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Oral toxicity management in head and neck cancer patients treated with chemotherapy and radiation: Xerostomia and trismus (Part 2). Literature review and consensus statement

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A B S T R A C T

Radiotherapy alone or in combination with chemotherapy and/or surgery is a well-known radical treatment for head and neck cancer patients. Nevertheless acute side effects (such as moist desquamation, skin erythema, loss of taste, mucositis etc.) and in particular late toxicities (osteoradionecrosis, xerostomia, trismus, radiation caries etc.) are often debilitating and underestimated.

A multidisciplinary group of head and neck specialists from Italy met in Milan with the aim of reaching a consensus on a clinical definition and management of these toxicities.

The Delphi Appropriateness method was used for this consensus and external experts evaluated the conclusions. The paper contains 20 clusters of statements about the clinical definition and management of stomatological issues that reached consensus, and offers a review of the literature about these topics.

The review was split into two parts: the first part dealt with dental pathologies and osteo-radionecrosis (10 clusters of statements), whereas this second part deals with trismus and xerostomia (10 clusters of statements).

1. Introduction

Radiotherapy (RT) with/without chemotherapy (CT) and/or surgery is an established form of therapy for the curative treatment or palliation of head and neck cancer patients (HNCPs). In recent years, better RT target definitions and healthy tissue avoidance criteria have evolved, aimed at better loco-regional disease control and higher survival rates (Parliament et al., 2005; Dirix and Nuyts, 2010; Retel et al., 2011; Vissink et al., 2003a). RT delivery techniques were also ameliorated thanks to the introduction of intensity modulated radiation therapy (IMRT). The resulting sharp dose gradients and the possibility of simultaneously delivering different fractional doses in the tumour and the surrounding healthy tissues allowed the radiobiological effects to be more effectively modulated.

Acute and late adverse events (AEs) occurring after radiotherapy (±chemotherapy and/or surgery) have been studied with increasing interest, since it has been realized that their occurrence may hamper the good clinical results obtained. The different types of treatment-related functional *sequels* can be grouped according to the anatomic and functional structures that, when damaged by radiation, give rise to some specific clinical dysfunctions such as dysphagia, xerostomia, and trismus.

Thus, numerous studies have tried to identify the Dysphagia/Aspiration-Related Structures (DARSs) (Eisbruch et al., 2004) (e.g. the pharyngeal constrictors, tongue base, and larynx), Altered-Mastication-Related Structures or (AMRSs) (Teguh et al., 2008; Johnson et al., 2010; Van der Molen et al., 2011, 2013) (e.g. the masseter, pterygoid muscles and the temporal mandibular joints, and the oral cavity), and Xerostomia-Related Structures or XRSs (Van de Water et al., 2009; Jellema et al., 2005) (e.g. the major and minor salivary glands) in recent years.

While health-related quality of life (HRQoL) after RT ± CT and or surgery may be ameliorated with the new techniques (Pow et al., 2006; Nutting et al., 2011; Bhide et al., 2009; Caudell et al., 2010; Eisbruch et al., 2011; Jensen et al., 2007a), dose-volume correlations between the sequels and the irradiated anatomical structures have not yet been precisely defined (Nutting et al., 2011; Caudell et al., 2010; Eisbruch et al., 2011; Jensen et al., 2007a; Levendag et al., 2007; Li et al., 2009; Bhide et al., 2012a). However, recently published reviews (Van der Laan et al., 2012a; Nutting, 2012; Wang et al., 2011; Goldstein et al., 1999) concluded that a number of the structures' dosimetric constraints might reduce the negative impact of RT on salivation and swallowing. It has also been stated that future studies examining the predictive power of dosimetric factors should include pre-treatment functional data, and more standardized, validated measurement protocols (Cartmill et al., 2012) in order to distinguish the tumour and the cancer therapy effects.

A task force of Radiation Oncologists (ROs), Medical Oncologists (MOs), Oral Care Physicians (OCPs), Radiologists (Rs), and Nurses (Ns) met in Milan with the aim of reaching a consensus on the supportive management of HNCPs' oral radio/chemo-induced pathologies.

This paper reports and discusses the statements regarding xerostomia and trismus that achieved consensus, whereas the statements concerning dental pathologies and osteo-radionecroses were reported in Part 1.

The consensus was focused particularly on those statements with limited evidence.

The results of the literature review and the statements that obtained a consensus have been reported and discussed in this paper.

2. Material and methods

The Delphi Appropriateness method was used for this Consensus (Loblaw et al., 2012).

The panel, a group of 37 multidisciplinary experts (ROs, MOs, OCPs, Rs, Ns), met in Milan on February 17–18, 2013 and appointed a facilitator board of 12 expert members, from different clinical settings (6 ROs, 4 OCPs, 2 MOs). The facilitator board performed a systematic review of the literature on xerostomia and trismus in Radio/Chemo-treated (RCT) HNCPs.

The MEDLINE database was searched for English-language studies published from 1992 to March 2013 containing the key words: head and neck; xerostomia; hyposalivation; dry mouth; trismus; CT; and RT.

Potentially relevant abstracts presented at annual meetings of the American Society of Clinical Oncology and the European Society of Medical Oncology were examined. The study selection included the following:

(a) Observational and prospective studies about assessment and treatment; (b) randomized, double-blind, placebo-controlled, or uncontrolled studies; (c) retrospective and uncontrolled studies; (d) systematic reviews and meta analyses; and (e) consensus guidelines. Furthermore, the electronic search results were supplemented by manual examination of reference lists from selected articles and were periodically updated to April 2014 (before the second meeting).

On the basis of this literature review, the facilitators identified a number of key statements.

All the experts rated these statements through a two-round process. A scale of 4 steps was used, where 1 was defined as "high consensus", 2 was defined as "low consensus", 3 was defined as "no consensus", and 4 was chosen by panellists when they felt "unable to express an opinion".

A web meeting was held before the second rating: the statements that received a weak approval (<75%) were redefined according to the observations of panellists. The second web meeting was held in order to formulate the statements that had reached consensus after the second-round rating.

Each expert (including facilitators) was equally weighted in scoring the statements.

External experts OCPs (JBV, ABa), MOs (BM, AB), and ROs (EGR,SMM) reviewed the statements.

The panellists had a second meeting in Milan on May 5, 2014 in order to approve the final version of the statements.

3. Results

Consensus-reached statements are listed in Table 1.

4. Discussion

4.1. Statements about xerostomia

4.1.1. Xerostomia general statement

Xerostomia or dry mouth is defined by the Common Toxicity Criteria of Adverse Events (CTCAEs) as a disorder characterized by reduced salivary flow in the oral cavity. In RT ± CT-treated HNCPs, xerostomia is due to both a decreased salivary output and a change in the salivary composition, resulting in the sense of a dry mouth and sticky saliva. Xerostomia exposes HNCPs to a higher incidence of caries.

4.1.1.1. Xerostomia is thought to be the most prominent complication after RT for HNCPs. Radio-induced damage to the salivary glands changes the volume, consistency, and pH of secreted saliva from thin secretions with a neutral pH to thick and tenacious secretions with a diminished buffer capacity, and a lowered salivary pH. Indeed, in the presence of food containing fermentable carbohydrates, the plaque pH decreases and the lack of clearance, due to decreased salivary flow, inhibits the return of the plaque pH to normal levels (Brown et al., 1975; Valdez et al., 1993; Eisbruch et al., 1999; Roesink et al., 2001; Vissink et al., 2003b). Consequently, the prolonged low pH environment impairs the balance between demineralisation and remineralisation leading to greater demineralization, which results in increased dental caries.

In addition, the acidic plaque pH provides optimal conditions for the shift of the oral flora to a cariogenic flora (Brown et al., 1975; Kielbassa et al., 2006).

HNCPs have oral discomfort or pain, difficulty in speaking, chewing, or swallowing (Vissink et al., 2003b), and polydipsia, which in turn leads to nocturia. The absence of the washing effect due to a reduced saliva flow may foster salivary-gland retrograde infections, which in turn cause a painful swelling of the glands themselves and risk of sepsis (Mirabile et al., 2015).

Ultimately, these problems can lead to decreased nutritional intake and weight loss. Radiation-induced xerostomia not only substantially reduces the patients' HRQoL (Pow et al., 2006; Harrison et al., 1997; Ramaekers et al., 2011; Hunter et al., 2013).

4.1.2. Xerostomia-assessment scales

Salivary dysfunction can be evaluated in different ways, using different clinical endpoints, including: (1) objective analytical endpoints (e.g. stimulated salivary flow) (Navazesh and Christensen, 1982; Jones et al., 1996; Van Acker et al., 2001; Buus et al., 2006); (2) Operator-rated outcomes (OROs) graded according to toxicity classification systems (e.g. the CTCAEs, LENT-Soma) (Vissink et al., 2003a; Bhide et al., 2012b; Braam et al., 2005); and (3) patient-rated outcomes (PROs) determined using questionnaires (Pow et al., 2006; Bjordal et al., 1994; Eisbruch et al., 2001, 2003; Meirovitz et al., 2006; Jensen et al., 2007b).

An ORO-grading scale is recommended in clinical practice (e.g. NCI-CTCAE), whereas a PRO-grading scale (e.g. EORTC QLQ) needs to be added in clinical trials (Tables 2–4).

4.1.3. Pretreatment

4.1.3.1. Radio-therapeutic precautions (dose distributions in the salivary glands and parotid-sparing IMRT). The probability of xerostomia depends on the dose distributions in the salivary glands and, therefore, precise delineation of these anatomic structures at the planning-CT scan is a prerequisite for treatment planning optimization (Eisbruch et al., 2001; Hazuka et al., 1993; Nishioka et al., 1997; Wu et al., 2000; Henson et al., 2001; Pacholke et al., 2005; Saarilahti et al., 2005; Chambers et al., 2007a). Delineation and incorporation of all salivary structures into the radiation treatment plan also appears useful to document the dose-volume parameters of each individual structure and to obtain the sparing of salivary structures (Dijkema et al., 2008; Clark et al., 2009; Deasy et al., 2010). The fraction of salivary tissue exposed to higher doses should be minimized if possible given the disease extension. Whereas delineation of the major salivary glands, including the parotid and submandibular glands, may appear relatively straightforward, very few studies have investigated the relationship between delineation and dose distributions in the minor salivary glands in regard to radiation-induced xerostomia. Therefore, the contribution of minor salivary gland damage to the development of patient-rated xerostomia has not been fully investigated (Eisbruch et al., 1999; Bhide et al., 2012b; Braam et al., 2005). Unfortunately, at the present time, even in this new-technology era, only part of the radiation injury to salivary glands can be avoided (Bhide et al., 2010; Logemann, 1997; Ward and Van As-Brooks, 2007).

Between 21 Jan 2003, and 7 Dec 2007, Nutting et al. (Nutting et al., 2011; Clark et al., 2009) undertook a randomised controlled trial that compared conventional RT (control) with parotid-sparing IMRT. The Authors found a significant reduction of radiation-induced xerostomia for patients treated with IMRT evaluated according to both the LENT SOMA and RTOG scales. Furthermore, they found a recovery of saliva flow using quantitative measurements, and a HRQoL improvement among xerostomia sufferers (by use of QLQC30 Global and HN35 dry mouth HRQoL). Their trial was the first to show that parotid-sparing IMRT reduces xerostomia in HNCPs (Van der Molen et al., 2013; Nutting et al., 2011; Van der Laan et al., 2012a, 2012b; Roe et al., 2010). Furthermore, Van de Water et al. (2009), Harrison et al. (1997), Bhide et al. (2012b) and Kam et al. (2007) showed that delineation guidelines for contouring in HNCPs may help improve uniformity among RO contourers.

4.1.4. During treatment

4.1.4.1. Amifostine. Amifostine has not gained large diffusion as a radiation protector to be given during RT to reduce the risk of xerostomia (Antonadou et al., 2002). Amifostine has been reported by HNCPs as improving their symptoms linked to xerostomia during and after radiation treatment, but the reduction of radiation-induced toxicities by amifostine should be weighed against the toxicities of this drug itself according to the individual treatment strategy (Gu et al., 2014). Thus, the panellists suggest caution in its use and it is not routinely recommended due to its side effects (e.g. nausea, emesis, transient hypotension and allergic reaction) (Antonadou et al., 2002; Büntzel et al., 1998; Bourhis et al., 2000; Brizel et al., 2000; Braaksma et al., 2005; Buentzel et al.,

Table 1
Consensus-reached statements.

Clusters	Phase	Description	Whom is it in charge of?
	Definition	CTCAE definition: Xerostomia or dry mouth. A disorder characterized by reduced salivary flow in the oral cavity.	
1.	General statement	Xerostomia is defined as the decrease in salivary output (hypo-salivation) and a change in salivary composition, resulting in the sense of a dry mouth and sticky saliva. Xerostomia has a significant AE on health-related quality of life.	• Clinical oncologist • Nurse
2.	Assessment scale	A Operator-rated outcome (ORO) grading scale is recommended in the clinical practice (e.g. NCI- CTCAE), whereas a PRO-grading scale (e.g. EORTC QLQ) needs to be added in the clinical trial.	• Clinical oncologist • Nurse
3.	Pre-treatment	Radiotherapic precautions (Dose distributions in the salivary glands and Parotid-sparing IMRT): • Delineation and incorporation of major salivary glands (i.e. the parotid and submandibular glands) into the radiation treatment is recommended, whereas dose-volume parameters to the minor salivary glands might be useful to be documented. • It is recommended adopting a parotid-sparing plan and minimizing the dose fraction to salivary tissue exposed to higher doses, but this should not jeopardize the coverage of the PTV with the prescribed dose.	• Clinical oncologist • Dentist
4.	During Treatment	Oral examination: (see also mucositis) • Patients may wish not to wear uncomfortable dentures during mucositis. • Sharp teeth or restorations should be appropriately fixed when they are uncomfortable during mucositis.	• Clinical oncologist • Dentist • Nurse • Patient
5.		No-recommended practices • At the moment Amifostine is not recommended in patients receiving radiotherapy +/− chemotherapy for head and neck cancer, because of its side effects and high costs	• Clinical oncologist
6.	After Treatment/ Follow up	Once chronic hypo-salivation occurs, treatment essentially relies upon: – stimulation of the residual secretory capacity of the salivary glands (Pilocarpine or Cevimeline), and gustatory stimuli such as acid substance and chewing gum). – saliva substitute solutions might be useful when the result of stimulation of the residual salivary flow is insufficient.	• Clinical oncologist • Nurse
	Definition	CTCAE definition: A disorder characterized by lack of ability to open the mouth fully due to a decrease in the range of motion of the muscles of mastication.	
7.	General statement	• Trismus, restricted mouth opening, may be caused by surgery or RT involving the masticatory space and TMJ.	• Clinical oncologist • Nurse
8.	Pre treatment	• Physiotherapy exercises appear to be useful in trismus management and should be recommended before, during, and after RT. Commercially available mechanical devices may be useful.	• Deglutologist (SLP)
9.	During Treatment	Radiotherapic precautions: It is desirable to reduce the dose to the masticatory muscles and temporomandibular joint to reduce the incidence of trismus, but this should not jeopardize the coverage of the PTV with the prescribed dose.	• Clinical oncologist
10.	Follow up	• Physiotherapy exercises (see pre-treatment) • Pentoxifylline appears to exert a modest therapeutic effect in patients with radiation-induced trismus.	• Clinical oncologist • Deglutologist (SLP) • Nurse

Table 2
Acute and Late radiation Bone morbidity and salivary gland toxicity according to the Radiation Therapy Oncology Group scoring criteria (RTOG) (Cox et al., 1995).

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Dry mouth	Slight dryness of mouth; good response on stimulation	Moderate dryness of mouth; poor response on stimulation	Complete dryness of mouth; no response on stimulation	Fibrosis	Death directly related to radiation late effects

2006; Jellema et al., 2006; Veerasarn et al., 2006) and its high cost (Braaksma et al., 2005).

4.1.4.2. Oral cavity and dental care. Oral hygiene is necessary. Daily fluoride rinses or combinations with chlorhexidine are effective in preventing caries after RT (Hancock et al., 2003; Papas et al., 2008; Curi and Dib, 1997; Harris, 1992; Rankin et al., 2009). Indeed, chlorhexidine improves oral hygiene, but its potential side effects of tooth staining, increased salivary calculi, and taste changes should

Table 3
Late radiation Mandible and Salivary gland morbidity according to the Late Effects of Normal Tissue/Somatic Objective (Lent Soma scales for all anatomic sites, 1995) Management Analytic scale[a] (SOMA scale).

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 pretreatment	51–75% of pre-treatment	26–50% of pre-treatment	0–25% of pre-treatment

[a] *Instruction*: Score the 9 SOM parameters with 1–4 (score 0 if there are no toxicities); total the score and divide by 9.

be considered (Hancock et al., 2003; Papas et al., 2008; Hong et al., 2010; Eliyas et al., 1996) when it is prescribed.

Additional use of remineralising solutions and dentifrices also seem to be beneficial (Papas et al., 2008), but availability may present a problem. Studies have shown that casein products increase the incorporation of fluoride into plaque and promote enamel remineralisation in situ (Reynolds et al., 2008).

Furthermore, dentures or obturators could become uncomfortable during mucositis, and HNCPs may wish not to wear dentures during this time.

Sharp teeth or restorations can become particularly uncomfortable during mucositis, therefore they should be appropriately adjusted.

4.1.5. After treatment/follow up

4.1.5.1. Chronic hypo-salivation. Once chronic hypo-salivation occurs, treatment essentially relies upon the stimulation of the residual secretory capacity of the salivary glands with drugs such as Pilocarpine or Cevimeline and/or gustatory stimuli. Yet, residual functional salivary gland parenchyma is needed in order for any sialogogue to be effective (Elad et al., 2014).

Pilocarpine is a cholinergic stimulant that acts on postganglionic cells that innervate smooth muscles and exocrine glands (e.g., the sweat and salivary glands). Best results were obtained with continuous treatment for 8–12 weeks (2.5 mg/three-times-per-day dosage).

Cevimeline, a more recent cholinergic stimulant, has fewer side effects (Petrone et al., 2002; Chambers et al., 2007b), because it selectively acts on salivary-gland M3-muscarinic receptors, but not on the lung/heart M2/M4-muscarinic ones (Nieuw Amerongen and Veerman, 2003).

Finally, gustatory stimuli with an acid tasting substance and tactile stimuli (e.g. chewing gum) may increase salivary secretion (Olsson et al., 1991; Dirix et al., 2006).

If the result of the residual salivary-flow stimulation is insufficient, saliva substitute solutions (mouthwashes, gels or sprays) (Dirix et al., 2006; Momm et al., 2005) might be useful.

4.2. Statements about trismus

4.2.1. Trismus general statements

4.2.1.1. Definition. CTCAE defines trismus as a disorder characterized by lack of ability to open the mouth fully due to a decrease in the range of motion of the mastication muscles (National Cancer Institute, 2009). Trismus can cause persisting problems with pain, chewing and eating, dry mouth, and lack of taste, all of which result in impaired HRQoL (Dijkstra et al., 2004; Lambade et al., 2013; Pauli et al., 2013). Trismus may be caused by surgery or RT involving the masseter and pterygoid muscles, and the temporal mandibular joints (Teguh et al., 2008; Johnson et al., 2010; Van der Molen et al., 2011, 2013; Dijkstra et al., 2004). Furthermore, perioral fibrosis may also limit mouth opening.

To date, there are few prospective studies regarding the incidence of trismus and patients' experience of trismus in their normal day-to-day activities. The percentages of trismus in HNCPs reported in literature vary from 6 to 86% and one of the reasons for this wide range is the lack of uniform criteria for its diagnosis (Dijkstra et al., 2004; Louise Kent et al., 2008). A recent systematic review (Bensadoun et al., 2010) revealed a weighted prevalence for trismus of 25.4% for conventional RT and 5% for IMRT.

4.2.2. During treatment

4.2.2.1. Radio-therapeutic precautions. Only a few studies have investigated the relationship between radiation doses and mouth opening/trismus. Some Authors (Teguh et al., 2008; Levendag et al., 2007; Goldstein et al., 1999; Herb et al., 2006) found a significant correlation between the measured and the perceived mouth opening and the radiation doses to AMRSs in their studies: dosage levels >70 Gy are more likely to cause it. However, the mean dose to the masseter muscle seems to be the strongest/most important predictive factor: the larger the volume exposed to higher doses,

Table 4
Dry-mouth toxicity according to the National Cancer Institute Common Toxicity Criteria (NCI-CTCAe) (National Cancer Institute, 2009).

GRADE	Grade 1	Grade 2	Grade 3	Grade 4
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	–

the higher the probability of functional damage. However, no clear thresholds have been reported in literature (Johnson et al., 2010; Dijkstra et al., 2006; Lee et al., 2012).

It is therefore desirable to reduce the dose to the masticatory muscles and temporomandibular joints to reduce the incidence of trismus as low as possible without risking a “geographic tumour miss”.

4.2.2.2. Physiotherapeutic exercises. Mandibular stretching exercises are particularly useful in the prevention of trismus because such manoeuvres are far less effective in treating trismus once onset has occurred (Van der Molen et al., 2013; Bensadoun et al., 2010).

4.2.3. After treatment/follow up

Physiotherapy exercises appear to be useful in trismus management: exercises using a Therabite® device (or other commercially available mechanical devices) or tongblades significantly increase mouth opening in the short term (Dijkstra et al., 2004; Bensadoun et al., 2010).

Pentoxifylline appears to exert only a modest therapeutic effect in HNCPs with radiation-induced trismus, consequently it is not advised (Dijkstra et al., 2004).

5. Conclusions

Xerostomia, and trismus are important RT complications that raise the risk of dental caries and osteo-radionecroses. Consequently, these AEs may affect the prognosis, leave patients physically and emotionally disabled and sometimes cause the death of potentially curable patients as a consequence of compromised clinical conditions (Clark et al., 2009; Logemann, 1997; Murthy et al., 2009).

Guidelines for prevention/treatment of these complications might be useful, particularly in the context of a multidisciplinary cancer care. Therefore, accurate reporting of stomatological complications of HNCP treatments is also strongly needed.

Conflict of interest

The Authors have no financial and personal relationships with other people or organisations that could inappropriately influence (bias) this work.

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