Dibble SL, et al. Randomized clinical trial of chlorhexidine versus placebo for prevention of oral mucositis in patients receiving chemotherapy. *Oncol Nurs Forum*. 1996;23:921-927.
58. Cooper JS, Fu K, Marks J, Silverman S. Late effects of radiation therapy in the head and neck region. *Int J Radiat Biol Phys*. 1995;31:1141-1164.
59. Bjordal K, Kaasa S, Mastekaasa A. Quality of life in patients treated for head and neck cancer: a follow-up study 7 to 11 years after radiotherapy. *Int J Radiat Oncol Biol Phys*. 1994;28:846-856.
60. Harrison LB, Zelefsky MJ, Pfister DG, et al. Detailed quality of life assessment in patients treated with primary radiotherapy for cancer of the base of tongue. *Head Neck*. 1997;19:169-175.
61. Henson BS, Inglehart MR, Eisbruch A, Ship JA. Preserved salivary output and xerostomia-related quality-of-life in head and neck cancer patients receiving parotid-sparing radiotherapy. *Oral Oncol*. 2001;37:84-93.
62. Lin A, Kim HM, Terrell JE, Dawson LA, Ship JA, Eisbruch A. Quality of life after parotid-sparing IMRT for head and neck cancer: A prospective longitudinal study. *Int J Radiat Oncol Biol Phys*. 2003;57:61-70.
63. Murphy BA, Ridner S, Wells N, Dietrich M. Quality of life research in head and neck cancer: a review of the current state of the science. *Crit Rev Oncol Hematol*. 2007;62:251-267.
64. Nelson GM. Biology of taste buds and the clinical problem of taste loss. *Anat Rec*. 1998;253:70-78.
65. Hamlet S, Faull J, Klein B, et al. Mastication and swallowing in patients with postirradiation xerostomia. *Int J Radiat Biol Phys*. 1997;37:789-796.
66. Logemann J, Smith C, Paulowski B, et al. Effects of xerostomia on perception and performance of swallow function. *Head Neck*. 2001;23:317-321.
67. Backstrom I, Funegard U, Andersson I, Franzen L, Johansson. Dietary intake in head and neck irradiated patients with permanent dry mouth symptoms. *Eur J Cancer B Oral Oncol*. 1995;31B:253-257.
68. Roh JL, Kim AY, Cho MJ. Xerostomia following radiotherapy of the head and neck affects vocal function. *J Clin Oncol*. 2005;23:3016-3023.
69. Rhodus NL, Moller K, Colby S, Bereuter J. Articulatory speech performance in patients with salivary gland dysfunction: a pilot study. *Quintessence Int*. 1995;26:805-810.
70. Haddad P, Karimi M. A randomized, double-blind, placebo-controlled trial of concomitant pilocarpine with head and neck irradiation for prevention of radiation-induced xerostomia. *Radiother Oncol*. 2002;64:29-32.
71. Reike JW, Hafermann MD, Johnson JT, et al. Oral pilocarpine for radiation-induced xerostomia: integrated efficacy and safety results from two prospective randomized clinical trials. *Int J Radiat Biol Phys*. 1995;31:661-669.
72. Fisher J, Scott C, Scarantino CW, et al. Phase III quality-of-life study results: impact on patients' quality of life to reducing xerostomia after radiotherapy for head and neck cancer—RTOG 97-09. *Int J Radiat Biol Phys*. 2003;56:832-836.
73. Gornitsky M, Shenouda G, Sultanem K, et al. Double-blind randomized, placebo-controlled study of pilocarpine to salvage salivary gland function during radiotherapy of patients with head and neck cancer. *Oral Surg Oral Med Oral Pathol*. 2004;98:45-52.
74. Fife RS, Chase WF, Dore RK, et al. Cevimeline for the treatment of xerostomia in patients with Sjogren syndrome: a randomized trial. *Arch Intern Med*. 2002;162:1293-1300.
75. Brizel DM, Wasserman TH, Henke M, et al. Phase III randomized trial of amifostine as a radioprotector in head and neck cancer. *J Clin Oncol*. 2000;18:3339-3345.
76. Seikaly H, Jha N, Harris JR, et al. Long-term outcomes of submandibular gland transfer for prevention of postradiation xerostomia. *Arch Otolaryngol*. 2004;130:956-961.
77. Rosenthal DI, Chambers MS, Weber RS, Eisbruch A. A phase II study to assess the efficacy of amifostine for submandibular/sublingual salivary sparing during the treatment of head and neck cancer with intensity modulated radiation therapy for parotid sparing. *Semin Oncol*. 2004;31(6 suppl 18):25-28.
78. Sitton E. Early and late radiation-induced skin alterations part 1: Mechanism of skin changes. *Oncol Nurs Forum*. 1992;19:801.
79. Blackmar A. Radiation-induced skin alterations. *Medsurg Nurs*. 1997;6:172-175.
80. Rubin P, Cassarett GW. *Clinical Radiation Pathology*. 1968, Philadelphia: Saunders.
81. Stohl R. The nursing role in radiation oncology: symptom management of acute and chronic reactions. *Oncol Nurs Forum*. 1988;15:429-434.
82. Rockson S. Lymphedema. *Am J Med*. 2001;110:288-295.
83. Micke O, Bruns F, Mucke R, et al. Selenium in the treatment of radiation-associated secondary lymphedema. *Int J Radiat Oncol Biol Phys*. 2003;56:40-49.
84. Cheville A. Lymphedema and palliative care. National Lymphedema Network. *Lymphlink*. 2002;14:1-4.
85. Weissleder H, Schuchhardt C. Lymphedema Diagnosis and Therapy. 2001: Koln, Germany: Viavital Verlag GmbH.
86. Hiss SG, Postma GN. Fiberoptic endoscopic evaluation of swallowing. *Laryngoscope*. 2003;113:386-388.
87. Williams WH, Witte CL, Witte MH, et al. Radionuclide lymphoscintigraphy in the evaluation of peripheral lymphedema. *Clin Nucl Med*. 2000;25:451-464.
88. Szuba A, Strauss W, Sirsak SP, et al. Quantitative radionuclide lymphoscintigraphy predicts outcome of manual lymphatic therapy in breast cancer-related lymphedema of the upper extremity. *Nucl Med Commun*. 2002;23:1171-1175.
89. de Wit R, van Dam F, Loonstra S, et al. The Amsterdam Pain Management Index compared to eight frequently used outcome measures to evaluate the adequacy of pain treatment in cancer patients with chronic pain. *Pain*. 2001;91:339-349.
90. Olszewski W. Inflammatory changes of skin in lymphedema of extremities and efficacy of benzathine penicillin administration. National Lymphedema Network LymphLink. 1996. 8: p. 1-2.
91. Hess M. Taste: the neglected nutritional factor. *J Am Diet Assoc*. 1997;97:S205-S207.
92. Smith BK, Barker K, Schork A, Kluger M. Development of altered taste preferences in tumor-bearing rats. *Appetite*. 1994;23:219-230.
93. Williams LR, Cohen MH. Altered taste thresholds in lung cancer. *Am J Clin Nutr*. 1978;31:122-125.
94. Carson JS, Gormican A. Taste acuity and food attitudes of selected patients with cancer. *J Am Diet Assoc*. 1977;70:361-365.
95. Mossman KL, Chencharick JD, Scherr AC, et al. Radiation-induced changes in gustatory function. *Int J Radiat Biol Phys*. 1979;5:521-528.
96. DeWys WD, Walters K. Abnormalities of taste sensation in cancer patients. *Cancer*. 1975;36:1888-1896.
97. Halyard MY, Jatio A, Sloan JA, et al. Does zinc sulfate prevent radiation-induced taste alterations ("dysgeusia") in head and neck cancer patients? A North Central Cancer Treatment Group (NCCTG) placebo-controlled trial (N01C4). Proceedings Multidisciplinary Head and Neck Cancer Symposium. 2007;111: Abstract 32.
98. Chaplin JM, Morton RP. A prospective, longitudinal study of pain in head and neck cancer patients. *Head Neck*. 1999;21:531-537.
99. Isitt J, Murphy BA, Beaumont JL, et al. Oral mucositis related morbidity and resource utilization is a prospective study of head and neck cancer patients. *Proc Am Soc Clin Oncol*. 2006;24:289. Abstract 5539.
100. Epstein JB, Beaumont JL, Gwene CK, et al. Longitudinal valuation of the oral mucositis weekly questionnaire - head and neck cancer, a patient-reported outcome questionnaire. *Cancer*. 2007;109:1914-1922.
101. Keefe DM, Garden A, Barasch A, et al. Oral mucositis is associated with increased resource use among patients receiving treatment for cancers of the head and neck. *Proc Am Soc Clin Oncol*. 2007;25. Abstract 6070.
102. Murphy BA, Chen A, Harari P, et al. Longitudinal oncology registry of head and neck carcinoma: (LORHAN), a new national cancer registry. Proceedings Multidisciplinary Head and Neck Cancer Symposium. 2007. Presentation 7.
103. Smit M, Balm AJ, Hilgers FJ, Tan IB. Pain as sign of recurrent disease in head and neck squamous cell carcinoma. *Head Neck*. 2001;23:372-375.
104. Wisawatapnimit P, Dwyer K, Murphy B. Life experience of head and neck cancer patients and their caregivers after treatment. Paper presented at: Southern Nursing Research Society Meeting, 2006; Memphis, Tenn.