Chapter 17
Approaches to Supportive Care

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Abstract Head and neck cancer is associated with substantial symptom and function loss. It is critical to understand the depth and breadth of issues face by patients in order to maximize quality of life. Symptoms and functional deficits may be secondary to either the cancer or its treatment. The mechanism of toxicity varies depending on the extent of tumor involvement, the site of tumor, treatment modality, and host factors. Toxicity is usually categorized as acute (occurring within 3 months of therapy) or late (occurring 3 months or after therapy). In addition, it is also important to distinguish local versus systemic toxicities. Although head and neck cancer therapy is associated with significant system effects, data pertaining to these toxicities are lacking. Thus, this chapter reviews the selected critical supportive care issues localized to the head and neck region. This includes: mucositis, nutrition, dysphagia, xerostomia and hyposalivation, oral health issues, and radiation dermatitis.

Keywords Head and neck cancer • Symptoms • Function • Pain • Mucositis • Nutrition • Dysphagia • Xerostomia • Trismus • Dental • Sialorrhea • Dermatitis

Introduction

Head and neck cancer and its treatment are associated with clinically significant symptom burden, alterations in function, and decrease in quality of life [1]. Due to the frequent compromise of structures which are critical for functions such as speech, swallowing, and breathing, supportive care has always been a critical albeit underappreciated component of head and neck cancer therapy. More recently, the role of supportive care has been highlighted due to a number of issues, including: the increased use of aggressive combined modality therapies which are associated with an increase in acute and late effects, the increasing numbers of survivors who are living with the late effects of therapy, and the recognition that without appropriate management, the cost of acute and late effects to both the patient and society can be staggering.

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Mechanism of Toxicity

Acute Tissue Damage

Normal tissues may be damaged by either cancer or its treatment. Surgical damage results from removal of the cancer and a surrounding rim of normal tissue. The degree to which surgical resection causes morbidity is related to the amount of tissue removed, the site of the tissue removed, and the ability to use reconstructive techniques to ameliorate the effect of normal tissue loss. Vascular and neurologic damage may contribute to surgical morbidity. Radiation therapy results in DNA and non-DNA damage to tissues within the radiation therapy port. The tissue damage initiates a sequence of biologic pathways that are involved in wound healing and tissue repair. In addition, both surgery and radiation may be associated with systemic effects [2] such as fatigue, deconditioning, pain, and altered mental status. These systemic effects of therapy are in part the result of: (1) proinflammatory cytokines and chemokines released as a component of acute tissue inflammation, (2) the humoral and neurologic stress response, and (3) drug-related toxicities.

Late Tissue Damage

Tissues damage by surgery or radiation must undergo repair. During the repair process, damaged tissue may be replaced by normal functioning tissue. Alternatively, tissue repair

J. Bernier (ed.), *Head and Neck Cancer: Multimodality Management*,
DOI 10.1007/978-1-4419-9464-6_17,

mechanisms may cause replacement of normal tissue with fibrotic tissue. Fibrosis results from a chronic inflammatory process that involves growth factors, proteolytic enzymes, angiogenic factors, and fibrogenic cytokines [3]. It is manifested by excessive deposits of extracellular matrix by fibroblasts with resultant abnormal tissue architecture. There are three histopathologic phases of fibrosis: (1) chronic inflammation without fibrosis, (2) active fibrosis with dense myofibroblasts, and (3) late fibrosis with associated atrophy and decrease in parenchymal cells [4]. Tissues become noncompliant, contracted, and atrophic resulting in altered function and significant symptom burden. Thus, fibrosis plays a critical role in the development and manifestations of late tissue damage in the head and neck cancer population.

Specific Acute and Late Effects of Therapy

Mucositis

Mucositis is a process that results from chemotherapy and radiation-induced damage to the mucosa and underlying soft tissue. Recent studies have helped to elucidate the complex biologic mechanism underlying the tissue repair response and its associated manifestations [5, 6]. The clinical hallmarks of mucositis are erythema and ulceration of the mucous membranes. In addition, the underlying soft tissue may become swollen and edematous. There are a number of systems that have been used to grade mucositis (Table 17.1), the most frequently used systems are the Common Toxicity Criteria and the World Health Organization (WHO) Toxicity Criteria. The Common Terminology for Adverse Events 3.0 contains two separate criteria for grading mucositis: (1) direct visualization of lesions and (2) assessment of the functional impact of mucositis. The WHO criteria combine symptoms, function, and mucosal pathology into one single measure. Thus, it should be noted that there may be differences in how patients' mucositis is graded based on the toxicity criteria used. Unfortunately, underreporting of the frequency and severity of mucositis by health care providers is common. To avoid some of the pitfalls associated with health care provider for mucositis assessment, a number of tools have been developed which use patient-reported outcomes to measure mucositis severity and symptom burden. The most commonly used tool is the Oral Mucositis Questionnaire Head and Neck (Daily and Weekly versions). Originally developed for use in the transplant setting, the OMQ-HN has been demonstrated to be a valid and reliable tool for assessment of mucositis-related symptom burden [7]. The questionnaire focuses on mucositis-related pain and function loss.

The risk for the development of mucositis is highly variable and is based on a number of predictive factors. It has long been known that primary site, radiation dose, radiation schedule, and port size correlate with the extent and severity of mucositis [8, 9]. Although radiation parameters are clearly important, the most powerful predictor for the development of severe mucositis is the use of concurrent chemotherapy. In a retrospective review of 33 clinical treatment trials, Trotti reported that the incidence of grade 3 and 4 mucositis rose from 25 to 40% with radiation therapy alone to 60–100% in patients treated with chemoradiation [10]. In addition to an increase in the incidence of oral mucositis, the use of concurrent chemoradiation has been noted to increase the duration of mucositis [9]. Although tumor and treatment-related factors clearly predict mucositis outcomes, the role of patient

Table 17.1 Mucositis scoring systems

	1	2	3	4	5
WHO [110]	Erythema and soreness; no ulcers	Ulcers; able to eat a solid diet	Ulcers; requires a liquid diet	Ulcers; not able to tolerate a solid or liquid diet; requires IV of tube feeding	NA
CTCAE v 3.0 [111] (clinical exam)	Erythema	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes	Tissue necrosis; significant spontaneous bleeding, life-threatening	Death
CTCAE v 3.0 (functional-symptomatic)	Minimal symptoms; normal diet; minimal respiratory symptoms but not interfering with function	Symptomatic but can eat and swallow modified diet; respiratory symptoms interfering with function but not with ADL	Symptomatic and unable to adequately aliment or hydrate orally; respiratory symptoms interfering with ADL	Symptoms associated with life-threatening consequences	Death

WHO World Health Organization, *CTCAE 3.0* Common Terminology Criteria for Adverse Events

characteristics remains unclear. Numerous patient-related factors have been studied, yet epidemiologic data is lacking to clearly link mucositis outcomes with specific demographic factors [11]. The contribution of genetics factors is unknown at this time.

Mucositis-related symptoms usually begin to manifest themselves within 2–3 weeks after radiation therapy is initiated. Initial complains include throat irritation and pain on swallowing. By week 5 of radiation, mucosal lesions have worsened substantially leading to moderate-to-severe pain. Unfortunately, mucositis-related pain is often refractory to opioid analgesics. Physical exam findings and symptoms usually peak within 2–3 weeks of completing therapy and gradually subsides thereafter. It is not uncommon for symptoms and ulcerative lesions to persist for 2–3 months after radiation therapy is completed. Occasionally, patients with developed ulcerative lesions fail to heal or heal over a protracted period of time. In this population, hyperbaric oxygen therapy or treatment with pentoxifylline may be attempted, however, data confirming efficacy is lacking.

Mucositis results in a number of adverse outcomes [12]. First and foremost, severe mucositis results in treatment breaks that may compromise disease control and survival [9, 10]. Second, mucositis is associated with significant symptom burden and alterations in function. The most common mucositis-related symptom is pain. Pain results in decreased speaking, swallowing, eating, and oral care [7]. Pain is worse on swallowing, thus leading to decreased oral intake [13]. For many patients, the pain becomes severe enough that adequate oral alimentation is not possible and a feeding tube is required. Data from the Longitudinal Oncology Registry for Head and Neck Cancer indicated that feeding tubes were placed in 59% of patients at academic centers and 48% of patients at community centers within the USA ($p=0.001$) [14]. Finally, mucositis results in an increase in the use of health care resources and associated increased cost of care [15]. The cost differential between patients with and without radiation-induced mucositis is variable based on the patient population and the severity of the mucositis. For patients with severe mucositis, the cost increment has been reported between $6,000 [9] and $18,000 [16].

Due to the high cost, investigators have attempted to identify effective preventive and treatment strategies for radiation-induced oral mucositis. A wide array of treatment interventions has been tested. To date, none have clearly demonstrated a marked impact on the incidence or duration of grade 3 and 4 mucositis. The Multinational Associate for Supportive Care in Cancer has a standing committee that has developed and updated an evidence-based guideline for the treatment, prevention, and palliation of mucositis. Their recommendations include the following: oral care protocols, adequate use of pain medications, and the use of conformation radiation techniques to minimize mucosal injury. Updated recommendations can be found on their Web site at www.mascc.org.

Swallowing Abnormalities

Dysphagia is one of the most common and concerning sequelae of head and neck cancer and its therapy. The normal swallowing mechanism is complex, requiring coordination of over 25 pairs of muscles [17], as well as an intact nervous system that mediates both voluntary and involuntary swallowing maneuvers [18]. The four phase of swallowing are: (1) the oral preparatory phase (food bolus formation), (2) the oral phase (bolus transported to the pharynx), (3) the pharyngeal phase (reflex closure of the larynx to prevent aspiration, coordinated contraction of the pharyngeal constrictors, and relaxation of the cricopharyngeus muscles) [19, 20], and (4) the esophageal phase (peristalsis of bolus into the stomach). Abnormalities in any of the above functions may result in clinically meaningful dysphagia.

Symptoms that indicate the presence of dysphagia are listed in Table 17.2. When dysphagia is suspected, a formal functional assessment is indicated. The clinical evaluation of swallowing (CES), which should be performed by an experienced Speech-Language Pathologists (SLP) [21], includes the following components: (1) identification of swallowing abnormalities, (2) recommendations for additional testing, (3) development of a treatment plan when indicated, (4) consultation with dieticians to develop a nutritional plan that is safe, and (5) assessment of aspiration risk. The SLP may recommend instrumental studies to assess swallowing function. The modified barium swallow study (MBSS) is a videofluoroscopic exam of the oral and pharyngeal function that identifies swallowing impairments and aspiration [22]. Food boluses of differing sizes and consistencies are assessed

Table 17.2 Triggers for dysphagia evaluation [112, 113]

- Inability to control food, liquids, or saliva in the oral cavity
- Pocketing of food in cheek
- Excessive chewing
- Drooling
- Coughing, choking, or throat clearing before, during, or after swallowing
- Abnormal vocal quality after swallowing – “wet” or “gurgly” voice
- Build-up or congestion after a meal
- Complaint of difficulty swallowing
- Complaint of food “sticking” in throat
- Nasal regurgitation
- Weight loss

leading to appropriate dietary recommendations as well as testing of compensatory measures that may enhance swallow efficacy and safety. Standard compensatory measures include postural techniques, increased sensory input, and voluntary swallowing maneuvers. In addition, direct visualization of the structures and functioning of the pharynx and larynx can be done using the Flexible Endoscopic Evaluation (FEES) [23] allowing identification of issues such as: (1) premature spillage, (2) pooling, (3) laryngeal penetration, (4) aspiration, and (5) laryngopharyngeal reflux [24].

Dysphagia related to physiologic damage by an infiltrative cancer may be present at the time of diagnosis; however, it is more commonly due to the acute and late effects of surgery and radiation therapy. Resection of structures that are critical for normal swallowing function or surgically induced neurologic damage may result in postoperative dysphagia. Studies have demonstrated that the extent of dysfunction correlates with the site and extent of tissue resected [25, 26]. Acutely, postoperative dysphagia may be exacerbated by tissue edema and pain, while long-term tissue fibrosis and scar may contribute to persistent or deteriorating swallow function over time.

Acute dysphagia secondary to radiation therapy induced tissue damage manifested by painful mucositis, soft tissue edema, and thick mucous production. As the soft tissues and mucosa heal, scaring may take place resulting in the formation of fibrotic, noncompliant tissues [3]. Fibrosis may result in altered function including abnormal swallowing. Eisbruch identified "dysphagia/aspiration-related structures" (DARS) [27]. When these structures sustain acute and chronic damaged secondary to radiation, patients are at high risk for dysphasia and aspiration. Minimizing radiation to these structures using radiation techniques such as intensity modulated radiation therapy (IMRT) has been shown to improve swallowing outcomes [28, 29]. It should be noted that the use of concurrent chemotherapy with radiation therapy is associated with an increase of acute mucosal and soft tissue damage [30]. Although the relationship remains difficult to prove [31], increased acute toxicities are postulated to result in increased late effects; thus, explaining the clinical observation that patients receiving aggressive CCR regimens have a higher incidence of late effect dysphagia and long-term feeding tube dependence.

Stricture formation is an extreme fibrotic process which is generally noted in the upper esophagus. It may contribute to or be wholly responsible for a patient's dysphagia. The majority of patients with upper esophageal stricture formation received high doses (>60 Gy) of radiation to the involved structures [32]. The use of concurrent chemoradiation does appear to increase the risk for strictures [33]. Usually identified on MBSSs, strictures may be treated with endoscopic balloon dilatation. Data would indicate that this technique is successful in a high percentage of patients; however, repeat dilation is often required [34].

There are numerous sequelae of dysphagia, of which aspiration is the most concerning. Acutely, aspiration may result in pneumonia. In the head and neck population, particularly those receiving particularly myelosuppressive chemotherapy, pneumonia has been associated with significant morbidity and mortality [35]. Long-term chronic aspiration can result in pulmonary fibrosis and permanent lung damage [36]. Moderate dysphagia may result in altered dietary intake. In some patients, this may lead to poor diet quality and dietary inadequacies [37, 38]. Patients with severe dysphagia and/or aspiration may require a permanent feeding tube in order to ensure adequate and safe nutritional intake [31]. Predictive factors for long-term feeding tube dependence includes: oro/hypopharyngeal primaries, stage III/IV disease, flap reconstruction, current tracheotomy, chemotherapy or increased age [39].

Nutrition

Nutrient intake is often compromised in head and neck cancer patients' either due to symptoms from their cancer or its treatment. Factors that may contribute to malnutrition include: (1) alimentary track obstruction or dysfunction, (2) radiation-induced acute effects such as mucositis, mucous production, and tissue edema, (3) chemotherapy side effects such as anorexia, nausea, and vomiting, (4) a history of substance abuse with associated nutrient deficiencies, (5) socioeconomic factors that inhibit patients from obtaining nutritionally replete diet or supplements, and (6) cancer cachexia syndrome with associated metabolic abnormalities that favor proteolysis. Overall, malnutrition is seen in 30 and 50% [40, 41] of head and neck patients; however, the numbers are substantially higher in patients with locally advanced disease [42, 43]. Weight loss is associated with numerous adverse outcome measures including: surgical complications [40], immune function [40], survival [41, 44, 45], and quality of life [45]. Thus, ongoing nutritional assessment is critical in all patients with head and neck cancer.

At diagnosis, a baseline nutritional assessment is vital for all head and neck cancer patients [46, 47]. This should include an accurate weight, weight loss history, and identification of barriers to adequate nutritional intake. Patients with a stable weight and adequate oral intake may be monitored prospectively. Patients with critical weight loss (see Table 17.3) should be seen by a dietician in order to generate an appropriate nutritional plan. Basal energy expenditure (BEE) can be calculated using the Harris Benedict equation [48] which takes weight, height, and age into consideration.

Table 17.3 Definition of critical weight loss [114]

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

Of note, the physiologic stress of therapy may substantially increase a patient's caloric requirement. This should be taken into account when counseling patient regarding caloric and protein goals.

$$\text{Men: BEE} = 66.5 + (13.75\ \text{kg}) + (5.003\ \text{cm}) - (6.775 \times \text{age}),$$
$$\text{Women: BEE} = 655.1 + (9.563\ \text{kg}) + (1.850\ \text{cm}) - (4.676 \times \text{age}).$$

The placement of a feeding tube may be necessary in order to ensure adequate nutritional intake. In the postoperative population, a nasogastric tube may be used in patients who are expected to have dysphagia of limited duration. For those patients who are expected to have protracted or permanent dysphagia, a percutaneous endoscopic gastrostomy (PEG) tube is usually placed [49, 50]. The role of feeding tubes in patients undergoing radiation therapy remains controversial. It is clear that radiation therapy results in painful mucositis, edema, and mucous, which decreases intake and contributes to treatment-associated weight loss. Reports indicate that the weight loss associated with radiation therapy is as high as 10% [51]. Data clearly demonstrate that the use of prophylactic feedings tubes reduces weight loss during and immediately after radiation therapy has been completed [52, 53]. Furthermore, the complication rate is low and most complications are generally minor [54]. However, there is concern that feeding tubes result in disuse atrophy and late effect dysphagia [31, 50]. Regardless of when a feeding tube is placed, posttube placement patients should be encouraged to continue to swallow as tolerated, to comply with swallowing exercises, and to wean off the feeding tube as quickly posttreatment as is feasible.

Once placed, the health care team work with the patient and caregiver to ensure that an appropriate nutritional plan is established and followed. It is important to recognize that the placement of a feeding tube does not in and of itself guarantee adequate caloric intake. The proper use and maintenance of a PEG or NG tube is complex and requires proper education and training. The patient's ability to master the use of feeding tube may be diminished by mental status changes, generalized weakness, and debility. Caregivers frequently spend considerable time helping in the care of head and neck cancer patients with feeding tubes [55].

Feeding tubes are associated with a number of management challenges. One of the most common issues difficult to achieve is the intake of the desired amount of formula. This is often secondary to gastrointestinal dysmotility. Dysmotility may result from medications (such as opioids), electrolyte imbalance, decrease in activity level, dehydration, and the physiologic stress response. Symptoms of dysmotility include: nausea and vomiting, early satiety, and bloating. Prokinetic agents such as metaclopromide can increase gastric motility and ameliorate symptoms. Tubes must be inspected routinely to evaluate for infection, dermal irritation, leakage around the tube, and damage to the tube which requires repair or replacement.

Upon completing therapy, patients should be encouraged to transition to oral nutrition as quickly as possible. That being said, many patients experience late effect dysphagia. For some patients, dysphagia is of sufficient severity that oral alimentation is not feasible; thus leading to long term or permanent feeding tube dependence. For others, dysphagia may be less severe, resulting in altered food choices. The dietary adaptations that patients make in order to maintain an oral diet may be adaptive or maladaptive depending on the resulting nutrient intake. When dietary adaptations result in dietary inadequacies, supplementation is indicated. It should be noted that dysphagia associated with nutritional deficiencies may persist long term; thus, ongoing and periodic assessment by a dietician should be included in routine follow-up for head and neck cancer patients [37, 56].

Cachexia refers to a hypermetabolic state that is associated with proinflammatory cytokines [57]. It is associated with a number of symptoms including: anemia, weight loss, weakness, muscle, and fat wasting [58, 59]. Anorexia, which results from the loss of balance in the peripheral and central orexigenic and anorexigenic hormonal and neuropeptide signals, commonly occurs in patients undergoing active treatment and those with advanced disease [60]. To date, there is no convincing evidence for efficacy of any pharmacologic intervention for the treatment of cachexia. The French National Federation of Cancer Centers [61] has recommended the use of megestrol acetate, corticosteroids, and medroxyprogesterone for the treatment of anorexia. Data on the use of these agents in head and neck cancer are limited. In one randomized trial in patients treated with chemoradiation, the use of megace is increased appetite ($p = 0.0001$) and resulted in decrease of weight loss [62].

Xerostomia and Hyposalivation

Xerostomia is the patient-reported symptom of dry mouth; hyposalivation is defined as a decrease in stimulated and/or unstimulated salivary flow. The normal unstimulated salivary flow is 0.3–0.5 ml/min and the normal stimulated flow rates

are 1–2 ml/min. CTCAE 3.0 criteria for xerostomia and hyposalivation are as follows: grade 1 – symptomatic (dry or thick saliva) without significant dietary alterations or unstimulated flow rate of >0.2 ml/min; grade 2 – symptomatic and significant oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, and moist foods) or unstimulated flow rate of 0.1–0.2 ml/min; Grade 3 symptoms lead to inability to adequately aliment orally, IV fluids, tube feedings, or TPN indicated or unstimulated flow rate of <0.1 ml/min. While xerostomia is associated with discomfort and decreased quality of life [63–65], hyposalivation has been associated with a number of adverse oral health outcomes. Of note, the correlation between the subjective symptom of xerostomia and the objective measure of hyposalivation may be poor; thus, it is important to assess both outcome parameters.

Saliva is a complex fluid of electrolytes, secretory proteins, and organic molecules [66]. It serves numerous physiologic functions that are integral to oral health including the following: lubrication of the mucous membranes, maintenance of the mucous membranes, aids in soft tissue repair, direct antibacterial effects, antiviral and antifungal effects, maintenance of pH, and maintenance of dental integrity [67]. Hyposalivation may result in increased symptom burden and functional loss (voice, swallowing, and sleep disturbance) as well as diminished oral health [68–72].

Although xerostomia and hyposalivation may be caused by a number of etiologic factors in the head and neck cancer population, the leading cause is radiation therapy induced damage to the salivary glands. Most patients note the development of symptoms within 2–3 weeks of initiating therapy [73]. Once therapy is completed, salivary gland function may return slowly over time. The severity of symptoms is related to the volume of salivary gland radiated [74]. Studies have shown that salivary gland damage is at least partially reversible when the total dose is 2,500–3,000 cGy. Above that dose, xerostomia may be permanent. Thus, considerable research has been conducted to identify methods to prevent or limit radiation-induced xerostomia and hyposalivation.

Approaches for the prevention of salivary gland damage from radiation therapy include: (1) surgical transplantation of the salivary glands out of the radiation port, (2) radiation techniques to minimize radiation-induced damage, and (3) pharmacologic techniques to prevent tissue damage. Salivary gland transfer is an technique during which the parotid gland is surgically transplanted to the submental space where it is shielded from radiation. Although numerous studies have demonstrated that this is a feasible and effective technique [75], it has not been broadly adopted. This may be due to the rapid increase in the use of IMRT as an alternative tissue sparing approach. Several pharmacologic agents have been investigated to determine their capacity as cytoprotective agents in patient receiving radiation therapy to the salivary glands. The most extensively studied agent is amifostine, a free radical scavenger. In a meta-analysis conducted by Sasse, amifostine was shown to modestly decreased acute and late effect xerostomia [76]. Furthermore, several small studies demonstrated that the use of amifostine resulted in improved dental outcomes [77, 78]. Use of IV amifostine was limited due to toxicity including nausea, vomiting, and hypotension. This led to the evaluation of subcutaneous administration which proved to be equally effective to IV administration but substantially less toxic [79]. Pilocarpine has also been evaluated as a potential cytoprotective agent to prevent radiation-induced xerostomia [80]. RTOG 97-09 randomized 245 patients with a planned radiation dose of ≥50 Gy to the oral cavity/pharynx to either pilocarpine or placebo. Patients receiving pilocarpine had a significant increase in unstimulated salivary flow post treatment and at week 13. No improvement was noted in stimulated salivary flow rates or QOL measures [81]. No oral health outcomes were reported.

Finally, intensity modulated radiotherapy (IMRT) is a technique that allows radiation to be directed at the tumor while minimizing the dose to normal tissue. While randomized control trials are limited [82], cumulative evidence supports the hypothesis that IMRT allows sparing of salivary tissue and decrease in late effect xerostomia without compromising the radiation dose to the tumor [83–85].

Once xerostomia develops, the clinician must direct attention to (1) assessment and minimization of long-term oral health implications of hyposalivation (see section on "Oral Health Issues" below), (2) maximizing residual salivary flow, and (3) maximizing patient comfort. Gustatory and pharmacologic stimulants may increase salivary flow. Commonly patients will use sugar-free lozenges or gum with some relief of symptoms. Pharmacologic agents include pilocarpine and cevamaline. Pilocarpine is a parasympathamimetic agent that functions as a nonselective muscarinic agonist. In a randomized trial of 207 patients with radiation-induced xerostomia, pilocarpine was associated with an increase in salivary flow, improved comfort, and improved speech [86]. A second agent, cevemaline, acts as a selective M3 muscarinic receptor agonist. Two large randomized trials demonstrated that cevemaline results in increased salivary flow rates; however, the effect on patient-reported symptoms was mixed [87]. A number of topical agents have been developed that are generally classified as "salivary substitutes" [88]. The efficacy of these agents is variable and patient specific. Patients should be encouraged to try several agents in appropriate dose and schedules to determine whether they receive benefit. For those patients who do not receive benefit from salivary substitutes, carrying a water bottle for frequent oral rinsing can provide temporary relief. The use of a humidifier, particularly at night, may diminish discomfort [89].

Oral Health Issues

Dental

The major constituent of the dental enamel is calcium phosphate. Like bone, the enamel is constantly remodeling. Ideally, demineralization of the enamel surface is balanced by re-mineralization. However, if the balance sways toward demineralization, dental carries may develop. A number of factors predispose to demineralization, including an acidic milieu, lack of enamel substrates (calcium and phosphate), and cariogenic bacteria (streptococcus and lactobacillus species). Protective factors include fluoride treatment, calcium–phosphate paste/rinse, certain foods, and routine dental care.

Radiation induces hyposalivation which in turn results in loss of salivary buffering capacity and a decrease in enamel substrates for re-mineralization. This predisposes to the development of carries. Postradiation dental carries can develop shortly after the completion of radiation and may progress very rapidly. Manifestations include demineralization, fracture of the enamel with chipping, and auto-amputation of the tooth at the root. Even with aggressive dental intervention, it may not be possible to salvage dentition that manifests severe and rapidly progressing radiation carries. Thus, it is clear that oral health must be addressed aggressively throughout the trajectory of a patient's treatment course and long term for survivors.

Prior to the initiation of radiation therapy patients should undergo a thorough dental evaluation [90]. Nonviable teeth should be extracted 10–14 days prior to radiator to allow adequate healing. Patients must be educated extensively about oral health measures and compliance monitored on a routine basis. Patients should be instructed to brush after every meal. Oral rinses, such as baking soda gargles, may be used to buffer an acid pH. Patients should avoid acidic or sugar containing candy, drinks, or medications. Fluoride treatment should be utilized to enhance re-mineralization [91]. Chlorhexidine rinse may be used to minimize colonization with cariogenic bacteria. In small studies, posttreatment stimulation of residual salivary function with sialogogues has decreased late dental carries.

Sialorrhea

Patients commonly complain of "excess" mucous production. In a cohort of patients, salivary production may be normal but physiologic abnormalities such as dysphagia and obstruction prevent normal handling of secretions. In this group, treatment should be directed at maximizing control over secretions. On the other hand, patients may actually have an increase in salivary production or altered salivary texture leading to difficulty in managing secretions. Commonly, patients undergoing radiation therapy will complain of copious, thick sputum that is difficult to expectorate or swallow. Clearing secretions is hampered by painful mucositis, dysphagia, and pharyngeal edema. Treatment is directed at suppression of mucous production with pharmacologic agents such as scopolamine or atropine, thinning of mucous by the use of mucolytics, night time postural techniques to prevent mucous pooling, and hydrating techniques such as a humidifier to keep mucous from hardening. Radiation-induced sialorrhea may result in difficulty swallowing, gagging with reflex vomiting, and altered sleep patterns. Generally, sialorrhea abates within 1–3 months treatment. Of note, patients undergoing radiation therapy may experience both xerostomia and sialorrhea. Unfortunately, treatment approaches that improve one symptom may exacerbate the other. Thus, treatment must be tailored to the individual to maximize symptom control. Chronic sialorrhea is more common in the postoperative setting and has been approached using a number of treatment techniques including anticholinergics, botulinum toxin, and salivary gland excision [92].

Trismus

Abnormalities in jaw motion resulting in either mal-occlusion or trismus are a common but frequently overlooked complication of head and neck cancer therapy. Normal occlusion requires the following structures: mandible, maxilla, muscles of mastication (including the pterygoids, masseter, and temporalis), dentition, an intact neurologic supply, and an adequate vascular supply. When the structures function normally, the mandible has six degrees of motion: depression, elevation, protrusion, retraction, and right and left lateral movement. Damage to any of these structures either by tumor or treatment may result in abnormal occlusion and/or decreased range of motion in the jaw.

Trismus is defined as a restriction in range of motion of the jaw. While differing criteria have been used to assess and report trismus, most studies report the maximal inter-incisor opening (MIO) measured in millimeter. Although the criteria for mild, moderate, and severe trismus varies, general guidelines are as follows: greater than 40 mm – normal, between 30 and 40 mm – mild trismus, 15–30 mm – moderate trismus, and <15 mm – severe trismus [93].

Radiation-induced trismus is secondary to fibrosis of the muscles of mastication. There is a strong correlation between the radiation dose to the muscles of mastication and subsequent development of alterations in jaw range of motion [94]. The incidence of radiation-induced trismus has not been well established. This is largely due to the variability in measurement techniques and the heterogenous populations

studied [95]. Rates as high as 45% have been reported in patients receiving curative doses of radiation therapy involving the muscles of mastication and/or the ligaments of the temporomandibular joint [96]. Current data do not demonstrate an increase in the incidence or severity of symptoms with the use of concurrent chemotherapy.

Trismus usually begins to develop 1–9 months after the completion of radiation therapy, however, late-onset trimus has been reported [97]. Trismus is usually permanent and may be progressive; thus, once it develops, ongoing supportive measures are required. Trismus is associated with a number of clinically important sequelae that merit close scrutiny. Decrease range of motion in the jaw may lead to alterations in oral intake, and when severe, patients may be limited to a liquid diet. Rigorous oral care, which is vital in patients with radiation-induced xerostomia, may be difficult or impossible. Speaking may be harder and patients may have trouble being understood. It is important to note that oral intubation or dental procedures may not be feasible in patients with severe decrease in jaw range of motion.

Treatment options for trismus are limited. Hyperbaric oxygen therapy, pentoxyfilline [98], and botulinum toxin [99] have been investigated as potential therapeutic interventions, however, data is lacking to support any of these methodologies. Physical therapy with stretching of the muscles is commonly recommended. Although patients with cancer-related trismus do not experience dramatic improvement in jaw range of motion with physical therapy, deterioration may be prevented [100]. Appliances have been developed to maximize stretching of muscles and soft tissues [95].

Mucosal Sensitivity

Radiation therapy is associated with a unique posttreatment pain syndrome – Post Radiation Mucosal Sensitivity (PRMS). Characteristically, patients will complain of burning oral or pharyngeal pain that persists after resolution of the visible ulcerative lesions of mucositis. Symptoms are often exacerbated by spicy or hot food, xerostomia, and dry air. Although symptoms may lesson over time, sensitivity may persist long term. PRMS is a neuropathic pain which may be related to peripheral nerve sensitization and up regulations of Na+ channels by mucositis-associated inflammatory [101]. The cornerstone of treatment for PRMS is to avoid foods or environmental conditions that provoke pain. For patients with oral symptoms requiring intervention, topical anesthetics such as lidocaine (Na+ channel blockers) or ketamine (NMDA inhibitors) may be highly effective. If these agents fail or if patients have pharyngeal pain at sites that preclude administration of topical agents, systemic agents may be needed. Opioids may partially alleviate symptoms in some patients, however, PRMS is a neuropathic pain, thus it tends to be opioid resistant. When indicated, adjunctive pain medication such as clonazepam, gabapentin, and other antidepressants may be tried.

Dermatitis

Radiation therapy damages radiosensitive keratinocytes found in the basal layer of the epidermis preventing normal maturation and repopulation. As progenitor cells die during radiation, few cells are left in the germinal layer to replenish the normally desquamating upper epithelium. This results in sloughing of the epidermis, exposing the underlying dermal tissue. Reactions are often worse in skin folds and areas of decreased tissue thickness such as around the pinna or at the laryngeal prominence. The administration of concurrent chemotherapy agents (such as cetuximab [102, 103], doxorubicin, actinomycin D, bleomycin, hydroxyurea, 5-fluorouracil, methotrexate, and taxanes) may increase the incidence and severity of symptoms. Other risk factors for the development of radiation dermatitis include: age, nutritional status, diabetes, and concurrent medications [104, 105].

A number of systems have been used to grade acute radiation dermatitis. The CTCAE 3.0 criteria are as follows: grade 1 – faint erythema or dry desquamation; grade 2 – moderate to brisk erythema or patchy moist desquamation, mostly confined to the skin folds and creases with moderate edema; grade 3 – confluent moist desquamation, ≥1.5 cm diameter, not confined to skin folds, with pitting edema; and grade 4 – skin necrosis or ulceration of full thickness dermis, may include bleeding not induced by minor trauma or abrasion. Acute radiation dermatitis usually begins within 2–3 weeks of initiating therapy and worsens over time. Once radiation has completed, the skin lesions resolve rapidly (over 2–3 weeks). Long-term patients may experience hypopigmentation, hyperpigmentation, textural changes, loss of hair follicles, and loss of sebaceous glands [106]. In addition, patient may experience fibrosis of the dermis and subcutaneous tissue leading tissue retraction and decreased range of motion or atrophy with increased skin fragility [106, 107]. Patients must be educated regarding the care of acute and late dermal effects of radiation therapy. The reader is referred to a number of manuscripts that provide thorough recommendations for the management of acute and late dermatitis [106, 108, 109].

Conclusions

Head and neck cancer is associated with a number of symptom control and functional issues. Although much attention has been directed at the acute effects of therapy, there is

increasing recognition of the importance of late effects. The acute and late effects of therapy span a wide range of clinical issues; thus, they require the expertise of a wide array of practitioners. In order to maximize symptom and functional outcomes, a coordinated multidisciplinary approach is needed. Bringing together a team that is able to care for patients in a holistic and proactive manner is challenging at best. Nonetheless, it is necessary.

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