Late Oral Adverse Effects of Cancer Treatments

Sharon Elad and Cyril Meyerowitz

Contents

Abstract

This chapter describes the late adverse events of cancer therapy involving the oral tissues. A summary of the normal anatomy and physiology is followed by a review of the clinical presentation and management of the late oral adverse events in cancer patients. As the oral tissues involved are variable, the nature and quantity of late oral complications are extremely diverse. The impact of these oral complications can result in significantly debilitating basic oral functions, negatively affecting the quality of life. It is well recognized that surgery, chemotherapy and radiotherapy are associated with oral and maxillofacial morbidity. Furthermore, cancer therapy modalities have developed substantially over the years, resulting in newer types of radiotherapy, newer concept of hematopoietic stem cell transplantation, and emerging novel targeted therapy. These new modalities introduced a new set of oral complications, in addition to the classical oral complications attributed to surgery, chemotherapy and radiotherapy. Notably some of the essential supportive therapies (such as bisphosphonates) have oral complications as well. The clinical approach to these oral complications will be outlined.

1 Introduction

The oral cavity is composed of numerous structures each responding differently to cancer treatment (Fig. 1). The mucosa, salivary glands, taste buds, bone, teeth, periodontium, muscles, nerves, blood vessels, lymphatic tissue, connective tissue and cartilage together with the oral flora comprise what can be considered as a complex organ. The

S. Elad (✉)
Division of Oral Medicine, Wilmot Cancer Center, Eastman Institute for Oral Health, University of Rochester Medical Center, Rochester, NY, USA
e-mail: SElad@URMC.Rochester.edu

C. Meyerowitz
Eastman Institute for Oral Health, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA
e-mail: cyril_meyerowitz@urmc.rochester.edu

P. Rubin et al. (eds.), *ALERT – Adverse Late Effects of Cancer Treatment*, Medical Radiology. Radiation Oncology,
DOI: 10.1007/978-3-540-75863-1_6,

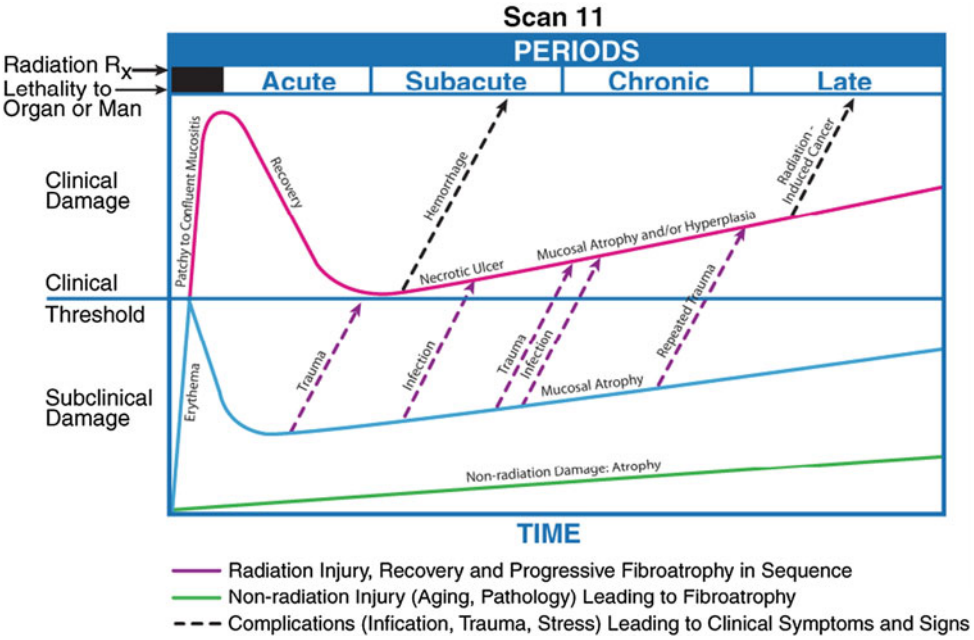


Fig. 1 Historic view on early and late mucosal effects related to radiotherapy (with permissions from Rubin and Casarett 1968)

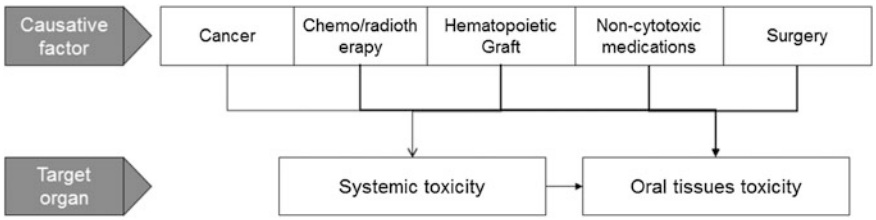


Fig. 2 Oral toxicities may be resulted from the cancer, treatment for the cancer, pharmacologic treatment for cancer complications or from systemic side-effects

simultaneous coordinated physiological activities of all these tissues enable essential oral functions. Impaired oral function has a tremendous negative impact on the well-being of patients.

Treatment for malignant disease produces unavoidable toxicities to normal cells. The oral tissues are highly susceptible to direct and indirect toxic effects of cancer chemotherapy and ionizing radiation. Some of the oral complications in cancer patients are related directly to the effects of chemo-radiotherapy on oral tissues and others are the indirect consequence of systemic toxicities (Fig. 2). Patients undergoing cancer treatment may develop oral complications associated with their modified immune status post hematopoietic stem cell transplantation (HSCT) or with the supportive care (e.g., bisphosphonate-related osteonecrosis). Surgical tumor removal may also cause oral and nutritional problems.

The tissue response depends on factors related to the form of cancer treatment and the patient. Treatment-related factors include: treatment modality (radiotherapy, chemotherapy, surgery, combination protocols, hematopoietic stem cell transplantation [HSCT]); the level of exposure to cytotoxic agents (e.g., intensity of protocol, field of radiation); and use of preventive measures. The patient-related factors include age, genetics, underlying malignant disease, immune status, co-morbidities, concurrent medications, nutritional status, history of previous cancer treatments, and compliance. Interaction of these elements governs the risk, course and severity of tissue injury.

With the emergence of new cancer treatments, the response is even more variable. For example, the introduction of reduced-intensity HSCT changed the profile of oral complications compared to those following myeloablative HSCT. Similarly, more advanced radiation technique may minimize some of the characteristic oral complications. Lastly, the introduction of targeted-therapy in oncology has caused a new series of oral complications.

Whereas the traditional bio-continuum of adverse effects (Fig. 1) was a linear progression from early acute oral complications to late chronic oral complications, the current understanding of the dynamics of the development of oral complications is multi-directional. Late complications may have an acute nature and vice versa. Tissue injury may be transient or permanent. The temporal behavior of each oral complication requires an appropriate clinical approach and patient education.

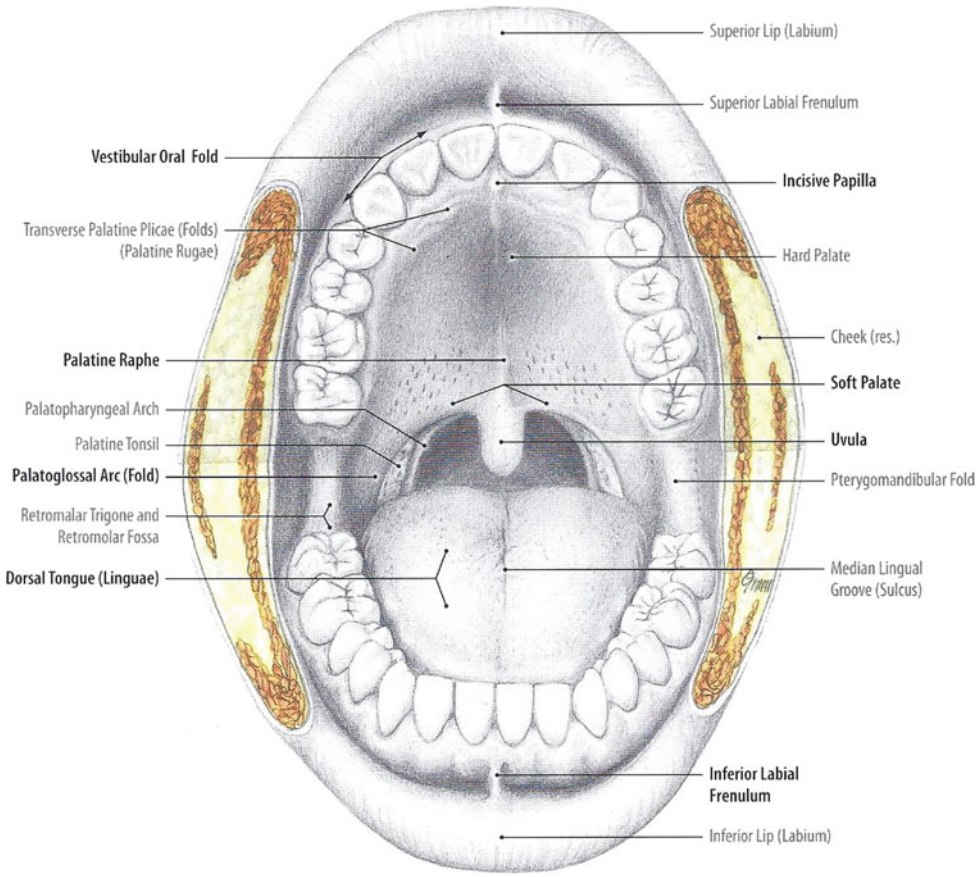


Fig. 3 Oral cavity: front view (With permission from Tillman and Elbermani 2007)

The late adverse oral effects, irrespective of their cause, are associated with loss of important oral functions such as eating, tasting, drinking, swallowing and speaking. Patients may also suffer dehydration, dysgeusia, ageusia, malnutrition and weight loss (Epstein et al. 2001, 2002). The patient's quality of life (QOL) can be severely affected, impacting their daily lives (Talmi 2002). When there are esthetic considerations such as mutilation or malformation, the impact on the psychological state of the patient can be profound (McMillan et al. 2004; Nordgren et al. 2008).

Details of the late oral complications in cancer patients are presented in this chapter, including their pathophysiology, clinical presentation, and potential treatment. According to the template of this textbook, a summary of the normal anatomy and physiology will provide the basis for understanding the pathology.

2 Anatomy and Histology

The oral cavity originates with the lips and extends posteriorly to the oropharynx (Fig. 3). It can be diagrammatically sketched as an elongated box with the cheeks contributing the side walls, the palate contributes the ceiling, and the floor of the mouth contributes the base. The supporting-frame for this three-dimensional box is composed of the dental arches positioned on the upper and lower jaw bones. Within this space lies the tongue. The oral mucosa covers the interior of the oral cavity, including the tongue, and merges into the gingival tissue covering the alveolar jaw bones. The major and minor salivary glands, the muscles, the blood vessels, the nerves, the lymphatic system and the taste buds are within the walls of the theoretic box structure of the oral cavity (Fig. 3).

Although the oral mucosa serves as a continuous coverage, the characteristic of the oral mucosal are not uniform through the oral cavity and are adjusted to the specific function of each oral surface. The mucous membranes of the oral cavity and pharynx are characterized as *masticatory, lining, or specialized*. The masticatory mucosa is bound down tightly by the lamina propria to the underlying bone. It covers the hard palate and gingiva and is characterized by keratinized epithelium that provides resistance to friction during mastication. The lining mucosa is characterized by non-keratinized epithelium, which provides flexibility and mobility that is needed during oral function. The specialized oral mucosa is found on the dorsum of the tongue and contains various types of papillae and taste buds (Fig. 4a).

The mucosal epithelium rests on a basement membrane. Below this, minor salivary glands and numerous small arteries, veins, and lymphatic vessels are found. Normal

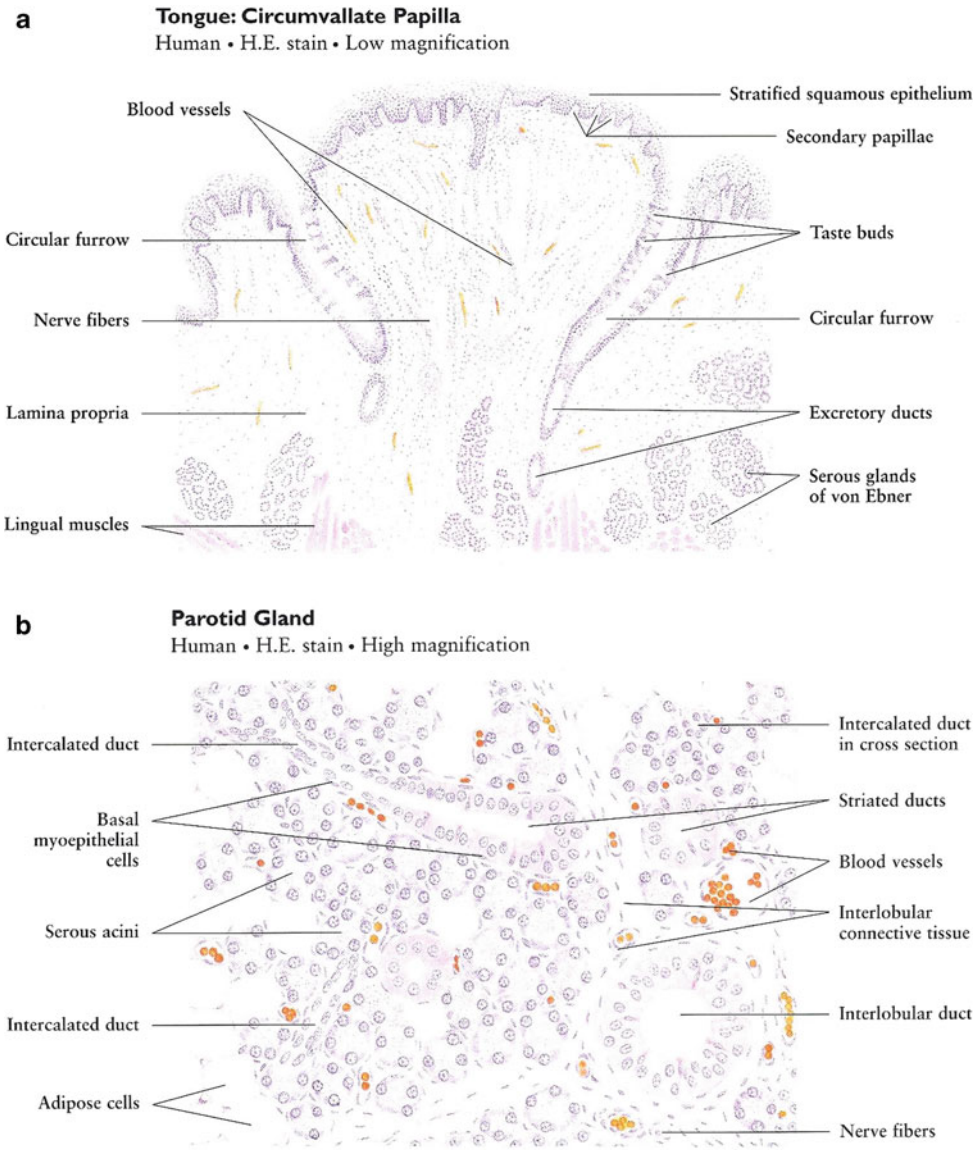


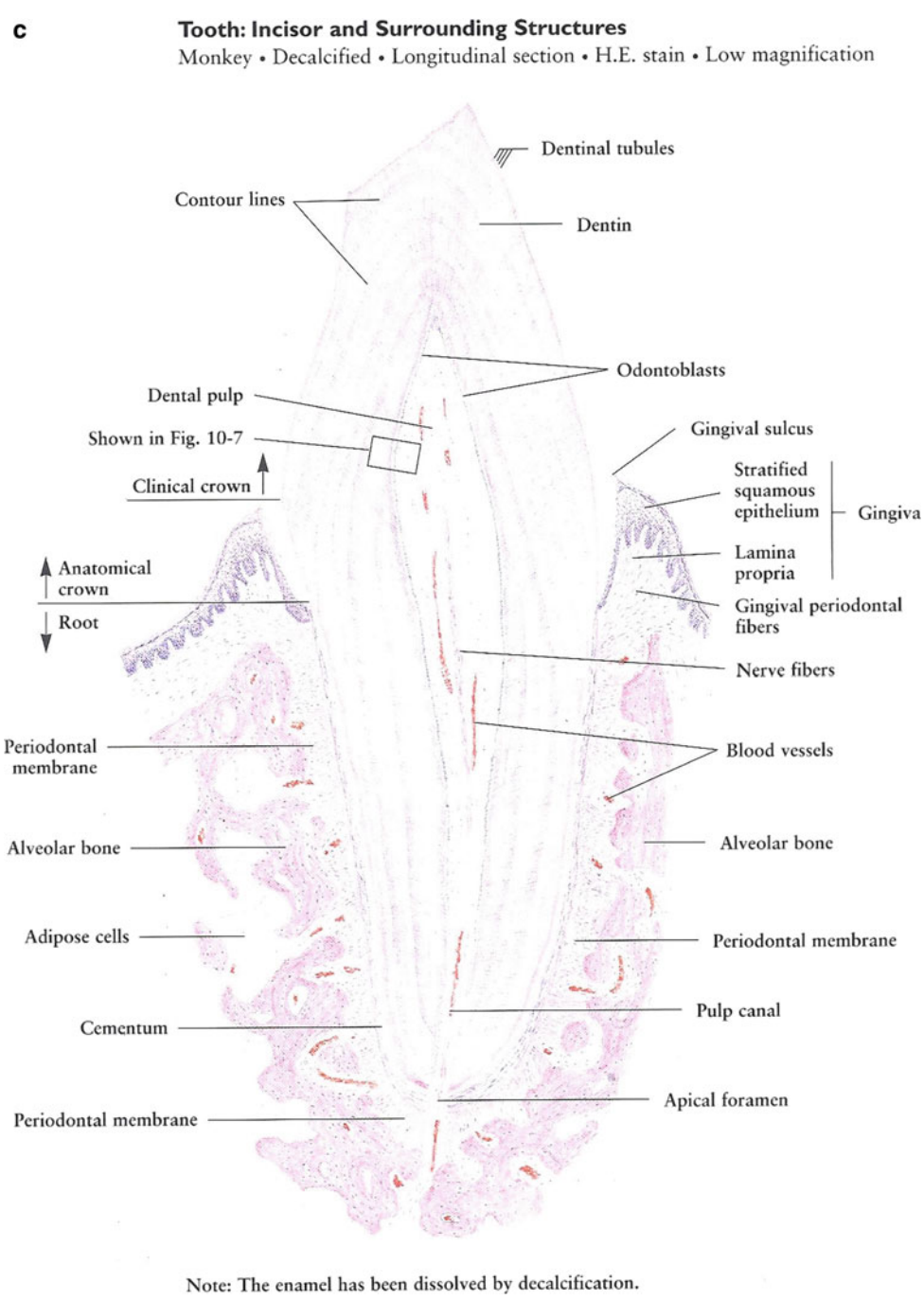
Fig. 4 **a** Tongue. **b** Parotid (With permission from Zhang 1999). **c** Tooth: Incisor and Surrounding Structures, decalcified, low magnification. (With permissions from Zhang 1999)

mucous membrane is pink to pale pink, depending on the thickness of the mucosal epithelium and amount of blood flowing through the underlying microvasculature.

There are three paired sets of major salivary glands—the parotid, submandibular, and sublingual glands—and hundreds of minor salivary glands scattered in the submucosa throughout the oral cavity, except the gingiva and anterior part of the maxilla. A typical salivary gland is a composite of numerous functional units: secretory end pieces known as acini, collecting ducts, and a framework of myoepithelial cells and connective tissue (Fig. 4b). There are two kinds of acinar cells, mucous and serous. Secretions from each of the acini pass through the intercalated ducts, then the striated (secretory) ducts and terminal lobar (excretory) ducts before traversing the major salivary duct into the oral cavity.

The main body of the tooth is made up of dentin (chemical composition of the calcium-phosphate-hydroxide apatite being 70 % inorganic and 30 % organic). Covering the crown portion of the tooth is the enamel (96 % inorganic, 4 % organic). The root portion is covered by cementum (50 % inorganic, 50 % organic), in which is imbedded protein fibrils that attach the tooth to the alveolar bone that surrounds the socket. The inner portion of the tooth—the pulp—is composed of blood vessels, lymphtics, nerves, and fibrous connective tissue (Fig. 4c). The tooth is embedded in alveolar bone. The compartment around the teeth is termed periodontium and the portion that supports the tooth in bone is the periodontal ligament. With aging and loss of teeth alveolar bone is physiologically resorbed.

Fig. 4 (continued)



The mandibular bone is characterized by cortical bone (lamellar bone and Haversian systems) that covers the spongy or marrow bone. The tooth sockets are lined by this compact bone. The posterior mandible (ramus) extends vertically ending in the condylar process that forms the temporomandibular joint, allowing opening and lateral movements for speech, mastication and expression.

The internal structure of mandibular bone responds to mechanical stresses by remodeling of marrow trabeculae, which are lined by osteoblasts and osteoclasts on the surface, and osteocytes in inner lacunae. The marrow itself contains blood vessels, fat, and fibrous connective tissue.

3 Physiology and Biology

The oral mucosa has an important role in protection as it creates a barrier between the oral environment and the circulation. Its capability to withstand friction allows food chewing and swallowing. Additionally, receptors in the oral

Table 1 Mucosa LENT SOMA

	Mucosa—oral and pharyngeal			
	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Pain	Occasional and minimal	Intermittent and tolerable	Persistent and intense	Refractory and excruciating
Dysphagia	Difficulty eating solid food	Difficulty eating soft food	Can take liquids only	Totally unable to swallow
Taste alteration	Occasional, slight	Intermittent	Persistent	
Objective				
Mucosal integrity	Patchy atrophy or telangiectasia	Diffuse atrophy or telangiectasia, superficial ulcer	Deep ulcer no bone or cartilage exposure	Deep ulcer with bone or cartilage exposure
Weight	<5 % loss	>5–10 % loss	>10–15 % loss	>15 % loss
Management				
Pain	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention
Ulcer		Cleanse	Antibiotics or oxidants	Debridement + other surgical intervention
Dysphagia	Lubricants, diet modification	Non-narcotic	Narcotic	PEG tube and/or surgical intervention
Taste alteration	Minor diet changes (non-acidic)	Minor diet changes (semi-soft)	Major diet changes (soft)	Major diet changes (liquid)
Analytic				
Color photo	Assessment of changes in appearance			
Cytology, biopsy, imaging	Rule out persistent tumor			
Smear, culture, antifungal trial	Rule out candidiasis			

mucosa respond to temperature, touch and pain and the tongue has the unique capability of taste detection.

The salivary glands generate saliva which has important physiologic functions. It protects the oral cavity by providing a washing effect. This clearance of bacteria, debri and sugars, is important to prevent infection and the development of dental and periodontal diseases. Saliva lubricates the oral mucosal surfaces, allowing for tissue protection. Its flow, electrolytes composition and buffering effect, helps prevent demineralization of teeth. Saliva proteins, such as lysozyme, lactoferrin, peroxidase, and secretory immunoglobulin A, have an antimicrobial action. Other salivary molecules, such as mucins and agglutinins, aggregate microorganisms and prevent them from adhering to the oral tissues. Additionally, saliva is important for taste perception and for digestion of the food. Lastly, the moistening of the oral cavity allows for speech and breathing.

Both the teeth and jaw bones are essential for mastication, intelligible speech, swallowing, appearance, and expressions.

Within the complex structure of the mouth, the biofilm of saliva and oral flora is an invisible component that is integrated into the normal physiology of this entire organ. The oral flora is characterized by harmonious interaction between hundreds of bacteria and fungi. This co-existence may alter during changes due to an exogenous triggers (e.g., antibiotics) or endogenous change (e.g., immunosuppression). Some of the normal oral micro-organisms may turn into opportunistic micro-pathogens when the harmonious balance between various oral residents is interrupted.

4 Clinical Presentation

4.1 Overview

Previous editions of this book addressed the oral mucosa, the salivary glands and the teeth and mandible (i.e., jaw bone). This clinical approach is based on the LENT SOMA system that categorizes and grades various toxicities (Tables 1, 2, and 3), and does not differentiate between early and late adverse events. As evidence-based data on oral complications of cancer patients expanded, scales were published for specific oral complications. Several global scales are currently used. For example, the National Cancer Institute published an update for the Common Toxicity Criteria for Adverse Events (CTC-AE ver. 4.0) and a new

Table 2 Salivary gland LENT SOMA

	Salivary gland			
	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Xerostomia	Occasional dryness	Partial but persistent dryness	Complete dryness, non-debilitating	Complete dryness, debilitating
Objective				
Saliva	Normal moisture	Scant saliva	Absence of moisture, sticky, viscous saliva	Absence of moisture, coated mucosa
Management				
Xerostomia		Occasional saliva substitute Sugarless candy or gum, Sialogogues	Frequent saliva substitute or water Sugarless candy or gum, Sialogogues	Needs saliva substitute or water in order to eat Sugarless candy or gum, Sialogogues
Analytic				
Salivary flow/quantity/ stimulation	76–95 % of pre-treatment	51–75 %of pre-treatment	26–50 % of pre-treatment	0–25 % of pre-treatment

Table 3 Mandible[a] LENT SOMA

	Mandible			
	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Pain	Occasional and minimal	Intermittent and tolerable	Persistent and intense	Refractory and excruciating
Mastication		Difficulty with solids	Difficulty with soft foods	
Denture use		Loose dentures	Inability to use dentures	
Trismus	Noted but unmeasurable	Preventing normal eating	Difficulty eating	Inadequate oral intake
Objective				
Exposed bone		< 2 cm	> 2 cm or limited sequestration	Fracture
Trismus		1–2 cm opening	0.5–1 cm opening	<0.5 cm opening
Management				
Pain	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention or resection
Exposed bone		Antibiotics	Debridement, hbo2	Resection
Trismus and mastication		Soft diet	Liquid diet, Antibiotics, Muscle relaxant meds	NG tube, gastrostomy
Analytic				
Mandibular radiograph	Questionable changes or none	Osteoporosis (radiolucent)	Sequestra	Fracture
		Osteosclerosis (radiodense)		
Panograph X-rays/ CT	Assessment of necrosis progression			

[a] Refers to the dentition, both jaws and the masticatory system

version is expected in the near future. Selected items from the CTC-AE are presented in Table 4.

Additional scales are listed in the RTOC website.

In this edition, common oral complications will be presented, including oral mucosal alterations (late-mucosal injury and cGVHD), taste disorders, salivary gland dysfunctions, infections, neuropathy and chronic pain, complications of the dentition and periodontium, trismus and loss of elasticity, osteoradionecrosis and osteonecrosis, developmental abnormalities and secondary malignancies.

Table 4 Common Toxicity Criteria for Adverse Events (CTC-AE ver. 4.0)

Adverse event	1	2	3	4	5	Definition
Cheilitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; intervention indicated	–	–	Disorder characterized by inflammation of the lip
Dental caries	One or more dental caries, not involving the root	Dental caries involving the root	Dental caries resulting in pulpitis or periapical abscess or resulting in tooth loss	–	–	A disorder characterized by the decay of a tooth, in which it becomes softened, discolored and/or porous
Dry mouth	Symptomatic (e.g., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow > 0.2 ml/min	Moderate symptoms; oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1–0.2 ml/min	Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva < 0.1 ml/min	–	–	A disorder characterized by reduced salivary flow in the oral cavity
Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing	Severely altered eating/swallowing; tube feeding or TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death	Disorder characterized by difficulty in swallowing
Gingival pain	Mild pain	Moderate pain interfering with oral intake	Severe pain; inability to aliment orally	–	–	Disorder characterized by a sensation of marked discomfort in the gingival region
Lip pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	–	–	A disorder characterized by a sensation of marked discomfort of the lip
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by inflammation of the oral mucosal
Oral cavity fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by an abnormal communication between the oral cavity and another organ or anatomic site

(continued)

Table 4 (continued)

Adverse event	1	2	3	4	5	Definition
Oral dysesthesia	Mild discomfort; not interfering with oral intake	Moderate pain; interfering with oral intake	Disabling pain; tube feeding or TPN indicated	–	–	A disorder characterized by a burning or tingling sensation on the lips, tongue or entire mouth
Oral hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	Disorder characterized by bleeding from the mouth
Oral pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	–	–	A disorder characterized by a sensation of marked discomfort in the mouth, tongue or lips.
Periodontal disease	Gingival recession or gingivitis; limited bleeding on probing; mild local bone loss	Moderate gingival recession or gingivitis; multiple sites of bleeding on probing; moderate bone loss	Spontaneous bleeding; severe bone loss with or without tooth loss; osteonecrosis of maxilla or mandible	–	–	A disorder in the gingival tissue around the teeth
Salivary duct inflammation	Slightly thickened saliva; slightly altered taste (e.g., metallic)	Thick, ropy, sticky saliva; markedly altered taste; alteration in diet indicated; secretion-induced symptoms; limiting instrumental ADL	Acute salivary gland necrosis; severe secretion-induced symptoms (e.g., thick saliva/oral secretions or gagging); tube feeding or TPN indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent intervention indicated	Death	Disorder characterized by inflammation of the salivary duct
Salivary gland fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; tube feeding indicated	Severely altered GI function; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death	Disorder characterized by an abnormal communication between a salivary gland and another organ or anatomic site
Tooth development disorder	Asymptomatic; hypoplasia of tooth or enamel	Impairment correctable with oral surgery	Maldevelopment with impairment not surgically correctable; disabling	–	–	A disorder characterized by a pathological process of the teeth occurring during tooth development
Tooth discoloration	Surface stains	–	–	–	–	A disorder characterized by a change in tooth hue or tint
Toothache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	–	–	A disorder characterized by a sensation of marked discomfort in the tooth

Selected items relevant to late oral complications

Table 5 Late oral complications post radiotherapy

Tissue involved	Type of cancer treatment				Oral complications
	CT	RT	HSCT	Surgery	
Oral mucosa	X	X	X		Mucosal changes
	X		X		Secondary oral infections
			X		Mucosal GVHD (lichenoid/plaque type)
	X	X	X		Secondary malignancy
Taste buds	X	X	X		Taste disorders
Salivary glands	X	X	X		Dry mouth
	X	X	X		Sialoadenitis
			X		Multiple mucocele
	X	X	X		Secondary oral infections
	X	X	X		Secondary malignancy
Teeth	X	X	X		Rampant caries
	X	X	X		Dental malformations
	?	X	X		Cervical sensitivity
Periodontium		?	?		Advanced periodontitis
			X		Desquamative gingivitis
Connective tissue and musculature		X	X	X	Trismus
		X	X	X	Loss of elasticity
		X	X	X	Limited mouth opening
Bone (jaw)		X			Osteoradionecrosis
	X		X		Bisphosphonate-related osteonecrosis
	X	X	X	X	Developmental malformations
Nerve	X	X	X	X	Neuropathy and chronic pain

May concur at any time: dysphagia, oral dysfunction (eating, drinking, speech), dehydration
CT-chemotherapy, RT-radiotherapy, HSCT-hematopoietic stem cell transplantation

The association between the various toxicities and therapies is provided in Table 5.

4.2 Oral Mucosal Alterations

The prominent effects of cancer treatment on the oral mucosa are seen in the early period following treatment and results in oral mucositis. Once mucositis has developed, the oral mucosa is more susceptible to the toxic effects of a second cycle of RT or CT (Sonis 2007). This clinical observation is supported by histomorphological evaluations of oral mucosal specimens taken from patients 6 to 12 months after RT. A decreased number of blood vessels, different expression patterns of adhesion molecules and subpopulations of integrins and macrophages are found (Prott et al. 2002). Patients complaining of a burning sensation months after their acute mucositis has apparently healed support this observation.

Targeted therapy was associated with various oral complications. Recently drugs belong to the Mammalian Target of rapamycin (mTOR) inhibitors were associated with aphthous-like oral lesions, mostly sirolimus, everolimus and temsirolimus. Other oral symptoms, such as dysphagia, dry mouth and dysguesia were reported in relation to mTOR inhibitors as well. Furthermore, additional groups of targeted therapies, such as monoclonal antibodies (cetuximab, bevacizumab) and tyrosine kinase inhibitors (sunitinib, sorafenib, and imatinib) were suggested to have oral adverse events.

Patients post allogeneic HSCT may develop oral mucosal GVHD. GVHD is an allo-immune inflammatory process, which results from a donor-origin cellular response against host tissues. The chronic form of GVHD (cGVHD) occurs in 30–50 % of allogneic transplants and oral involvement is seen in up to 80 % of them (Schubert and Correa 2008). The clinical presentation includes lichenoiod, erythematous, or ulcerative lesions which may be occasionally asymptomatic, but more often is associated with pain, burning sensations, or a rough texture of the oral surfaces. Painful mucosal lesions may represent a significant impediment to nutritional intake and performing oral hygiene.

Clinical examination of the oral tissues can support the diagnosis of GVHD. Correlation of oral changes with systemic manifestations should be considered, although the

Table 6 NIH scale for oral cGVHD activity assessment

Mucosal change	No evidence of cGVHD		Mild		Moderate		Severe	
Erythema Lichenhold Ulcers Mucoceles[a]	None	0	Mild enythema or moderate erythema (< 25 %)	1	Moderate (> 25 %) or Severe erythema (< 25 %)	2	Servere erythema (25 %)	3
	None	0	Hyperkeratotic changes (< 25 %)	1	Hyperkeratotic changes (25–20 %)	2	Hyperkeratotic changes (50 %)	3
	None	0	None	0	Uicers involving (20 %)	3	Servere ulcerations (20 %)	6
	None	0	1–5 mucoceles	1	6–10 scattered mucocel3es	2	Over 10 mucoceles	3
							Total score for all mucosa chages	

http://asbmt.affiniscape.com/associations/11741/files/ResponseCriteriaAPPENDIXAFormA.pdf

[a] Mucoceles scored for lower labial and soft palate only

oral cavity may be the only site affected. Histopathologic evaluation may be complementary to clinical evaluation (Bradley et al. 2003). Scoring of oral cGVHD was addressed by the NIH in 2006 (Pavletic et al. 2006) (Table 6). Other scales may be used for research (Piboonniyom et al. 2005; Elad et al. 2003).

Importantly, GVHD is one of the potential risk factors associated with the development of secondary solid cancers including those presenting in the head and neck area (see "Secondary Malignancy").

4.3 Taste Disorders

When the oral and pharyngeal mucosa is exposed to radiation, taste receptors are damaged and taste discrimination becomes increasingly compromised (National Cancer Institute 2008; Ruo Redda and Allis 2006; Gamper et al. 2012; Epstein et al. 2010). Loss of saliva flow (hyposalivation) impairs the transport and solubilization of gustatory stimulants to the taste buds, which leads to taste disorders. The outcome may be a reduction in taste sensitivity (hypogeusia), absence of taste sensation (ageusia), or a distortion of normal taste (dysgeusia). Studies in RT patients showed mixed results about the pattern of taste impairment. Some studies showed that sensitivity to sweet mainly decreases and that sensitivity to bitter increases. Others showed that sensitivity to bitter and salty simulants is mainly decreased (Ruo Redda and Allis 2006) and that umami was the only taste to be impaired (Shi et al. 2004).

After 3–4 weeks of radiation it is common for patients to complain of an absence of a sense of taste. It will generally take upwards of several months after the end of radiation therapy for taste receptors to recover and become functional, but it may require up to 2 years (Ruo Redda and Allis 2006).

Radioactive iodine in the form of (Paulino et al. 2000) I^{131} is used to treat thyroid cancer and reportedly causes taste alterations in approximately 10 % of patients (Rosenbluth et al. 2005, Lee JN et al. 2010).

Most commonly used cytotoxic agents have been linked to chemosensory disorders (Comeau et al. 2001; Bernhardson et al. 2007; Berteretche et al. 2004), and are known to damage chemosensory structures and disrupt saliva and mucus production, which indirectly affects the sense of taste (Schiffman and Zervakis 2002). Research into the side effects of cytotoxic chemotherapies indicates that 46–77 % of patients receiving chemotherapy report changes in taste (Lindley et al. 1999; Foltz et al. 1996; Rhodes et al. 1994; Wickham et al. 1999; Youngblood et al. 1994). However, most of these changes resolve within a few months after chemotherapy ends with little long-term impact (Bernhardson et al. 2007).

Approximately 20 % of patients 90–100 days post HSCT report moderate to severe levels of taste change (Epstein et al. 2002). More patients report reduced intensity of taste and abnormal tastes. However, it seems that these taste changes have a limited impact on QOL (Epstein et al. 2002). In patients 24–30 months post HSCT taste changes are also noted (Marinone et al. 1991). In patients that received allogeneic transplants, hypogeusia to salt and sour, but no difference in sweet or bitter are reported. In recipients of autologous transplants statistically significant taste changes are seen (Marinone et al. 1991). These finding are ambiguous as other studies show recovery in 80 % of patients 1 year-post HSCT (Mattsson et al. 1992). It is important to note that in pediatric patients undergoing HSCT taste changes may resolve faster (Cohen et al. 2012).

4.4 Salivary Gland Dysfunction

Long-term salivary gland dysfunction is a common complication of cancer treatment, predominantly in RT and in allogeneic HSCT patients. Salivary gland impairment is also well recognized following CT, and generally recovers within 6 months (Chaushu et al. 1995).

The RT-induced damage to the salivary gland results in a quantitative and qualitative change in saliva. Consequently, there is loss of salivary function, reduction in salivary flow and symptoms of dry mouth. The irradiated volume of salivary gland tissue correlates directly with the severity of oral complications (Cheng et al. 1981; Eisbruch et al. 1999; Roesink et al. 2001). The bottom range of the mean doses which have been found to cause significant salivary flow reduction is from 26 to 39 Gy (Roesink et al. 2001; Eisbruch et al. 2001). Changes in quantity of saliva occur shortly after radiotherapy. With cumulative RT dose of 60–70 Gy, more irreversible extensive damage to salivary flow rate is detected (Vissink et al. 2003). The implementation of alternative fractionation schedules, like hyper fractionation and accelerated fractionation has only a negligible positive effect on salivary gland function and morphology in animal models (Vissink et al. 2003; Price et al. 1995; Coppes et al. 2002). However, evidence in humans shows that xerostomia (a sensation of decreased saliva) is worse in accelerated fractionation compared to conventional fractionation (Awwad et al. 2002).

The introduction of IMRT allows more accurate delivery of a specific radiation dose to the tumor and spares the surrounding tissues, including major salivary glands. There is much encouraging data suggesting that salivary gland impairment is reduced by using IMRT compared to traditional radiotherapy techniques (Rathod et al. 2013). A systematic review concluded that the benefits of IMRT on salivary gland function, xerostomia, and xerostomia-related QOL are most pronounced late ($\geq$ 6 months) after radiotherapy and there are improvements in xerostomia-related QOL over time (Jensen et al. 2010).

It is unclear yet what the sparing effect of novel radiation techniques such as cyberknife, protons and carbon ions is (Thariat et al. 2011).

Dry mouth in HSCT patients is a multifactorial condition. The most common etiologies are the conditioning regimen, chronic GVHD (cGVHD) and chronic administration of medication. In addition altered oral intake may be associated with dehydration.

(1) *The conditioning regimen*: Salivary secretion is substantially reduced during the conditioning stage of HSCT (Chaushu et al. 1995). Gradual flow rate recovery typically begins a few days following HSCT. Patients conditioned with chemotherapy or chemotherapy and total lymph node irradiation display earlier and complete recovery of saliva secretions 2–5 months after engraftment. Recovery is delayed and incomplete when total body irradiation (TBI) is added to the conditioning regimen, suggesting that TBI induces irreversible damage to the parotid glands resulting in permanent hyposalivation (Chaushu et al. 1995).
(2) *GVHD*: 60 % of cGVHD patients experience hyposalivation and a direct correlation is observed between the degree of hyposalivation and the severity of GVHD (Nagler et al. 1996; Alborghetti et al. 2005).
(3) *Chronic medication use*: As the vast majority of HSCT patients remain under polypharmacy treatment, the added risk of drug-induced dry mouth, in addition to the impact of the cGVHD, exists.

Cancer treatment and cGVHD also result in a change of salivary composition. Clinically, saliva color becomes yellowish to brownish, mucoid, sticky and viscous. The qualitative changes in saliva include increased viscosity, reduced buffering capacity, altered salivary electrolyte concentrations, and increased levels of anti-bacterial proteins including sIgA, lysozyme and lactoferin (Vissink et al. 2003; Makkonen et al. 1986; Valdez et al. 1993; Izutsu et al. 1985; Hiroki et al. 1994; Nagler et al. 1996). When flow rates and buffer capacity is diminished, salivary pH is lowered. In the presence of food containing fermentable carbohydrates, plaque pH is decreased and the lack of clearance, due to decreased salivary flow, inhibits the rise of the plaque pH back to normal levels. The prolonged low pH environment impairs the balance between demineralization and remineralization predisposing to greater demineralization and results in dental caries. In the absence of preventive therapy, primarily fluoride, the dental caries progress very rapidly (see following paragraphs about "Dentition and Periodontium"). In addition, the acidic plaque pH provides optimal conditions for the shift of the oral flora to a cariogenic flora (Brown et al. 1975). Since the decrease in salivary flow rate is greater than the increase in immunoprotein and lysozyme levels, a significant immunoprotein deficit compromises saliva's protective role (Kielbassa et al. 2006).

Patients complaining about xerostomia often describe that the discomfort increases during night and that adhesion of the tongue to the palate necessitates repeated arousal to drink water during their night sleep. This polydypsia lead to nocturnal polyuria. Clinical evaluation will reveal a dry appearance of the oral mucosa. In extreme oral dryness the oral mucosa may be atrophic, erythematous and fissured. Some patients may describe episodic painful swelling of the salivary glands, which is usually caused by retrograde infection due to the absence of the washing effect of saliva in the salivary ducts. When such an acute sialoadentitis exists, the salivary gland region may be swollen, the

covering skin may be erythematous and tender, and salivary expression upon milking will be missing.

The typical manifestation of cGVHD involving the minor salivary glands is multiple mucoceles, with labial and soft-palate mucosa being the most frequently involved sites. Mucoceles often cause a disturbed sensation in the mouth but not pain (Schubert et al. 2004). In rare cases mucoceles may evolve into a large mucocele or ranule.

Hyposalivation has multiple additional consequences (Schubert and Correa 2008; Vissink et al. 2003). Oral function such as speech, chewing and swallowing, is negatively affected due to insufficient wetting and lubrication of the mucosal surfaces, as well as insufficient moistening of the food by saliva. These conditions lead to increased friction of the mucosal surfaces and a tendency to easily traumatize the oral mucosa. In edentulous patients hyposalivation causes intolerance to prosthetic appliances and reduced retentiveness of the prosthesis. Additionally lack of saliva predisposes the patients to oral infections, most commonly candidal infection.

Oral assessment of patients with xerostomia should include a thorough evaluation of oral tissues, salivary flow rate and, when necessary, imaging to rule out local salivary gland obliteration. However, the data on the radiation-induced severe drop in flow rate of both the parotid and submandibular glands does not correspond to the functional data derived from scintigraphic studies (Liem et al. 1996). Therefore, it is suggested that the combination of measurement of salivary flow rate and patient questionnaires is preferred for assessment of xerostomia over scintigraphic studies (Vissink et al. 2003).

4.5 Infections

Viral, bacterial and fungal infections are common in cancer patients and may manifest years after cancer therapy (Belazi et al. 2004; Redding et al. 1999).

Candidal infection is the most prevalent oral fungal infection in cancer patients, either post-RT or post-CT. The diminished amount of saliva, the lack of salivary immunoproteins and the lack of washing affect predisposes these patients to infections. The clinical presentations include pseudomembranous candidiasis (thrush), erythematous candidiasis (red appearance), hyperplastic candidiasis (white tissue overgrowth) and angular cheilitis (redness at the corners of the mouth).

Herpes Simplex Virus (HSV) reactivation, is common in CT and HSCT patients but rarely occurs during radiation therapy (Epstein et al. 2002). Most of the viral infections occur when the white blood count drops. Typically the lips and keratinized mucosa are affected, however, during periods of immunosuppression other oral mucosal surfaces also be affected. The clinical presentation ranges from single to numerous vesicles to isolated confluent extensive ulcerations.

Bacterial infections are common during immunosuppression, which can persist or recur in patients post chemotherapy or HSCT. The micropathogens isolated most frequently are Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterobacter cloacae and Staphylococcus aureus. There is no characteristic clinical presentation; however, a non-specific ulceration should raise the index of suspicion for bacterial infection.

Infected and ulcerated periodontal pockets may be a niche for a wide variety of microorganisms, bacterial cell wall components and pro-inflammatory cytokines that may translocate into adjacent anatomical structures or the blood stream and induce systemic infectious complications (Raber-Durlacher et al. 2002; Benoliel et al. 2007; Epstein et al. 2007). However, this risk in patients treated with irradiation is probably not as large as in patients administered chemotherapy, due to the relatively minor systemic immunosuppression that RT induces.

4.6 Neuropathy and Chronic Pain

Chronic pain and specifically neuropathy are frequent in cancer management protocols (surgery, RT, CT and HSCT). In addition to the effect of cancer treatment, orofacial pain can be related to the recurrence of cancer (Benoliel et al. 2007).

Postradiation neuropathy (sensory or motor) is well documented following the treatment of head and neck cancers; the interval between treatment and onset ranges from 1 to 10 years, and radiation dosages from 62.5 to 100 Gy (Benoliel et al. 2007; Epstein et al. 2007; Mizobuchi and Kincaid 2003; King et al. 1999). The incidence of neuropathy varies with protocols used and areas irradiated (Chen et al. 2007; Kang et al. 2000; van Wilgen et al. 2004; LeCouteur et al. 1989).

Radiation induced peripheral nerve injury may occur by at least 4 mechanisms: Direct damage to neural tissues by high dose irradiation is one mechanism observed in experimental animal models; Electron microscopy findings are suggestive of axon damage and subsequent nerve fiber loss due to radiation induced hypoxia as a mechanism of late radiation injury to the peripheral nerve (Vujaskovic 1997), particularly large nerve fibers at doses higher than 20 Gy; Radiation is also known to suppress proliferation of Schwann cells (Love et al. 1986); and lastly, connective tissue fibrosis has been postulated to mediate neuropathy (Kang et al. 2000).

Surgically related pain involves inflammatory and neuropathic pain mechanisms and is dependent on the extent of surgery and its anatomic location. Functional consequences are often secondary to pain, but may involve wound

contractures and scarring (Epstein et al. 2007; Gellrich et al. 2002). In a series of patients that underwent neck dissection, with and without radiotherapy, for head and neck cancer, persistent neck pain and loss of sensation were commonly encountered (van Wilgen et al. 2004). Myofascial pain was most commonly detected (46 %), and correlated to the extent of dissection. Neuropathic pain of the neck was present in 32 % and correlated with radiotherapy and dissection level. Patients with neuropathic pain experienced symptoms (hyperpathia, allodynia) during everyday activities such as shaving, exposure to wind or low temperatures. Loss of sensation of the neck was present in 65 % and was also related to type of neck dissection and radiation therapy.

Surgery to orofacial structures increases the risk for neuropathy and chronic pain. Resection of the mandible for tumor excision will inevitably lead to sensory impairment (Chow and Teh 2000), with 50 % experiencing regional hyperalgesia or allodynia. It has been reported that at 2–5 years post maxillectomy 88–90 % of patients report persistent pain (Rogers et al. 2003). In an analysis of patients treated for laryngeal cancer, ablative surgery (with adjuvant chemo- and/or radiotherapy) was associated with more chronic pain and psychosocial morbidity than in patients treated by chemoradiation alone (Terrell et al. 1999), underscoring the negative effects of tissue loss on pain and psychosocial well-being. Fortunately there is a tendency for symptoms to improve with time (Hammerlid et al. 2001). At 54–60 months post-surgery, about 15 % have persistent pain in any of the above sites (Gellrich et al. 2002). Long term H&N cancer survivors (> 3 years) still suffer from significantly more pain and functional problems than matched control subjects, but with a relatively quicker return to normal general function and mental health (Hammerlid et al. 2001; Hammerlid and Taft 2001).

Some cytotoxic agents may cause jaw pain and neuropathy. Most of these drugs are administered for a limited duration and thus have no long-term effect (e.g., vincristine, vinblastine, platinum) (Hilkens et al. 1997). Additionally non-cytotoxic drugs often employed in cancer treatment (e.g., interferons, thalidomide) or in supportive protocols (e.g., amphotericin-B) also induce paresthesias and other sensory neuropathies (Benoliel et al. 2007). Significant oral neuropathies seem unusual (Elad et al. 1997; Zadik et al. 2010).

4.7 Dentition and Periodontium

In the absence of effective preventive regimens, advanced dental caries is observed in patients with dry mouth. This is mostly seen in patients post RT or in patients suffering from cGVHD of the salivary glands. This form of dental caries progress rapidly and is typically localized at the cervical aspects of the teeth. However, it has been noted that accelerated dental caries can be present in other cancer patient populations, including patients post CT, though to a lesser extent. For example, in a comparison of cancer pediatric patients to their siblings, the long-term survivors had a significantly higher number of decayed surfaces as compared with their siblings (Duggal et al. 1997).

As has been described before, dental-caries risk increases secondary to a number of factors including decreased clearance and prolonged plaque pH depressions, shifts to a cariogenic flora, reduced concentrations of salivary antimicrobial proteins, and loss of mineralizing components (Kielbassa et al. 2006; Silverman 2003). Tooth hypersensitivity which is observed in many of cancer patients may be due to the same mechanisms but occur before dental decay is clinically obvious (Kielbassa et al. 2006). There are no histological differences between initial radiation caries lesions and healthy incipient lesions and the demineralization and remineralization mechanisms appear to be the same for both (Kielbassa et al. 2006).

A number of studies show that periodontal attachment loss and tooth loss due to periodontal disease is greater in irradiated areas than in non-radiated areas. The periodontal impairment is manifested in increased probing depth, increased recession on the facial aspects and increased mobility of teeth (Epstein et al. 1998; Marques and Dib 2004). This periodontal response to RT is probably due to decreased vascularity and acellularity of the periodontal membrane with rupturing, thickening, and disorientation of Sharpey's fibers and widening of the periodontal space (Vissink et al. 2003).

The long-term effects of chemotherapy are of less concern than those associated with high dose radiation therapy, because chemotherapy effects are reversible. In neutropenic patients, acute exacerbations of chronic periodontal disease can be potentially life threatening requiring aggressive antimicrobial therapy (Epstein and Stevenson-Moore 2001).

Data are scarce about the risk of periodontal disease post HSCT. Pattni et al. did not find periodontal health to be decreased when patients were followed 6 months post allogeneic HSCT and no significant alterations in the prevalence of periodontal pathogens occurred during the study period (Pattni et al. 2000). However, this study included patients that were relatively periodontally healthy prior to HSCT and follow up time was short. A recent study reported that the risk of developing dental caries or periodontal attachment loss after transplant is associated with HLA type (Dobr et al. 2007). There is anecdotic evidence that periodontal infection may trigger GVHD and oral GVHD ameliorates when periodontal treatment is provided (Schubert and Correa 2008). While no clinical trial addressed the association of GVHD and periodontal disease fully, it is noteworthy that one of the typical presentations of oral cGVHD is desquamative gingivitis. The combination of chronic inflammation with long-

term steroid treatment may lead to gingival atrophy. The vulnerable atrophic gums may deteriorate and the patient may present with advanced gingival recession.

These findings emphasize the need for proper periodontal treatment. Mechanical oral hygiene procedures, such as brushing and flossing, to remove the etiologic factors of inflammatory periodontal disease are beneficial (Epstein and Stevenson-Moore 2001).

4.8 Trismus and Loss of Elasticity

Trismus may be caused by fibrosis of the muscles of mastication after high-dose RT to the oral cavity or oropharynx (Manon et al. 2008). A systematic review of trismus in head and neck oncology showed that radiotherapy (follow-up: 6–12 months), involving the structures of the temporomandibular joint and or pterygoid muscles, reduces mouth opening by 18 % (Dijkstra et al. 2004).

The underlying disease and the surgery may amplify tissue fibrosis. Perioral fibrosis may limit mouth opening, thus significantly impacting the quality of life of the patient. In addition to difficulty with oral intake, trismus may compromise speech, oral hygiene, tumor surveillance, the ability to safely secure an airway and may increase the risk of aspiration. Furthermore, in patients who use an obturator after maxillectomy, trismus may limit proper postoperative maintenance of the appliance (Bhrany et al. 2007).

Motor deficits following HSCT are not uncommon, and have two major etiologies, the most dominant being cGVHD of sclerodema-like type, which is less common than the lichenoid type. However, it may deteriorate into an inability to activate the mastication apparatus. Scleroderma-tous changes can result in perioral fibrosis that decreases oral opening and limited tongue movement, interfering with oral function (Schubert and Correa 2008). TBI administered during the conditioning regimen is a contributing factor for fibrosis and limitation of mouth opening. However, the effect of radiotherapy in the doses typically used in myeloablative HSCT (1,200 Gy), is not as pronounced compared to those typically used to treat head and neck cancers (4,500–7,000 Gy). The effect of TBI is most pronounced when administered at young age (Dahllof et al. 1994).

4.9 Osteoradionecrosis and Osteonecrosis of the Jaws

Osteoradionecrosis (ORN) is a relatively uncommon clinical entity related to hypocellularity, hypovascularity, and ischemia, with a higher incidence after cumulative radiation doses to the bone which exceed 65 Gy (Vissink et al. 2003). This process may be spontaneous, but it is usually related to trauma such as a tooth extraction and may progress to pathological fracture, infection of surrounding soft tissues, and severe pain. The risk of ORN does not diminish over time and may even increase.

Bisphosphonates are commonly prescribed for the treatment of hypercalcemia associated with breast and prostate cancers, osteolysis associated with metastatic bone disease, especially multiple myeloma, Paget's disease, and for the treatment and prevention of post-menopausal corticosteroid-induced osteoporosis (Lindsay 2001). Since late 2003, there have been reports a possible association between bisphosphonate use and the appearance of osteonecrosis of the jaw (ONJ) (Pogrel 2004; Wang et al. 2003). Clinical signs and symptoms of this pathological process are pain, erythema, bone exposure, fistula, purulent secretion, sensory abnormality or swelling (Khosla et al. 2007). These may deteriorate into pathological jaw fractures, oro-antral fistulae, and airway obstruction. The impact on the quality of life is extreme as all essential oral functions are affected.

ONJ probably results from the inability of hypodynamic and hypovascular bone to meet an increased demand for repair and remodeling owing to physiologic stress (mastication), iatrogenic trauma (tooth extraction or denture-induced local injury), or tooth infection in an environment that is both trauma-intense and bacteria-laden. Coexisting factors may include the use of other medications with anti-angiogenic properties such as glucocorticoids, diabetes mellitus, irradiation of the jawbone, peripheral vascular disease and hyperviscosity syndrome (Khamaisi et al. 2007).

The incidence of ONJ is higher if intravenous bisphosphonates are administered, compared to oral bisphosphonates and the risk increases with duration of exposure. The reported frequency of ONJ ranges from 0.6 to 6.2 % in breast cancer patients, from 0 to 18 % in prostate cancer patients, and from 1.7 to 15 % in patients with multiple myeloma (Hoff et al. 2011). The incidence of ONJ is 1.5 % among patients treated with these agents for 4–12 months, rising to 7.7 % after treatment for 37–48 months (Bamias et al. 2005).

The American Association of Oral and Maxillofacial Surgeons position paper outlined a staging system (Ruggiero 2009).

- At risk: No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates.
- Stage 0: No clinical evidence of necrotic bone, but non-specific clinical findings and symptoms.
- Stage 1: Exposed and necrotic bone in asymptomatic patients without evidence of infection.
- Stage 2: Exposed and necrotic bone associated with infection and pain and erythema in the region of exposed bone with or without purulent discharge.
- Stage 3: Exposed and necrotic bone in patients with pain and infection and one or more of the following: exposed and necrotic bone extending beyond the region of

alveolar bone, (i.e., inferior border and ramus of the mandible, maxillary sinus and zygoma) resulting in pathological fracture, extraoral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible or the sinus floor.

Osteonecrosis may be associated to medications other than bisphosphonates, such as denozumab, bevacizumab and sunitinib is new (Hellstein et al. 2011; Sivolella et al. 2013). It seems that the overall incidence of denosumab-related ONJ is similar to that of bisphosphonate-related ONJ. The incidence of ONJ due to the anti-angiogenic drugs is lower. Although this complication is considered rare following bevacizumab or sunitinib, its seriousness requires taking a cautious approach and avoiding risk factors known in bisphosphonates-related ONJ.

4.10 Developmental Abnormalities

Skeletal and dental growth abnormalities may result in patients that are treated with irradiation during their childhood or adolescence. For this reason RT is nowadays avoided in this population. Several studies about the late effect in long-term survivors of children cancer have been reported (Paulino et al. 2000; Duggal et al. 1997; van der Pas-van Voskuilen et al. 2009; Otmani 2007; Duggal 2003; Oguz et al. 2004).

Disturbances in odontogenesis in irradiated pediatric patients result in microdontia, short or blunted roots, small crowns, incomplete calcification, enlarged pulp chambers, premature closure of apices and delayed, hypodontia or arrested development of teeth. These changes in the teeth can cause malocclusions (Otmani 2007; Duggal 2003).

Long term effects of HSCT on dental development in children are observed in nearly all patients examined, including agenesis, short roots, and arrested root development (van der Pas-van Voskuilen et al. 2009; Dahllof et al. 1989). In one study, children who were under 3 years of age at the start of cytotoxic treatment presented with the highest number of missing teeth (van der Pas-van Voskuilen et al. 2009). Another study identified 5 years of age at the start of cytotoxic treatment as the age in which most severe disturbances are found (Dahllof et al. 2001). The observation that the most severe disturbances takes place between the ages of 3–5 is compatible with the fact that calcification of permanent teeth starts approximately at the time of birth. Root formation is completed after the tooth has erupted into the oral cavity. During active growth teeth are susceptible to environmental disturbances; similar long-term effects on dental structures were reported in children with non-Hodgkin lymphoma, including enamel discoloration (Oguz et al. 2004).

The development of the craniofacial skeletal structures may be abnormal (Otmani 2007; Denys et al. 1998; Karsila-Tenovuo et al. 2001; Gevorgyan et al. 2007). These changes are secondary to the effects of radiation on cartilaginous growth centers located in condyles of the mandible and on the sutural growth centers of the maxilla. Such skeletal abnormalities include mandibular and maxillary hypoplasia (Paulino et al. 2000). Facial growth is affected by lower doses of RT, such as the doses given in the conditioning regimen to the HSCT. Significant reductions in length of both jaws and a decrease in the alveolar height have been observed (Dahllof et al. 1994). Craniofacial and dental abnormalities can cause severe cosmetic or functional sequelae, necessitating surgical or orthodontic intervention.

4.11 Secondary Malignancy

Secondary malignancies in the oral tissues have been reported, particularly in HSCT patients. Data are also available for patients post RT to the head and neck.

Patients undergoing allogeneic HSCT are at a high risk of developing secondary neoplasms. Studies assessing the risk of cancer among long-term survivors of HSCT have demonstrated a low but significant risk of secondary neoplasms, with the reported incidence being 4–7 fold that of the general population (Bhatia et al. 1996; Witherspoon et al. 1989). Malignancies occurring after HSCT may be of hematologic or lymphoproliferative origin, or may be solid tumors. The first category is relatively frequent and develops early in the post-transplant period, while secondary solid tumors are less common and the incidence appears to increase over time (Demarosi et al. 2005).

Post-transplantation lymphoproliferative disorder (PTLD) has been defined by the WHO as a lymphoid proliferation or lymphoma that develops as a consequence of immunosuppression in a recipient of a solid organ or bone marrow allograft (Harris et al. 2001). PTLD is associated with compromised immune function and Epstein–Barr virus infection (Bhatia et al. 1996; Witherspoon et al. 1989). Manifestations of PTLD include lymphoma-related B-symptoms, compression of organs and anatomical structures by the malignant mass or a disease mimicking viral infection (Micallef et al. 1998; Loren et al. 2003). Oral involvement of PTLD is rare. Most oral presentations are reported for PTLD following solid organ transplantation (Elad et al. 2008; Ojha et al. 2008). PTLD manifesting as a gingival crater-like defect and an ulcerated dark-red mass has been reported post HSCT (Elad et al. 2008; Raut et al. 2000).

Since the oral cavity is one of the most prevalent sites for solid cancers post-HSCT, oral cancer is not as rare as oral PTLD (Curtis et al. 1997). The risk of new oral cancer post-HSCT is increased 11-fold in patients post allogeneic HSCT; however this increases 70-fold in over 10 year survivors; (Bhatia et al. 1996; Witherspoon et al. 1989;

Curtis et al. 1997) The vast majority of cases are oral squamous cell carcinoma (Demarosi et al. 2005). Salivary gland tumors are reported as well (Curtis et al. 1997).

The risk for any solid cancer following HSCT, including oral cancer, is higher for recipients who are younger at the time of transplantation than for those who are older and for patients treated with higher doses of TBI. Furthermore, specific risk factors for oral cancer has been identified, including cGVHD (Demarosi et al. 2005; Curtis et al. 1997). GVHD treatment may also be associated with the development of cancer (Deeg et al. 1996).

Additional risk factors have been suggested contributing to the development of post-transplant neoplasms, including being male (Demarosi et al. 2005), viral infection and antigenic stimulation by viral or donor-recipient histocompatibility differences, and genetic predisposition (Demarosi et al. 2005).

The nature of oral cancer in GVHD patients is aggressive, and tends to include repeating primary tumors and multifocality (Mawardi et al. 2011). Therefore, in cGVHD patients vigilant follow-up and coordination of care are critical.

Of special interest are patients with Fanconi Anemia (FA) who undergo HSCT. FA long-term survivors of HSCT have increased risk of solid tumors, particularly of the oral cavity, which is even higher than the already high "baseline" risk of neoplasia in untransplanted FA patients (Alter 2005). Most of these cancers are squamous cell carcinomas.

The carcinogenic effect of ionizing radiation has long been recognized. The latent interval between RT and the development of cancer varies from several to many years. Early studies concluded that moderate or high-dose RT did not produce any new squamous cell carcinomas of the oral mucosa (Loprinzi et al. 2004). A later study showed contrary trends with radiation becoming a risk factor after 10 years of follow-up for solid cancers of the oral cavity, pharynx, esophagus, lung (2.8, 5.9, 3.9, 1.5 times fold than in the healthy population, respectively), and after 1–5 years of follow-up for second primary leukemia (2.5 times fold than in the healthy population) (Hashibe et al. 2005).

An association has been noted between RT and thyroid tumors. The latent period is usually 10–30 years. Almost all reported cases have followed low doses of RT (Loprinzi et al. 2004). Not all thyroid neoplasms after RT are malignant, and many of the malignant neoplasms that do develop are curable with surgery.

5 Management

5.1 General Preventive Dental Care

Prior to the initiation of cancer treatment, especially head and neck RT and myelocytotoxic chemotherapy, a thorough oral and dental evaluation, including radiographic imaging, should be performed. The treatment plan should aim to remove or minimize potential sources of infection in order to prevent immediate infections and late complications (Bradley et al. 2003; Manon et al. 2008). Dental prophylaxis including scaling, root cleaning, and polishing reduces the number of potential sites of infections. Patient education in oral hygiene techniques is of utmost important. Patient should perform thorough oral hygiene measures, using a soft toothbrush and floss or an interproximal brush, and a fluoridated toothpaste. In addition they should use a topical fluoride rinse or gel daily (Bradley et al. 2003; Rankin 2008). Custom-made dental fluoride trays can be fabricated, and the daily application of a neutral 1.1 % sodium fluoride gel or a 0.4 % stannous fluoride gel should be recommended. Neutral pH fluoride products are designed to reduce irritation to the oral mucosa.

Several products may curb demineralization and enhancing remineralization (Papas et al. 2008). For example a supersaturated Ca–P rinse, casein phosphopeptide-amorphous calcium phosphate (CPP-ACP), or casein derivatives complexed with calcium phosphate (CD-CP). Human in situ studies have shown that casein products are buffered by saliva which stabilizes and localizes amorphous calcium phosphate in the plaque and maintains a state of supersaturation compared to enamel (Reynolds et al. 2008).

Restorative dental procedures including endodontic treatment should be performed for restorable teeth. Sharp dental cusps or anything that could cause intra-oral trauma should be eliminated in order to minimize mucosal injury during RT. Poor restorations with loose contact points should be repaired in order to prevent food impaction and papillitis. Alternatively, patients should be instructed to keep meticulous oral hygiene using interproximal dental hygiene aids.

Before RT, dentition in poor condition should be considered for extraction to minimize the subsequent risk of osteoradionecrosis. Such teeth include teeth in high-dose radiation areas that demonstrate significant periodontal disease, advanced caries, dentoalveolar abscess and apically involved teeth within the radiation field or teeth that are unrestorable. In addition, impacted teeth and teeth that have no antagonist to oppose should be considered for extraction. Poor oral hygiene is a factor supporting the extraction of teeth that are marginal. Gingival morphology resulting in an operculum, which creates a sanctuary for micropathogens, should be considered for operculectomy or extraction of the involved tooth. A similar approach is appropriate prior to initiation of therapy with bisphosphonate, denosumab and anti-angiogenic agents.

Timing of the dental treatment is a factor to consider. The optimum management for the patient receiving chemotherapy requires that the patient be seen by the dental

practitioner before chemotherapy begins. In general, oral care should be completed at least 1 week before chemotherapy starts. This will leave approximately 2 weeks before the patient will be at greatest risk of oral complications (Bradley et al. 2003). If an extraction is required, neutrophil count and platelet count will be critical. With neutrophil counts of $> 2{,}000/mm^3$ and platelet counts $> 75{,}000/mm^3$, no other preoperative interventions are necessary. However, if counts are lower, supplementation may be needed, such as prophylactic antibiotics, injection of granulocyte growth factor or platelet transfusion. It is advantageous to the patient to set this baseline before the initiation of CT.

After RT, patients should be monitored frequently. Dental routine procedures can be performed (Loprinzi et al. 2004). However, invasive periodontal or surgical procedures should be avoided. When the surgical procedure is necessary, atraumatic techniques should be utilized and primary closure should be obtained. Prophylactic antibiotics should be considered and hyperbaric oxygen may be an adjuvant according to well-known protocols (Bradley et al. 2003; Koga et al. 2008; Rankin 2008).

After chemotherapy the dental recall schedule should enable the implementation of optimal preventive measures (Bradley et al. 2003; Rankin 2008). Prior to any dental intervention hematologic status should be determined. Optimal oral health should be maintained, especially in light of the potential to have future myelosuppression episodes.

During the first 100 days after HSCT the patient is at increased risk for multiple complications. These complications are reduced after day 100 and decrease thereafter. Therefore, up to 100 days post-transplant, only emergency oral care should be delivered (Bradley et al. 2003). From 100 to 365 days post-transplant the spectrum of dental treatment can be extended. After 365 days post-transplant routine dental care can be provided with adjustments of the dental treatment plan, if manifestations of cGVHD are present.

5.2 Oral Mucosal Alterations

During late post-therapy period most CT- or RT-induced ulceration has resolved and chronic pain is managed using topical or systemic pharmacologic interventions. The first line of treatment is topical anesthetics (e.g., viscous xylocaine). However their efficacy for chronic pain is limited. The efficacy of mixtures of topical anesthetics with antihistamines, coating agents, anti-inflammatory or antibiotics to prevent secondary infections has been reported in the literature. Sometimes pain requires treatment with systemic analgesics or narcotics. Scrupulous hygiene is essential to prevent secondary infections.

Management of oral GVHD includes appropriate systemic therapy combined with proper oral hygiene and use of topical drugs (Schubert and Correa 2008; Imanguli et al. 2006). Because extensive cGVHD often involves multiple organs, systemic treatment is indicated. Systemic therapy starts with steroids and, if unsuccessful, other immunosuppressive agents or immunomodulators, such as azathioprine, mycophenolate mofetil and thalidomide, are used alone or in combination (Imanguli et al. 2006). Topical treatment is needed when the oral mucosa does not respond to high doses of systemic corticosteroids or when the only lesions are on the oral mucosa (Couriel et al. 2006). In general, topical steroid preparations, such as flucinonide and clobetasol gel, and steroid elixirs (dexamethasone or betamethasone), are used as local treatment for GVHD. Budesonide is a highly potent steroid and its very low bioavailability when absorbed through mucosal surfaces minimizes systemic side effects. (Elad et al. 2003; Sari et al. 2007; Elad et al. 2012) Additional approaches to the local management of oral GVHD may be considered, including topical anti-inflammatory and immunosuppressive agents such as azathioprine (Epstein et al. 2001). cyclosporine (Epstein and Truelove 1996; Eckardt et al. 2004), and oral psoralen plus ultraviolet A (PUVA) therapy (Redding et al. 1998). Other local modalities including CO_2 laser and ultraviolet B (UVB) have been employed with anecdotal reports of success (Elad et al. 1999).

5.3 Taste Disorders

Although sporadic studies suggest the benefits of certain interventions, two systematic reviews failed to demonstrate any significant improvement in dysgeusia (National Cancer Institute 2008; Ruo Redda and Allis 2006; Hovan et al. 2010; Gamper et al. 2012).

Amifostine, a cytoprotective agent, has been used during radio-chemotherapy to prevent the loss of taste (Loprinzi et al. 2004; Vissink et al. 2003; Buntzel et al. 2002), however the results are questionable because of the heterogeneity of the study populations.

Zinc sulfate supplements reportedly help with taste recovery (National Cancer Institute 2008), however others found this supplements ineffective (Halyard et al. 2007).

Dietary counseling helps adaptation to the loss of taste and serves to prevent reduced food intake which results in weight loss and nutritional deficiencies.

5.4 Salivary Gland Dysfunction

The most effective intervention for hyposalivation is its prevention. Prevention of RT damage to the salivary glands

is best achieved by limiting the areas exposed to radiation using three-dimensional treatment planning and conformal dose-delivery techniques (Hazuka et al. 1993; Nishioka et al. 1997; Henson et al. 2001). IMRT reduces the incidence of late salivary gland toxicity (Eisbruch et al. 2001; Wu et al. 2000; Saarilahti et al. 2005; Pacholke et al. 2005; Chambers et al. 2007). Of secondary importance, as a preventive strategy, is the pharmacological stimulation of salivary flow with sialogogues (Zimmerman et al. 1997). Continuous pilocarpine administration may protect the glands (Vissink et al. 2003). The benefits of pilocarpine may be due to stimulation of the minor salivary glands or parts of the major salivary glands (Vissink et al. 2003). According to the MASCC/ISOO systematic review, early use of pilocarpine to prevent the salivary gland damage is not supported by consistent evidence and therefore is not recommended (Jensen et al. 2010). Another strategy to spare the salivary glands is the use of a radioprotector such as amifostine (a free-radical scavenger) (Antonadou et al. 2002; McDonald et al. 1994). Unfortunately multiple side-effects of this drug, together with the potential protection of the tumor impede its acceptance. An unusual technique reported to prevent RT damage to the salivary glands is surgical transfer of the submandibular gland (out of the radiation field) prior to RT (Seikaly et al. 2001). The long-term outcomes of this technique showed prevention of xerostomia in 83 % of the patients 2 years post RT (Seikaly et al. 2004). Based on a systematic review it was suggested that the obtained level of sparing by submandibular salivary gland transfer might be of clinical significance (Jensen et al. 2010).

Once it occurs, treatment of chronic xerostomia essentially relies upon the use of saliva substitutes for palliation and/or mechanical, gustatory or chemical sialogogues to stimulate the flow rate.

Water and glycerin preparations, or commercially prepared "artificial saliva" are used. Newer artificial saliva solutions added electrolytes and enzymes to mimic the natural consistency of saliva.

Several pharmacologic sialogugous have been reviewed in the literature. (Vissink et al. 2003; Dirix et al. 2006) The use of several agents has been reported including bromhexine, anethole-trithione, bethanechol chloride, potassium iodide, neostigmine, and reserpine. However, the side effects of these agents led patients and clinicians to abandon them.

Pilocarpine has been widely used for the last three decades in RT and HSCT patients (Singhal et al. 1995). Pilocarpine is a cholinergic stimulant that acts on postganglionic cells that enervate smooth muscles and exocrine glands (e.g., the sweat and salivary glands). Best results were obtained with continuous treatment for 8–12 weeks with doses > 2.5 mg three times per day. There was no major drug-related toxicity. Residual functional salivary gland parenchyma is needed in order for any sialogogue to be effective.

In recent years cevimeline, a cholinergic stimulant, has gained recognition for its effectiveness and with fewer side effects (Petrone et al. 2002; Chambers et al. 2007; Carpenter et al. 2006). Cevimeline acts on M3 muscarinic receptors which are mainly found in the salivary and lacrimal glands, therefore it has minimal limited effects on the lungs and heart, which have M2 and M4 muscarinic receptors (Nieuw Amerongen and Veerman 2003). Gustatory stimuli with an acid-tasting substance and tactile stimuli with chewing gum can increase salivary secretion and may be an important component in the palliation of xerostomia (Dirix et al. 2006; Olsson et al. 1991). Another principal component of palliation is saliva substitute solutions, gels or sprays (Dirix et al. 2006; Momm et al. 2005). However, the moistening effect of saliva substitutes is of limited duration, and therefore patients often use water. Hypnosis, guided imagery and acupuncture may assist some patients (Braga et al. 2008). Gene transfer technology is currently being investigated and may open new therapeutic opportunities for these patients (Cotrim et al. 2006).

5.5 Infections

Oral infections can be prevented by good oral hygiene, routine rinsing and moistening of the oral cavity and, when indicated, anti-fungals, anti-virals or anti-bacterials. Various topical and systemic medications are available. There seems to be evidence supporting the use of systemic antifungal and anti-viral agents, but clearly these medications have side effects (Lalla et al. 2010; Elad et al. 2010.

5.6 Neuropathy and Chronic Pain

Treatment depends on the type of chronic pain as suggested by the American Headache Society (AHS) and International Association for the Study of Pain (IASP). It includes tricyclic-antidepressants, gabapentine and its derivatives (Benoliel et al. 2007; Merskey and Bogduk 1994). For drug-induced neuropathy, dose-adjustment of suspected drug is needed. Physiotherapy may relieve post-operative musculoskeletal pain (Benoliel et al. 2007; Epstein et al. 2007).

5.7 Dentition and Periodontium

Treatment strategies must be directed to each component of the caries process. The frequency of consumption of fermentable carbohydrates should be reduced. Optimal oral hygiene must be maintained. Xerostomia should be managed whenever possible via salivary substitutes or

stimulants. Caries resistance can be enhanced with use of topical fluorides and/or remineralizing agents (Meyerowitz and Watson 1998; Meyerowitz et al. 1991). Efficacy of topical products may be enhanced by increased contact time on the teeth by application using vinyl carriers (National Cancer Institute 2008; Chambers et al. 2007; Dirix et al. 2006; Hay and Thomson 2002). If carious lesions develop, removal and restoration should take place immediately.

Whenever possible, teeth should be retained to support tooth-borne appliances. Although tissue-borne prostheses are not contraindicated, mucosa that appears fibrosed, telangiectatic, and atrophic is at greater risk of subsequent damage from prostheses. The periodontium should be maintained in optimal condition by periodic routine periodontal care. There are no particular contraindications for endodontic procedures.

5.8 Trismus and Loss of Elasticity

Physical therapy interventions such as mandibular stretching exercises as well as prosthetic aids designed to reduce the severity of fibrosis are beneficial (Dijkstra et al. 2004; Bensadoun et al. 2010). This appears to be particularly useful in the prevention of trismus because once contraction occurs, such maneuvers are far less effective. Less expensive tongue blades may be inserted between the teeth to increase the interincisor distance until slight pain is encountered. The exercises should be performed for 30 s every few hours, and heating the muscle area before and after exercise may increase flexibility. Anti-inflammatory and muscle relaxant drugs may be prescribed in selected cases (Bradley et al. 2003). Microcurrent electrotherapy and pentoxifylline significantly increase mouth opening, but these modalities are rarely employed (Dijkstra et al. 2004). A recent paper describing a limited intra-oral surgical approach in an oral cGVHD patient reported success (Treister et al. 2012).

5.9 Osteoradionecrosis and Osteonecrosis of the Jaws

Often conservative treatment of ORN with antibiotics and surgical debridement is unsuccessful. Hyperbaric oxygen is highly effective in the treatment of ORN (National Cancer Institute 2008; Harding et al. 2008). The boost of oxygenation in the irradiated poorly healing wounds is probably the explanation for this. Hyperbaric oxygen stimulates angiogenesis, with increased neovascularization and optimization of cellular levels of oxygen for osteoblast and fibroblast proliferation, collagen formation, and support of ingrowing blood vessels. The hypoxic, acellular matrix in the postirradiated field is changed to a hypercellular, hyperoxic/normoxic situation (Myers and Marx 1990). Furthermore, hyperbaric oxygen –based preventive protocol are accepted as a standard of care before dental extraction and include 20 or more presurgical HBO treatments and 10 or more postsurgical HBO treatments. If ORN is diagnosed, protocol calls for 1 compression/decompression cycle per day for 5 days per week. Patients who meet the definition of ORN begin with staged treatment (Bradley et al. 2003):

- Stage I: If the wound shows definitive clinical improvement after 30 compression/decompression cycles, the patient is given a full course of 60 compression/decompression cycles. If there is no improvement after 30 compression/decompression cycles, the patient is advanced to stage II.
- Stage II: A transoral alveolar sequestrectomy with primary closure is done and the compression/decompression cycles are resumed. If healing progresses without complication, a total of 60 compression/decompression cycles are completed. If there is incomplete healing, the patient is advanced to stage III.
- Stage III: The patient undergoes a resection of the necrotic bone, the margins of which are determined by the presence of bleeding bone or by TCN fluorescence. Compression/decompression cycles are continued until healthy mucosal closure is obtained or a total of 60 compression/decompression cycles are given. The patient is then advanced to stage III-R. A patient can enter this stage directly if he/she presents with a pathologic fracture, orocutaneous fistula, or radiographic evidence of resorption to the inferior border. An initial course of 30 compression/decompression cycles are given in these cases.
- Stage III-R: Ten weeks after resection, 20 additional compression/decompression cycles are given and bone graft reconstruction is accomplished from a transcutaneous approach.

Several position papers on the presentation, predisposition, prevention and recommendations for treatment of osteonecrosis of the jaw in patients receiving bisphosphonates have recently been published (Khosla et al. 2007; Ruggiero 2009; Migliorati et al. 2005). The underlying principle is prevention of ONJ since no curative treatment is available. The main goal of treatment is palliation and infection control. Surgery other than the removal of loose bony sequestra, without exposing uninvolved bone, is to be avoided. Empiric antibiotic regimens have been implemented for various durations.

5.10 Developmental Abnormalities

Orthodontic treatment may be required in case of disturbed orofacial growth. A study in long-term survivors after pediatric HSCT showed that ideal treatment results were not

always achieved. The patients sample was too small to conclude the reason for this unsatisfactory result (Dahllof et al. 2001). Yet the orthodontic treatment did not produce any harmful side effects, even though most of the treated children exhibited severe preexisting disturbances in dental development (Dahllof et al. 2001).

5.11 Secondary Malignancy

Treatment for PTLD consists of anti-viral medication and reduction of immunosuppression, which may lead to complete resolution of PTLD. Treatment may include intervention with chemotherapy and/or radiotherapy, cytokines (interferon or Interleukin-6), intravenous immunoglobulins, anti-B cell antibodies or cellular immunotherapy (Loren et al. 2003). Surgery may be considered when the lesion is accessible.

Lifelong surveillance is imperative in cGVHD patients because of the increased cancer risk over time after transplantation. Frequency of recalls is higher when a dysplastic or malignant lesion is diagnosed. In addition, it is crucial that patients should avoid carcinogenic exposures, such as smoking. The treatment of oral cancer following HSCT generally follows the standards in non-HSCT patients. However, it is unclear if the use of RT in patients with GVHD will further increase the risk for secondary oral cancer.

6 Future Research

The field of oral medicine in oncology patients is broad and there are many topics of research. New frontiers include:

1. Validation of a predictive salivary function model that will enable the development of specific preventive measures. The extent of tissue sparing and preservation of salivary gland function by the new radiotherapy techniques is unknown.
2. Identification of markers that determine the risk for osteonecrosis of the jaws may facilitate the formulation of a protective algorithm that can be adjusted to meet the needs of specific sub-population. Genetics may be a key factor in this form of personalized medicine.
3. Considering the chronic nature of GVHD and its diffuse variable presentation, sophisticated microscopic imaging tools, such as confocal microscopy, may allow early detection of potentially malignant lesions. Development of targeted focal treatments such as photodynamic therapy may address the multi-focality and the recurrence of oral cancers.

7 Summary

Given early and more refine diagnosis of cancer patients and the efficacy of anti-cancer therapies, the number of long-term cancer survivors has increased. In addition, the number of patients undergoing HSCT has steadily increased. Improvement in survival rate following HSCT has resulted in a need to assess issues related to long-term complications. Cancer treatments lead to substantial oral and dental complications. Early and comprehensive dental treatment and oral care is essential and it requires a multidisciplinary health team. Attention to dental and oral health before and after cancer therapy can ensure that important oral functions, such as eating, talking, swallowing and speaking are maintained for the remainder of the cancer patient's life.

References

Alborghetti MR, Correa ME, Adam RL, Metze K, Coracin FL, de Souza CA et al (2005) Late effects of chronic graft-vs.-host disease in minor salivary glands. J Oral Pathol Med 34(8):486–493

Alter BP (2005) Fanconi's anemia, transplantation, and cancer. Pediatr Transplant 9(Suppl 7):81–86

Antonadou D, Pepelassi M, Synodinou M, Puglisi M, Throuvalas N (2002) Prophylactic use of amifostine to prevent radiochemotherapy-induced mucositis and xerostomia in head-and-neck cancer. Int J Radiat Oncol Biol Phys 52(3):739–747

Awwad HK, Lotayef M, Shouman T, Begg AC, Wilson G, Bentzen SM et al (2002) Accelerated hyperfractionation (AHF) compared to conventional fractionation (CF) in the postoperative radiotherapy of locally advanced head and neck cancer: influence of proliferation. Br J Cancer 86(4):517–523

Bamias A, Kastritis E, Bamia C, Moulopoulos LA, Melakopoulos I, Bozas G et al (2005) Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: incidence and risk factors. J Clin Oncol 23(34):8580–8587

Belazi M, Velegraki A, Koussidou-Eremondi T, Andreadis D, Hini S, Arsenis G et al (2004) Oral Candida isolates in patients undergoing radiotherapy for head and neck cancer: prevalence, azole susceptibility profiles and response to antifungal treatment. Oral Microbiol Immunol 19(6):347–351

Benoliel R, Epstein J, Eliav E, Jurevic R, Elad S (2007) Orofacial pain in cancer: part I–mechanisms. J Dent Res 86(6):491–505

Bensadoun et al (2010) Support Care Cancer 18(8):1033

Bernhardson BM, Tishelman C, Rutqvist LE (2007) Chemosensory changes experienced by patients undergoing cancer chemotherapy: a qualitative interview study. J Pain Symptom Manage 34(4):403–412

Berteretche MV, Dalix AM, d'Ornano AM, Bellisle F, Khayat D, Faurion A (2004) Decreased taste sensitivity in cancer patients under chemotherapy. Support Care Cancer 12(8):571–576

Bhatia S, Ramsay NK, Steinbuch M, Dusenbery KE, Shapiro RS, Weisdorf DJ et al (1996) Malignant neoplasms following bone marrow transplantation. Blood 87(9):3633–3639

Bhrany AD, Izzard M, Wood AJ, Futran ND (2007) Coronoidectomy for the treatment of trismus in head and neck cancer patients. Laryngoscope 117(11):1952–1956

Bradley LL, Chambers M, Conklin CE, Fox PC, Garden AS, Haveman CW, et al (2003) Oral Health in Cancer Therapy. A Guide for Health Care Professionals. In: Rankin KV, Jones DL, Redding SW (eds) Oral health in cancer therapy. Dental Oncology Education Program; American Cancer Society, Texas Division; Texas Dental Foundation, San Antonio

Braga FP, Sugaya NN, Hirota SK, Weinfeld I, Magalhaes MH, Migliari DA (2008) The effect of acupuncture on salivary flow rates in patients with radiation-induced xerostomia. Minerva Stomatol 57(7–8):343–348

Brown LR, Dreizen S, Handler S, Johnston DA (1975) Effect of radiation-induced xerostomia on human oral microflora. J Dent Res 54(4):740–750

Buntzel J, Glatzel M, Kuttner K, Weinaug R, Frohlich D (2002) Amifostine in simultaneous radiochemotherapy of advanced head and neck cancer. Semin Radiat Oncol 12(1 Suppl 1):4–13

Carpenter PA, Schubert MM, Flowers ME (2006) Cevimeline reduced mouth dryness and increased salivary flow in patients with xerostomia complicating chronic graft-versus-host disease. Biol Blood Marrow Transplant 12(7):792–794

Chambers MS, Rosenthal DI, Weber RS (2007a) Radiation-induced xerostomia. Head Neck 29(1):58–63

Chambers MS, Posner M, Jones CU, Biel MA, Hodge KM, Vitti R et al (2007b) Cevimeline for the treatment of postirradiation xerostomia in patients with head and neck cancer. Int J Radiat Oncol Biol Phys 68(4):1102–1109

Chaushu G, Itzkovitz-Chaushu S, Yefenof E, Slavin S, Or R, Garfunkel AA (1995) A longitudinal follow-up of salivary secretion in bone marrow transplant patients. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 79(2):164–169

Chaushu et al (1995) Oral Surg Oral Med Oral Pathol Oral Radiol Endod 79(2):164

Chen AM, Bucci MK, Singer MI, Garcia J, Kaplan MJ, Chan AS et al (2007) Intraoperative radiation therapy for recurrent head-and-neck cancer: the UCSF experience. Int J Radiat Oncol Biol Phys 67(1):122–129

Cheng VS, Downs J, Herbert D, Aramany M (1981) The function of the parotid gland following radiation therapy for head and neck cancer. Int J Radiat Oncol Biol Phys 7(2):253–258

Chow HT, Teh LY (2000) Sensory impairment after resection of the mandible: a case report of 10 cases. J Oral Maxillofac Surg 58(6):629–635

Cohen et al (2012) Support Care Cancer 20:3019

Comeau TB, Epstein JB, Migas C (2001) Taste and smell dysfunction in patients receiving chemotherapy: a review of current knowledge. Support Care Cancer 9(8):575–580

Coppes RP, Vissink A, Konings AW (2002) Comparison of radiosensitivity of rat parotid and submandibular glands after different radiation schedules. Radiother Oncol 63(3):321–328

Cotrim AP, Mineshiba F, Sugito T, Samuni Y, Baum BJ (2006) Salivary gland gene therapy. Dent Clin North Am 50(2):157–173

Couriel D, Carpenter PA, Cutler C, Bolanos-Meade J, Treister NS, Gea-Banacloche J et al (2006) Ancillary therapy and supportive care of chronic graft-versus-host disease: national institutes of health consensus development project on criteria for clinical trials in chronic Graft-versus-host disease: V. Ancillary Therapy and Supportive Care Working Group Report. Biol Blood Marrow Transplant 12(4):375–396

Curtis RE, Rowlings PA, Deeg HJ, Shriner DA, Socie G, Travis LB et al (1997) Solid cancers after bone marrow transplantation. N Engl J Med 336(13):897–904

Dahllof G, Forsberg CM, Ringden O, Bolme P, Borgstrom B, Nasman M et al (1989) Facial growth and morphology in long-term survivors after bone marrow transplantation. Eur J Orthod 11(4):332–340

Dahllof G, Krekmanova L, Kopp S, Borgstrom B, Forsberg CM, Ringden O (1994) Craniomandibular dysfunction in children treated with total-body irradiation and bone marrow transplantation. Acta Odontol Scand 52(2):99–105

Dahllof G, Jonsson A, Ulmner M, Huggare J (2001) Orthodontic treatment in long-term survivors after pediatric bone marrow transplantation. Am J Orthod Dentofacial Orthop 120(5):459–465

Deeg HJ, Socie G, Schoch G, Henry-Amar M, Witherspoon RP, Devergie A et al (1996) Malignancies after marrow transplantation for aplastic anemia and fanconi anemia: a joint Seattle and Paris analysis of results in 700 patients. Blood 87(1):386–392

Demarosi F, Lodi G, Carrassi A, Soligo D, Sardella A (2005) Oral malignancies following HSCT: graft versus host disease and other risk factors. Oral Oncol 41(9):865–877

Denys D, Kaste SC, Kun LE, Chaudhary MA, Bowman LC, Robbins KT (1998) The effects of radiation on craniofacial skeletal growth: a quantitative study. Int J Pediatr Otorhinolaryngol 45(1):7–13

Dijkstra PU, Kalk WW, Roodenburg JL (2004) Trismus in head and neck oncology: a systematic review. Oral Oncol 40(9):879–889

Dirix P, Nuyts S, Van den Bogaert W (2006) Radiation-induced xerostomia in patients with head and neck cancer: a literature review. Cancer 107(11):2525–2534

Dobr T, Passweg J, Weber C, Tichelli A, Heim D, Meyer J et al (2007) Oral health risks associated with HLA-types of patients undergoing hematopoietic stem cell transplantation. Eur J Haematol 78(6):495–499

Duggal MS (2003) Root surface areas in long-term survivors of childhood cancer. Oral Oncol 39(2):178–183

Duggal MS, Curzon ME, Bailey CC, Lewis IJ, Prendergast M (1997) Dental parameters in the long-term survivors of childhood cancer compared with siblings. Oral Oncol 33(5):348–353

Eckardt A, Starke O, Stadler M, Reuter C, Hertenstein B (2004) Severe oral chronic graft-versus-host disease following allogeneic bone marrow transplantation: highly effective treatment with topical tacrolimus. Oral Oncol 40(8):811–814

Eisbruch A, Ten Haken RK, Kim HM, Marsh LH, Ship JA (1999) Dose, volume, and function relationships in parotid salivary glands following conformal and intensity-modulated irradiation of head and neck cancer. Int J Radiat Oncol Biol Phys 45(3):577–587

Eisbruch A, Ship JA, Kim HM, Ten Haken RK (2001) Partial irradiation of the parotid gland. Semin Radiat Oncol 11(3):234–239

Elad S, Galili D, Garfunkel AA, Or R (1997) Thalidomide-induced perioral neuropathy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 84(4):362–364

Elad S, Garfunkel AA, Enk CD, Galili D, Or R (1999) Ultraviolet B irradiation: a new therapeutic concept for the management of oral manifestations of graft-versus-host disease. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 88(4):444–450

Elad S, Or R, Garfunkel AA, Shapira MY (2003) Budesonide: a novel treatment for oral chronic graft versus host disease. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 95(3):308–311

Elad S, Meyerowitz C, Shapira MY, Glick M, Bitan M, Amir G (2008) Oral posttransplantation lymphoproliferative disorder: an uncommon site for an uncommon disorder. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 105(1):59–64

Elad et al (2010) Support Care Cancer 18(8):993

Elad S, Zeevi I, Finke J, Koldehoff M, Schwerdtfeger R, Wolff D, Mohrbacher R, Levitt M, Greinwald R, Shapira MY (2012) Improvement in oral chronic graft-versus-host disease with the administration of effervescent tablets of topical budesonide-an open, randomized, multicenter study. Biol Blood Marrow Transplant 18(1):134–140

Epstein JB, Stevenson-Moore P (2001) Periodontal disease and periodontal management in patients with cancer. Oral Oncol 37(8):613–619

Epstein JB, Truelove EL (1996) Topical cyclosporine in a bioadhesive for treatment of oral lichenoid mucosal reactions: an open label clinical trial. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 82(5):532–536

Epstein JB, Lunn R, Le N, Stevenson-Moore P (1998) Periodontal attachment loss in patients after head and neck radiation therapy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 86(6):673–677

Epstein JB, Robertson M, Emerton S, Phillips N, Stevenson-Moore P (2001a) Quality of life and oral function in patients treated with radiation therapy for head and neck cancer. Head Neck 23(5):389–398

Epstein JB, Gorsky M, Epstein MS, Nantel S (2001b) Topical azathioprine in the treatment of immune-mediated chronic oral inflammatory conditions: a series of cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 91(1):56–61

Epstein JB, Phillips N, Parry J, Epstein MS, Nevill T, Stevenson-Moore P (2002a) Quality of life, taste, olfactory and oral function following high-dose chemotherapy and allogeneic hematopoietic cell transplantation. Bone Marrow Transplant 30(11):785–792

Epstein JB, Gorsky M, Hancock P, Peters N, Sherlock CH (2002b) The prevalence of herpes simplex virus shedding and infection in the oral cavity of seropositive patients undergoing head and neck radiation therapy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 94(6):712–716

Epstein JB, Elad S, Eliav E, Jurevic R, Benoliel R (2007) Orofacial pain in cancer: part II–clinical perspectives and management. J Dent Res 86(6):506–518

Epstein et al (2010) Oral Oncol 46(2):77

Foltz AT, Gaines G, Gullatte M (1996) Recalled side effects and self-care actions of patients receiving inpatient chemotherapy. Oncol Nurs Forum 23(4):679–683

Gamper et al (2012) J Pain Sympt Manage 44(6):880

Gamper et al. Journal of Pain and Symptom Management 2012 Dec;44(6):880

Gellrich NC, Schramm A, Bockmann R, Kugler J (2002) Follow-up in patients with oral cancer. J Oral Maxillofac Surg 60(4):380–386; discussion 387–388

Gevorgyan A, La Scala GC, Neligan PC, Pang CY, Forrest CR (2007) Radiation-induced craniofacial bone growth disturbances. J Craniofac Surg 18(5):1001–1007

Halyard MY, Jatoi A, Sloan JA, Bearden JD 3rd, Vora SA, Atherton PJ et al (2007) Does zinc sulfate prevent therapy-induced taste alterations in head and neck cancer patients? Results of phase III double-blind, placebo-controlled trial from the North Central Cancer Treatment Group (N01C4). Int J Radiat Oncol Biol Phys 67(5):1318–1322

Hammerlid E, Taft C (2001) Health-related quality of life in long-term head and neck cancer survivors: a comparison with general population norms. Br J Cancer 84(2):149–156

Hammerlid E, Silander E, Hornestam L, Sullivan M (2001) Health-related quality of life three years after diagnosis of head and neck cancer–a longitudinal study. Head Neck 23(2):113–125

Harding SA, Hodder SC, Courtney DJ, Bryson PJ (2008) Impact of perioperative hyperbaric oxygen therapy on the quality of life of maxillofacial patients who undergo surgery in irradiated fields. Int J Oral Maxillofac Surg 37(7):617–624

Harris N, Swerdlow S, Frizzera G, Knowles D (eds) (2001) World Health Organization Classification of Tumours: Pathology & Genetics. IARC press, Tumours of Haematopoietic and Lymphoid Tissues. Lyon France

Hashibe M, Ritz B, Le AD, Li G, Sankaranarayanan R, Zhang ZF (2005) Radiotherapy for oral cancer as a risk factor for second primary cancers. Cancer Lett 220(2):185–195

Hay KD, Thomson WM (2002) A clinical trial of the anticaries efficacy of casein derivatives complexed with calcium phosphate in patients with salivary gland dysfunction. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 93(3):271–275

Hazuka MB, Martel MK, Marsh L, Lichter AS, Wolf GT (1993) Preservation of parotid function after external beam irradiation in head and neck cancer patients: a feasibility study using 3-dimensional treatment planning. Int J Radiat Oncol Biol Phys 27(3):731–737

Hellstein et al (2011) J Am Dent Assoc 142(11):1243

Henson BS, Inglehart MR, Eisbruch A, Ship JA (2001) Preserved salivary output and xerostomia-related quality of life in head and neck cancer patients receiving parotid-sparing radiotherapy. Oral Oncol 37(1):84–93

Hilkens PH, Verweij J, Vecht CJ, Stoter G, van den Bent MJ (1997) Clinical characteristics of severe peripheral neuropathy induced by docetaxel (Taxotere). Ann Oncol 8(2):187–190

Hiroki A, Nakamura S, Shinohara M, Oka M (1994) Significance of oral examination in chronic graft-versus-host disease. J Oral Pathol Med 23(5):209–215

Hoff et al (2011) Ann NY Acad Sci 1218

Hovan et al (2010) Support Care Cancer 18(8):1081

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

http://www.rtog.org/ResearchAssociates/AdverseEventReporting.aspx

Imanguli MM, Pavletic SZ, Guadagnini JP, Brahim JS, Atkinson JC (2006) Chronic graft versus host disease of oral mucosa: review of available therapies. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 101(2):175–183

Izutsu KT, Menard TW, Schubert MM, Ensign WY, Sullivan K, Truelove EL et al (1985) Graft versus host disease-related secretory immunoglobulin A deficiency in bone marrow transplant recipients. Findings in labial saliva. Lab Invest 52(3):292–297

Jensen et al (2010) Support Care Cancer 18(8):1061

Kang MY, Holland JM, Stevens KR Jr (2000) Cranial neuropathy following curative chemotherapy and radiotherapy for carcinoma of the nasopharynx. J Laryngol Otol 114(4):308–310

Karsila-Tenovuo S, Jahnukainen K, Peltomaki T, Minn H, Kulmala J, Salmi TT et al (2001) Disturbances in craniofacial morphology in children treated for solid tumors. Oral Oncol 37(7):586–592

Khamaisi M, Regev E, Yarom N, Avni B, Leitersdorf E, Raz I et al (2007) Possible association between diabetes and bisphosphonate-related jaw osteonecrosis. J Clin Endocrinol Metab 92(3):1172–1175

Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D et al (2007) Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 22(10):1479–1491

Kielbassa AM, Hinkelbein W, Hellwig E, Meyer-Luckel H (2006) Radiation-related damage to dentition. Lancet Oncol 7(4):326–335

King AD, Leung SF, Teo P, Lam WW, Chan YL, Metreweli C (1999) Hypoglossal nerve palsy in nasopharyngeal carcinoma. Head Neck 21(7):614–619

Koga DH, Salvajoli JV, Alves FA (2008) Dental extractions and radiotherapy in head and neck oncology: review of the literature. Oral Dis 14(1):40–44

Lalla et al (2010) Support Care Cancer 18(8):985

Lee JN et al (2010) Compr Canc Netw 8(11):1277

LeCouteur RA, Gillette EL, Powers BE, Child G, McChesney SL, Ingram JT (1989) Peripheral neuropathies following experimental intraoperative radiation therapy (IORT). Int J Radiat Oncol Biol Phys 17(3):583–590

Liem IH, Olmos RA, Balm AJ, Keus RB, van Tinteren H, Takes RP et al (1996) Evidence for early and persistent impairment of salivary gland excretion after irradiation of head and neck tumours. Eur J Nucl Med 23(11):1485–1490

Lindley C, McCune JS, Thomason TE, Lauder D, Sauls A, Adkins S et al (1999) Perception of chemotherapy side effects cancer versus noncancer patients. Cancer Pract 7(2):59–65

Lindsay R (2001) Osteoporosis. In: Braunwald E, Kasper D, Hauser S, Long D, Jameson J (eds) Harrison's Principles of Internal Medicine. McGraw-Hill, New York, pp 2226–2237

Loprinzi CL, Gastineau DA, Foote RL (eds) (2004) Clinical oncology, 3rd edn. Elsevier, Churchill Livingstone, Philadelphia

Loren AW, Porter DL, Stadtmauer EA, Tsai DE (2003) Post-transplant lymphoproliferative disorder: a review. Bone Marrow Transplant 31(3):145–155

Love S, Jacobs JM, Myers R (1986) Chronic demyelination in mouse peripheral nerve produced by lysophosphatidyl choline and X-irradiation: ultrastructural observations. J Neurocytol 15(2):155–167

Makkonen TA, Tenovuo J, Vilja P, Heimdahl A (1986) Changes in the protein composition of whole saliva during radiotherapy in patients with oral or pharyngeal cancer. Oral Surg Oral Med Oral Pathol 62(3):270–275

Manon RR, Meyrs JN, Khuntia D, Harari PM, Levendag PC, Teguh DN, et al (2008) Oral Cavity Cancer and Oropharynx. In: Helperin EC, Perez CA, Brady LW (eds) Principles and practice of radiation oncology, 5th edn. Lippincott Williams & Wilkins, a Wolters Kluwer business, Philadelphia, pp 891–957

Marinone MG, Rizzoni D, Ferremi P, Rossi G, Izzi T, Brusotti C (1991) Late taste disorders in bone marrow transplantation: clinical evaluation with taste solutions in autologous and allogeneic bone marrow recipients. Haematologica 76(6):519–522

Marques MA, Dib LL (2004) Periodontal changes in patients undergoing radiotherapy. J Periodontol 75(9):1178–1187

Mattsson T, Arvidson K, Heimdahl A, Ljungman P, Dahllof G, Ringden O (1992) Alterations in taste acuity associated with allogeneic bone marrow transplantation. J Oral Pathol Med 21(1):33–37

Mawardi et al (2011) Bone Marrow Transplant 46(6):884

McDonald S, Meyerowitz C, Smudzin T, Rubin P (1994) Preliminary results of a pilot study using WR-2721 before fractionated irradiation of the head and neck to reduce salivary gland dysfunction. Int J Radiat Oncol Biol Phys 29(4):747–754

McMillan AS, Pow EH, Leung WK, Wong MC, Kwong DL (2004) Oral health-related quality of life in southern Chinese following radiotherapy for nasopharyngeal carcinoma. J Oral Rehabil 31(6):600–608

Merskey H, Bogduk N (eds) (1994) Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms, 2nd edn. IASP Press

Meyerowitz C, Watson GE 2nd (1998) The efficacy of an intraoral fluoride-releasing system in irradiated head and neck cancer patients: a preliminary study. J Am Dent Assoc 129(9):1252–1259

Meyerowitz C, Featherstone JD, Billings RJ, Eisenberg AD, Fu J, Shariati M et al (1991) Use of an intra-oral model to evaluate 0.05% sodium fluoride mouthrinse in radiation-induced hyposalivation. J Dent Res 70(5):894–898

Micallef IN, Chhanabhai M, Gascoyne RD, Shepherd JD, Fung HC, Nantel SH et al (1998) Lymphoproliferative disorders following allogeneic bone marrow transplantation: the Vancouver experience. Bone Marrow Transplant 22(10):981–987

Migliorati CA, Schubert MM, Peterson DE, Seneda LM (2005) Bisphosphonate-associated osteonecrosis of mandibular and maxillary bone: an emerging oral complication of supportive cancer therapy. Cancer 104(1):83–93

Mizobuchi K, Kincaid J (2003) Accessory neuropathy after high-dose radiation therapy for tongue-base carcinoma. Muscle Nerve 28(5):650–651

Momm F, Volegova-Neher NJ, Schulte-Monting J, Guttenberger R (2005) Different saliva substitutes for treatment of xerostomia following radiotherapy. A prospective crossover study. Strahlenther Onkol 181(4):231–236

Myers RA, Marx RE (1990) Use of hyperbaric oxygen in postradiation head and neck surgery. NCI Monogr 9:151–157

Nagler R, Marmary Y, Krausz Y, Chisin R, Markitziu A, Nagler A (1996a) Major salivary gland dysfunction in human acute and chronic graft-versus-host disease (GVHD). Bone Marrow Transplant 17(2):219–224

Nagler RM, Laufer D, Nagler A (1996b) Parotid gland dysfunction in an animal model of chronic graft-vs-host disease. Arch Otolaryngol Head Neck Surg 122(10):1057–1060

National Cancer Institute (2008) Oral Complications of Chemotherapy and Head/Neck Radiation (PDQ®) (2008) November 6th [cited 28th December 2008]. Available from: http://www.cancer.gov/cancertopics/pdq/supportivecare/oralcomplications/HealthProfessional

Nieuw Amerongen AV, Veerman EC (2003) Current therapies for xerostomia and salivary gland hypofunction associated with cancer therapies. Support Care Cancer 11(4):226–231

Nishioka T, Shirato H, Arimoto T, Kaneko M, Kitahara T, Oomori K et al (1997) Reduction of radiation-induced xerostomia in nasopharyngeal carcinoma using CT simulation with laser patient marking and three-field irradiation technique. Int J Radiat Oncol Biol Phys 38(4):705–712

Nordgren M, Hammerlid E, Bjordal K, Ahlner-Elmqvist M, Boysen M, Jannert M (2008) Quality of life in oral carcinoma: a 5-year prospective study. Head Neck 30(4):461–470

Oguz A, Cetiner S, Karadeniz C, Alpaslan G, Alpaslan C, Pinarli G (2004) Long-term effects of chemotherapy on orodental structures in children with non-Hodgkin's lymphoma. Eur J Oral Sci 112(1):8–11

Ojha J, Islam N, Cohen DM, Marshal D, Reavis MR, Bhattacharyya I (2008) Post-transplant lymphoproliferative disorders of oral cavity. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 105(5):589–596

Olsson H, Spak CJ, Axell T (1991) The effect of a chewing gum on salivary secretion, oral mucosal friction, and the feeling of dry mouth in xerostomic patients. Acta Odontol Scand 49(5):273–279

Otmani N (2007) Oral and maxillofacial side effects of radiation therapy on children. J Can Dent Assoc 73(3):257–261

Pacholke HD, Amdur RJ, Morris CG, Li JG, Dempsey JF, Hinerman RW et al (2005) Late xerostomia after intensity-modulated radiation therapy versus conventional radiotherapy. Am J Clin Oncol 28(4):351–358

Papas A, Russell D, Singh M, Kent R, Triol C, Winston A (2008) Caries clinical trial of a remineralising toothpaste in radiation patients. Gerodontology 25(2):76–88

Pattni R, Walsh LJ, Marshall RI, Cullinan MP, Seymour GJ, Bartold PM (2000) Changes in the periodontal status of patients undergoing bone marrow transplantation. J Periodontol 71(3):394–402

Paulino AC, Simon JH, Zhen W, Wen BC (2000) Long-term effects in children treated with radiotherapy for head and neck rhabdomyosarcoma. Int J Radiat Oncol Biol Phys 48(5):1489–1495

Pavletic SZ, Martin P, Lee SJ, Mitchell S, Jacobsohn D, Cowen EW et al (2006) Measuring therapeutic response in chronic graft-versus-host disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: IV. Response Criteria Working Group report. Biol Blood Marrow Transplant 12(3):252–266

Petrone D, Condemi JJ, Fife R, Gluck O, Cohen S, Dalgin P (2002) A double-blind, randomized, placebo-controlled study of cevimeline in Sjogren's syndrome patients with xerostomia and keratoconjunctivitis sicca. Arthritis Rheum 46(3):748–754

Piboonniyom SO, Treister N, Pitiphat W, Woo SB (2005) Scoring system for monitoring oral lichenoid lesions: a preliminary study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 99(6):696–703

Pogrel MA (2004) Bisphosphonates and bone necrosis. J Oral Maxillofac Surg 62(3):391–392
Price RE, Ang KK, Stephens LC, Peters LJ (1995) Effects of continuous hyperfractionated accelerated and conventionally fractionated radiotherapy on the parotid and submandibular salivary glands of rhesus monkeys. Radiother Oncol 34(1):39–46
Prott FJ, Handschel J, Micke O, Sunderkotter C, Meyer U, Piffko J (2002) Long-term alterations of oral mucosa in radiotherapy patients. Int J Radiat Oncol Biol Phys 54(1):203–210
Raber-Durlacher JE, Epstein JB, Raber J, van Dissel JT, van Winkelhoff AJ, Guiot HF et al (2002) Periodontal infection in cancer patients treated with high-dose chemotherapy. Support Care Cancer 10(6):466–473
Rankin (2008) Guide for health care providers
Rathod et al (2013) Oral Oncol 49(6):634
Raut A, Huryn J, Pollack A, Zlotolow I (2000) Unusual gingival presentation of post-transplantation lymphoproliferative disorder: a case report and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 90(4):436–441
Redding SW, Callander NS, Haveman CW, Leonard DL (1998) Treatment of oral chronic graft-versus-host disease with PUVA therapy: case report and literature review. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 86(2):183–187
Redding SW, Zellars RC, Kirkpatrick WR, McAtee RK, Caceres MA, Fothergill AW et al (1999) Epidemiology of oropharyngeal Candida colonization and infection in patients receiving radiation for head and neck cancer. J Clin Microbiol 37(12): 3896–3900
Reynolds EC, Cai F, Cochrane NJ, Shen P, Walker GD, Morgan MV et al (2008) Fluoride and casein phosphopeptide-amorphous calcium phosphate. J Dent Res 87(4):344–348
Rhodes VA, McDaniel RW, Hanson B, Markway E, Johnson M (1994) Sensory perception of patients on selected antineoplastic chemotherapy protocols. Cancer Nurs 17(1):45–51
Roesink JM, Moerland MA, Battermann JJ, Hordijk GJ, Terhaard CH (2001) Quantitative dose-volume response analysis of changes in parotid gland function after radiotherapy in the head-and-neck region. Int J Radiat Oncol Biol Phys 51(4): 938–946
Rogers SN, Lowe D, McNally D, Brown JS, Vaughan ED (2003) Health-related quality of life after maxillectomy: a comparison between prosthetic obturation and free flap. J Oral Maxillofac Surg 61(2):174–181
Rosenbluth B et al (2005) Int J Radiat Oncol Biol Phys 63:1419
Rubin P, Casarett GW (1968) Alimentary tract: esophagus and stomach. In: Rubin P, Casarett GW (eds) Clinical radiation pathology, vol 1, 1 edn. W. B. Saunders Company, Philadelphia p 517
Ruggiero (2009) J Oral Maxillofac Surg 67(5 Suppl):2
Ruggiero SL, Dodson TB, Assael LA, Landesberg R, Marx RE, Mehrotra B (2009) American association of oral and maxillofacial surgeons position paper on Bisphosphonate-Related osteonecrosis of the Jaw–2009 update. Aust Dent J 35(3):119–130
Ruo Redda MG, Allis S (2006) Radiotherapy-induced taste impairment. Cancer Treat Rev 32(7):541–547
Saarilahti K, Kouri M, Collan J, Hamalainen T, Atula T, Joensuu H et al (2005) Intensity modulated radiotherapy for head and neck cancer: evidence for preserved salivary gland function. Radiother Oncol 74(3):251–258
Sari I, Altuntas F, Kocyigit I, Sisman Y, Eser B, Unal A et al (2007) The effect of budesonide mouthwash on oral chronic graft versus host disease. Am J Hematol 82(5):349–356
Schiffman SS, Zervakis J (2002) Taste and smell perception in the elderly: effect of medications and disease. Adv Food Nutr Res 44:247–346
Schubert MM, Correa ME (2008) Oral graft-versus-host disease. Dent Clin North Am 52(1):79–109 viii-ix
Schubert M, Peterson D, Lloid M (2004) Oral Complications. In: Thomas E, Blume K, Forma S (eds) Hematopoietic Stem Cell Transplantation. Blackwell Science, Maiden, pp 911–928
Seikaly H, Jha N, McGaw T, Coulter L, Liu R, Oldring D (2001) Submandibular gland transfer: a new method of preventing radiation-induced xerostomia. Laryngoscope 111(2):347–352
Seikaly H, Jha N, Harris JR, Barnaby P, Liu R, Williams D et al (2004) Long-term outcomes of submandibular gland transfer for prevention of postradiation xerostomia. Arch Otolaryngol Head Neck Surg 130(8):956–961
Shi HB, Masuda M, Umezaki T, Kuratomi Y, Kumamoto Y, Yamamoto T et al (2004) Irradiation impairment of umami taste in patients with head and neck cancer. Auris Nasus Larynx 31(4):401–406
Silverman SJ (ed) (2003) Complications of treatment. BC Decker Inc, Hamilton
Singhal S, Mehta J, Rattenbury H, Treleaven J, Powles R (1995) Oral pilocarpine hydrochloride for the treatment of refractory xerostomia associated with chronic graft-versus-host disease. Blood 85(4):1147–1148
Sivolella S et al (2013) Anticancer Res 33(5):1793
Sonis ST (2004) The pathology of mucositis. National Rev Cancer 4:47
Sonis ST (2007) Pathobiology of oral mucositis: novel insights and opportunities. J Support Oncol 5(9 Suppl 4):3–11
Talmi YP (2002) Quality of life issues in cancer of the oral cavity. J Laryngol Otol 116(10):785–790
Terrell JE, Nanavati K, Esclamado RM, Bradford CR, Wolf GT (1999) Health impact of head and neck cancer. Otolaryngol Head Neck Surg 120(6):852–859
Thariat et al (2011) Anticancer Drugs 22(7):596
Tillman BN, Elbermani W (2007) (eds) Atlas of human anatomy, clinical edition, 1st edn. Mud Puddle Books Inc, New York, pp. 60
Treister et al (2012) Blood 120(17):3407
Valdez IH, Atkinson JC, Ship JA, Fox PC (1993) Major salivary gland function in patients with radiation-induced xerostomia: flow rates and sialochemistry. Int J Radiat Oncol Biol Phys 25(1):41–47
van der Pas-van Voskuilen IG, Veerkamp JS, Raber-Durlacher JE, Bresters D, van Wijk AJ, Barasch A, et al (2009) Long-term adverse effects of hematopoietic stem cell transplantation on dental development in children. Support Care Cancer
van Wilgen CP, Dijkstra PU, van der Laan BF, Plukker JT, Roodenburg JL (2004) Morbidity of the neck after head and neck cancer therapy. Head Neck 26(9):785–791
Vissink A, Jansma J, Spijkervet FK, Burlage FR, Coppes RP (2003a) Oral sequelae of head and neck radiotherapy. Crit Rev Oral Biol Med 14(3):199–212
Vissink A, Burlage FR, Spijkervet FK, Jansma J, Coppes RP (2003b) Prevention and treatment of the consequences of head and neck radiotherapy. Crit Rev Oral Biol Med 14(3):213–225
Vujaskovic Z (1997) Structural and physiological properties of peripheral nerves after intraoperative irradiation. J Peripher Nerv Syst 2(4):343–349
Wang J, Goodger NM, Pogrel MA (2003) Osteonecrosis of the jaws associated with cancer chemotherapy. J Oral Maxillofac Surg 61(9):1104–1107

Wickham RS, Rehwaldt M, Kefer C, Shott S, Abbas K, Glynn-Tucker E et al (1999) Taste changes experienced by patients receiving chemotherapy. Oncol Nurs Forum 26(4):697–706

Witherspoon RP, Fisher LD, Schoch G, Martin P, Sullivan KM, Sanders J et al (1989) Secondary cancers after bone marrow transplantation for leukemia or aplastic anemia. N Engl J Med 321(12):784–789

Wu Q, Manning M, Schmidt-Ullrich R, Mohan R (2000) The potential for sparing of parotids and escalation of biologically effective dose with intensity-modulated radiation treatments of head and neck cancers: a treatment design study. Int J Radiat Oncol Biol Phys 46(1):195–205

Youngblood M, Williams PD, Eyles H, Waring J, Runyon S (1994) A comparison of two methods of assessing cancer therapy-related symptoms. Cancer Nurs 17(1):37–44

Zadik et al (2010) J Endod 36(9):1588

Zhang S-X (1999) An atlas of histology. Springer-Verlag Inc, New York, pp. 209–212

Zimmerman RP, Mark RJ, Tran LM, Juillard GF (1997) Concomitant pilocarpine during head and neck irradiation is associated with decreased posttreatment xerostomia. Int J Radiat Oncol Biol Phys 37(3):571–575