Treatment of late sequelae after radiotherapy for head and neck cancer

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Abstract

Radiotherapy (RT) is used to treat approximately 80% of patients with cancer of the head and neck. Despite enormous advances in RT planning and delivery, a significant number of patients will experience radiation-associated toxicities, especially those treated with concurrent systemic agents. Many effective management options are available for acute RT-associated toxicities, but treatment options are much more limited and of variable benefit among patients who develop late sequelae after RT. The adverse impact of developing late tissue damage in irradiated patients may range from bothersome symptoms that negatively affect their quality of life to severe life-threatening complications. In the region of the head and neck, among the most problematic late effects are impaired function of the salivary glands and swallowing apparatus. Other tissues and structures in the region may be at risk, depending mainly on the location of the irradiated tumor relative to the mandible and hearing apparatus. Here, we review the available evidence on the use of different therapeutic strategies to alleviate common late sequelae of RT in head and neck cancer

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patients, with a focus on the critical assessment of the treatment options for xerostomia, dysphagia, mandibular osteoradionecrosis, trismus, and hearing loss.

Introduction

Radiotherapy (RT) plays a pivotal role in the treatment of patients with head and neck cancer (HNC). Approximately 80% (range 73.9 – 84.4%) of all HNC patients will receive RT at least once during the course of their disease [1].

The main principle of action of RT is to restrict the reproductive potential of tumor cells to induce cell death through apoptosis, necrosis, mitotic catastrophe, senescence, and autophagy [2]. Not only tumor cells are irradiated during an RT course. Some degree of damage is inflicted on normal cells adjacent to the tumor and associated target volumes. The clinical manifestation of resultant damage depends on the radiation sensitivity and cellular organization of the irradiated tissues as well as on the distribution pattern, temporal and geographical, of the radiation dose accumulated in these tissues [3].

Acute side effects that develop during RT can negatively impact its execution but usually resolve within weeks or months after the completion of RT. Late complications of radiation arise, by conventional definition, 3 months or more after the completion of RT. Many late effects progress over time and can, in the long run, adversely impact the quality of patients' lives [4–6]. Relative recovery or progression of late effects may vary depending on the nature of the problem. For instance, feeding tube dependence may decrease in initial years of survivorship with adequate follow-up [7–9]. The relationship between the duration and severity of acute side and late effects is also well established. The classic concept of consequential late side effects persisting as adverse outcomes of severe acute side effects not completely repaired has also been supported in the literature, particularly in the area of acute mucositis in relationship to late dysphagia [10,11].

The volume of normal tissues irradiated is determined by the size of the target and RT technique [12]. Modern RT technology allows the effective implementation of several radiation beams, precisely collimated with simultaneous modulation of their intensity, which results in the formation of a high-dose volume that can conform to the three-dimensional shape of the target. Improved conformity and relatively steep dose gradients created on the margin of a high-dose region offers better protection of normal tissues that do not overlap target volumes from higher radiation doses. At the same time, a larger amount of body tissues is irradiated to a lower dose when intensity modulated radiotherapy (IMRT), stereotactic radiosurgery, or other modern RT techniques are used [13]. Similarly, many functionally critical structures, such as pharyngeal constrictors and laryngeal framework, are near target volumes such that complete avoidance of toxicity is not always possible even with advanced, highly conformal RT delivery methods.

No technology can entirely protect normal tissues from irradiation and patients will always experience some degree of radiation-associated toxicity. In the head and neck region, perhaps the most prevalent and challenging adverse late effects of RT are connected with the impaired functioning of the salivary glands and swallowing apparatus [14]. However, other tissues and structures in the region can also be at risk, depending mainly on the location of the tumor, e.g. the mandible and hearing apparatus. In the context of modern treatment scenarios, in many patients the damage caused by radiation is further aggravated by concurrent systemic cytotoxic agents [15].

The most effective way to limit RT-induced toxicity is to decrease the exposure of functionally critical normal tissues adjacent to the target from excessively high radiation doses that are above the tolerance threshold levels of organs at risk (OAR). Because this is not always possible, either due to limitations of available technology or to the proximity of the target to important normal structure(s), strategies were developed to counteract the existing damage caused by RT. The objective of the present review is to evaluate the available methods used to alleviate the most common late sequelae of RT in HNC patients, i.e. xerostomia, dysphagia, mandibular osteoradionecrosis (ORN), trismus, and hearing loss.

Xerostomia

Xerostomia is the subjective sensation of a dry mouth characterized by a marked decrease and/or thickening of the saliva. It results from salivary gland hypofunction (reduced volume of saliva secretion) or a change in salivary composition and is usually associated with problems with swallowing and speech, and oral health. RTOG grade 3/4 xerostomia is statistically related to excess burden in emotional functioning, fatigue, social functioning and sleeping domains on quality of life (QOL) scales, indicating the multidimensional nature of xerostomia [6,16]. Xerostomia scores may worsen even 5 years or more post-RT [17].

Stimulated saliva production depends on the major salivary glands. During sleep, the main source of saliva is the submandibular glands, although the contribution of minor salivary glands is not negligible. The content and production of saliva by different salivary glands display circadian variations affecting different aspects of symptoms related to salivary dysfunction [18,19]. Objective presentation of salivary gland hypofunction does not necessarily reflect a subjective perception of xerostomia [20].

RT is a well-known cause of xerostomia although other factors, i.e. gender, age, smoking, alcohol-containing mouthwashes, concurrent platinum-based chemotherapy, and some medications, also play a role [21]. Among different salivary glands in the head and neck region, minor palatal glands have both greater resistance and recovery when compared with the serous secreting parotid glands [22].

The reported incidence of moderate to severe late xerostomia in studies implementing two-dimensional RT planning was 60–75% and was around 40% in more recent series employing modern RT techniques, such as IMRT [6,23,24]. In the randomized study of Kam et al. [25], comparing 2-dimensional RT and IMRT in nasopharyngeal cancer patients, better saliva and observer-reported xerostomia was found in the IMRT group with no difference in patient-

reported xerostomia between the two groups. In another randomized controlled trial (PARSPORT), HNC patients were randomly assigned to receive either three-dimensional conformal radiotherapy (3D-CRT) without parotid sparing or IMRT [24]. Grade 4 salivary flow dysfunction decreased from 100% to approximately 50% with IMRT in the PARSPORT trial, while significant reduction were observed for both physician-rated as patient-reported xerostomia in the first 2 years after completion of treatment. The reason for this failure of parotid-sparing IMRT is the need to spare not only the serous parotid glands but also the mucinous submandibular and minor salivary glands in the oral cavity [26]. Thus, despite significant improvements in RT planning and delivery introduced during the last number of decades, the need for effective alleviation of dry mouth syndrome is still present in a substantial proportion of HNC patients.

Pilocarpine

Pilocarpine is a nonselective cholinergic parasympathomimetic agonist which exerts its action by stimulating muscarinic receptors on the surfaces of the salivary gland cells. Thus, parts of the gland with preserved function are compulsory for a positive pilocarpine effect and, from this viewpoint, the pattern of dose distribution is important. It has been shown that stem cells and progenitor cells reside in the region of the parotid gland containing the major ducts and that prophylactic pilocarpine treatment enhances the proliferation of undamaged acinar, and progenitor cells in a rat model [27,28].

Pilocarpine was extensively studied concurrently with RT and its protective effect has recently been confirmed by meta-analysis of 8 randomized phase III studies, though only on unstimulated salivary flow [29]. In post-RT patients who have already developed xerostomia, the use of pilocarpine can also be recommended for the improvement of xerostomia [30] (Table 1). According to the results of two randomized placebo-controlled trials, approximately 50% of treated patients will benefit from reactive use of oral pilocarpine; yet, in placebo groups the response rates were in the range of 25% [31,32]. Symptoms of post-irradiation xerostomia exhibited a time dependent manner of improvement with the best response observed at the end of the treatment period, probably due to changes in the oral mucosa as pilocarpine increased the amount of saliva production. Pilocarpine treatment was found to increase stimulated and unstimulated whole salivary flow rates and those from the parotid glands and the palatal glands [22,31,32]. However, the increase in the salivary flow varied through the treatment period and did not necessarily correlate with the subjective improvement. The latter was observed even after a small increase in the amount of saliva secretion.

The main problems related to pilocarpine treatment are the fact that the beneficial effect of the drug expires soon after termination of drug administration, and the adverse reactions due to cholinergic stimulation, among others bronchospasm, bradycardia, vasodilatation and diarrhea. In the reported randomized studies, toxicity was common (in a great majority of the patients), usually described as mild but occasionally also of higher grades, and dominated by sweating, flu-like syndrome, and urinary symptoms which generally occurred within 60 min after dosing and were short lived. The adverse effects were the reason for premature withdrawal from the studies in 9–16.9% of the patients [31–33], and were found

to be clearly dose-dependent as 5.5% of the patients in the 5-mg group and 29% in the 10-mg group had to stop treatment due to toxicity [31]. Continuous pilocarpine treatment for more than 8 weeks with doses around 5 mg three times a day resulted in the best efficacy/toxicity ratio, with some patients experiencing additional benefit at doses up to 10 mg t.i.d [32,33]. However, due to the irreversible character of the salivary glands' impairment by irradiation the life-long administration of the drug is required which can be a problem or even contraindicated in some patients with certain pulmonary, cardiovascular or eye diseases, despite the generally low toxicity profile of the drug. According to the results of a maintenance study reported by Jacobs and van der Pas [34], during 36 months of 5 mg t.i.d pilocarpine treatment, 18.1% of 265 included patients discontinued use of the drug due to an adverse experience but, on the other hand, lack of efficacy was the reason in only 12.8% of cases and the initial drug dose was safely escalated above 5 mg in 48.3% of the patients. There was a significant improvement in all the evaluated criteria of oral function and no evidence of a decrease in therapeutic effect was observed over time.

To alleviate the systemic toxicity of pilocarpine and to maximize the local response other forms of the drug were tested, i.e. a topical administration of pilocarpine suspended in candy-like pastilles [35], a lozenge [36], or a mouthwash [37,38]. As these studies were small, further investigations are warranted to confirm some of the promising results observed.

Cevimeline is another cholinergic agonist with a high affinity for muscarinic M3 receptors which has also been tested in a post-irradiation setting. It was found to be effective in a dose of 30–45 mg t.i.d. administered orally for 12 or 52 weeks with a documented increase in unstimulated salivary flow rate, improvement of oral dryness, and mild-to-moderate though frequent side effects [39,40]. In 17.6% of the patients cevimeline-related toxicity was the reason for abandoning the study medication. Recently, cevimeline was compared with oral pilocarpine in a small randomized, cross-over, double blind study, showing a slightly higher, though non-significant, incremental increase in saliva production at the end of four weeks with pilocarpine [41].

Acupuncture

The stimulation of salivary gland secretion with acupuncture and the alleviation of xerostomia can only be seen when a portion of the salivary gland remains functional. Little is known about acupuncture's mechanisms that could explain its therapeutic qualities [42]. Regeneration of salivary gland tissue after electrical stimulation of the parasympathetic nerve to the parotid and submandibular glands has been demonstrated in an animal study [43]. True acupuncture was found to be associated with neuronal activations which were absent during sham acupuncture stimulation [44]. Acupuncture was found to be effective also in pilocarpine-resistant patients [45] and as a preventive measure [46]. Recently, an attempt to standardize the procedure in patients with radiation-induced xerostomia was reported [47].

Acupuncture and acupuncture-like transcutaneous electrical nerve stimulation (ALTENS) were evaluated in 5 clinical randomized trials with modest to high degrees of clinical benefit observed in all trials (Table 2, [48–52]). An increase in whole saliva secretion, and

subjective alleviation of related symptoms, was observed for at least 6 months after intervention [53] and up to 3 years with additional acupuncture therapy [54]. The favorable toxicity profile of acupuncture and ALTENS was associated with good treatment tolerance in all reported studies which is of paramount importance when considering a maintenance strategy.

In two prospective randomized, controlled trials classical (real) acupuncture was compared with superficial (placebo/sham) acupuncture [48,49] and in two other randomized trials with usual oral care [50] or group oral care education (ARIX trial, [51]). Although the sample sizes were small (12–58 patients), with one exception (145 patients; [51]), subjective benefits were recorded from acupuncture in all of these trials using different measurement tools. However, no objective gain from the intervention was observed as the flow rates, though increased over time by acupuncture, also improved in the control groups, which resulted in non-significant differences between the experimental and control groups [48–50]. Positive outcomes observed in the control groups may be due to the stimulation of skin receptors by the superficial needle insertion as a placebo, which also enhance the functional recovery of the salivary glands, though to a lesser degree (sham acupuncture); a therapist-patient relationship (i.e. the Hawthorne effect); or the patient's expectation of benefit from the intervention. Only the ARIX trial controlled for these effects by a randomized crossover design, giving both interventions (acupuncture and oral care educational sessions) in both arms; yet, acupuncture resulted in improved xerostomia-related QOL compared to educational sessions [51].

In a recently reported RTOG 0537 phase III randomized study, ALTENS was compared with standard pilocarpine treatment (5 mg t.i.d. for 12 weeks); there was no difference in radiation-induced xerostomia symptom burden at 6 months after treatment between the two arms [52]. However, there was a consistent trend towards greater improvement in the xerostomia quality of life scale (XeQOLS) scores at all follow-up time points, a higher percentage of positive responders (defined as 20% improvement from the baseline XeQOLS scores; at 12 months' post-therapy, 83% vs. 63%, p=0.04), and significantly less non-hematological toxicity (CTCAE v3.0 grade 3, 20.8% vs. 61.6%) in patients receiving ALTENS. Notably, the statistical power of the trial was limited due to the low proportion of evaluable patients (52 of 148, 35.1% of recruited patients failed to complete the planned assessments, particularly in the pilocarpine group).

Other strategies and emerging approaches

These include hyperbaric oxygen therapy (HBOT), gustatory/masticatory stimulation and the use of lubricants or saliva substitutes, whereas gene therapy and stem cell therapy are recent emerging approaches.

The assumption that *HBOT* may provide some relief to patients suffering from RT-induced xerostomia was based on its effectiveness in the treatment of bone ORN and soft tissue necrosis. Only a few studies analyzed the role of HBOT in post-RT xerostomia, with a limited number of patients included, and were extensively elaborated in a systematic review by Fox et al. [55]. In six studies, 227 patients were treated 2 years or more after RT; all but one study were prospective cohort trials and one was a randomized controlled trial, with an

average number of HBOT dives between 20 and 43, respectively. [56–62]. Increases in the stimulated salivary flow rates [60,61] and scores on the visual analog scale quantifying xerostomia severity [58,61], as well as an improvement in the salivary viscosity and the EORTC H&N35 scores for sensation of dry mouth [56,57,62] were demonstrated but not accompanied by an overall QOL improvement within a year of completion of HBOT [57,62]. Some studies suggested a long-term benefit of HBOT, up to 18 months after its completion. However, the low number of treated patients, only one study with a control group (i.e. not allowing a fair discrimination between the HBOT effect and the placebo effect), lack of appropriate details on RT reported, heterogeneous patient populations (regarding indications for HBOT as the majority was treated for other RT sequelae which could confound the results), and the possibility of publication bias (negative studies may have not been published) limit the strength of the conclusions. Also, no risk assessment was done for cancer recurrence [55].

The utilization of *gustatory or masticatory stimulants, lubricants and saliva substitutes* is a purely symptomatic measure. Nevertheless, it could be an esteemed provision in patients with insufficient residual secretion of saliva on stimulation. These agents cannot replace the antimicrobial and immunological properties of saliva. A wide variety of different acid-tasting substances, including sugar-free chewing gum, sweets, vegetables and fruits, and pharmacological sialologues have been tested in small cohort studies but also randomized controlled trials with different levels of success. In general, gustatory and masticatory stimulation by acidic substances showed some increase in whole saliva secretion and amelioration of oral dryness; oral lubricants and saliva substitutes usually exert a short-term effect over the placebo effect [63]. Constituents resembling the physical properties of glycoproteins and the antibacterial components of saliva are commercially available in the form of over-the-counter gels, mouthwashes, or sprays. Chemically, they are based on carboxymthylcellulose, mucin or xanthan gum, the latter two being characterized with superior rheological and wetting properties and, therefore, preferred by patients with xerostomia [64–67]. Recommendations for the use of oral lubricants and saliva substitutes to alleviate hyposalivation as proposed by Regelink et al. [68] are shown in table 3.

Gene therapy is based on a viral vector injection, conveying genetic information into a tissue to result in some beneficial change. It represents a promising new approach to the treatment of RT-induced xerostomia. Salivary gland tissue was found to be a good target for gene transfer due to stable, well-differentiated and slowly dividing epithelial cells, limited leakage of the vector, and direct access via duct orifices [69]. The most studied is the adenovirus transfer of the human aquaporin-1 gene (hAQP1), which encodes a water channel protein involved in the osmotic movement of water in radiation-surviving salivary duct epithelial cells in the damaged gland. The strategy proved to be safe and effective in a phase I/II clinical study in humans previously irradiated for HNC, showing an increase in the saliva flow rate and a reduction of xerostomia-related symptoms which can continue years after hAQP1 delivery [70,71]. Recently, a non-viral approach employing ultrasound-assisted AQP1 cDNAs transfer was successfully tested in an animal model, allowing multiple gene administrations to maintain elevated salivary flow as opposed to the viral vectors where only a single administration is possible [72]. The hedgehog pathway appeared to be another gene therapy target to overcome RT-induced hyposalivation. Its transient activation in mouse

salivary glands by overexpressing the Sonic hedgehog transgene or administering a smoothened agonist showed the potential to restore salivary function in pre-irradiated glands [73,74].

Like other organs, also in salivary glands, the *stem cells* play a central role in tissue homeostasis [75]. As precursors of progenitor cells, which have a lower self-renewal capacity and may be tissue-specific, they focus on extensive tissue regeneration and salivary bioengineering research at the cell culture level, and in animal models but not yet in humans. Stem/progenitor cells from the major and minor salivary glands have been successfully isolated, cultured and transferred to rat glands [76], though minor salivary glands, bone marrow and adipose tissue-derived mesenchymal stem cells have also been identified as a possible source for the repair of radiation-damaged tissue [77–79]. In addition, the self-duplication potential of already differentiated acinar cells, which also play a role in salivary gland homeostasis (i.e. the replacement of aging and injured cells), appears to be another option to counteract salivary gland dysfunction and xerostomia [75].

Current clinical standards

Despite substantial progress with various approaches tested in clinic to alleviate RT-induced xerostomia, there are no consensus standards for xerostomia management. No uniform treatment protocol can be recommended for wide clinical adoption, and still limited advice can be given to the patient who is complaining over a dry mouth. The empirical first step is to introduce symptomatic measures recommending gustatory and masticatory stimulants, lubricants and saliva substitutes. However, many patients may prefer frequent moistening of oral tissues with water rather than the use of saliva substitutes due to the short duration of relief they provide. A published recommendation is to test different saliva substitutes by individual patients to select the most effective one as her/his preference may also be of importance for the success of this treatment [67]. In patients without history of cardiovascular and eye diseases (glaucoma, inflammation or infection) or uncontrolled asthma, a course of pilocarpine 5 mg t.i.d can be tested with possible increase to 10 mg t.i.d in selected patients who do not experience adverse effects. The duration of pilocarpine therapy should be adjusted to the drug effectiveness and exerted side effects. If available, acupuncture is an option in those not amenable for or resistant to pilocarpine therapy.

Dysphagia

Difficulty in swallowing is a common consequence of RT for HNC. In a prospective cohort study of 238 HNC patients treated with 3-dimensional conformal RT (65%) or IMRT (35%) concurrent with chemotherapy (11%), the prevalence of grade 2–4 swallowing dysfunction according to the RTOG/EORTC Late Radiation Morbidity Scoring Criteria was 22% at 6 months, and 14% at 12 and 24 months [9]. Late dysphagia was recognized as one of the key adverse factors in QOL testing of HNC patients, with feeding-tube dependency having the most negative impact [80,81]. Similarly, clinician-graded dysphagia correlates strongly with QOL with larger effect sizes than xerostomia in long-term follow-up after curative RT [82]. Fortunately, permanent feeding tube dependency in disease-free patients, particularly those treated with RT alone, is rare [7,83]. However, even mild late dysphagia is a major correlate

of QOL [82]. Moreover, it is well recognized that absence of a feeding tube does not equate to a safe or efficient swallow. For instance, half of radiographically-detected chronic aspirators after larynx preserving RT are gastrostomy free, essentially electing to eat despite their dysphagia but with excess risk of pneumonia and related morbidity [84].

Dysphagia is a complex neuromuscular toxicity. More than 25 pairs of muscles, located from the oral cavity to the esophagus, are involved in swallowing. Swallowing requires extreme precision to coordinate the hemispheric cortical centers, the brainstem central pattern generator, associated cranial nerves, muscles, and sensory receptors [85]. Impairment in any segment of this complex process can result in an aberrant cough reflex and aspiration with consequent pneumonia and chronic bronchial inflammation as aspects of dysphagia alone or together with oropharyngeal inefficiency. Inefficient bolus clearance impacts risk of prolonged or even permanent feeding tube dependency, weight loss, nutritional deficiencies and life-threatening malnutrition [86].

Radiation-associated dysphagia (RAD) evolves in various ways as recently demonstrated with longitudinal cluster analysis of 238 consecutive patients with HNC followed serially with clinical assessment of dysphagia for 24 months [9]. Using clinician graded RTOG/EORTC dysphagia endpoint, roughly 16% of patients treated with definitive 3D-CRT or IMRT had substantial late burden of dysphagia attributable to one of two patterns: "severe persistent" [8%, grade 2 at 6 months that remained up to 2 years) or "progressive" [8%, grade <2 at 6 months, subsequently progressed to grade 2) dysphagia. Distinct patterns of RAD were felt to possibly signal different biologic processes underlying swallowing dysfunction in long-term survivors.

Mechanisms of late dysphagia after RT for HNC are poorly understood. Soft tissue fibrosis has long been considered the primary source of RAD, with associated restriction in the compliance and contractility of underlying musculature due to post-inflammatory scarring processes and lymphedema. Compounding the dysfunction caused by local RT damage, muscle atrophy (with associated weakness) may also result from disuse of the oropharyngeal musculature during RT when patients often stop eating normal foods and may require several months of tube feeding to sustain nourishment while acute RT toxicities are at their peak [87]. Sensory loss is quite poorly understood, yet is likely another underreported contributor to RAD, given that roughly half of chronic aspirators do so silently without the normal sensory response to clear the airway of foreign bolus entry [88–90].

Baseline function and early recovery of swallowing are critical clinical predictors of late effects. Pre-treatment swallowing dysfunction induced by the tumor-driven destruction of normal tissue is possible, particularly with locally advanced stage disease. Baseline dysfunction increases risk of chronic or persistent RAD [91]. Likewise, the prognostic relevance of acute radiation-induced symptoms for the development of late dysphagia underscores the etiologic role of inflammation [11]. Edema is currently under study in a prospective cohort as another acute sequela along the continuum to soft tissue fibrosis, suggesting the potential adjunctive role of lymphedema therapy strategies for dysphagia management [92]. The etiologic role of inflammation and edema may be more relevant for classic forms of persistent dysphagia as a consequential late effect of acute reactions. There

is emerging work to suggest a unique subtype of dysphagia in HNC survivors referred to as late- RAD [93,94] Late-RAD is defined by presentation with severe oropharyngeal dysphagia after a long interval of adequate functioning after acute effects of RT resolved. Early work suggests a median latency of 8 years to presentation of late-RAD with de novo lower cranial neuropathies preceding the deterioration in swallowing function in most cases. Thus, denervation appears to be a major source of the neuromuscular dysfunction in late-RAD rather than predominant edema and stricture as in more classic, earlier forms of RAD.

The degree of swallowing dysfunction depends on the distribution of the delivered RT dose. Thus, substantial efforts are underway to understand how best to optimize radiation planning to achieve better and more durable swallow preservation. Pharyngeal constrictors and the larynx were first identified by multiple investigators as primary dysphagia-aspiration-related organs (DARS) [95]. Beyond the classic DARS, emerging work suggests relevance of dose/ volume distributions to submental musculature (i.e., geniohyoid, mylohyoid) that are critical to elevate the hyolaryngeal complex and assist with cervical esophageal opening [96,97]. Reporting normal tissue complications probabilities as a function of DARS, Eisbruch et al. gave solid ground for efforts to reduce dysphagia in the IMRT era [95,98,99]. Work by Christianen et al. [100] further supports the dose constraints to classic DARS, finding mean dose to the superior pharyngeal constrictor muscle and supraglottic larynx as the most important predictive parameters for the occurrence of grade 2–4 RTOG/EORTC swallowing dysfunction at 6 months after completion of (chemo)RT. Interestingly, the importance of the latter (supraglottic dose) declined over time, while the effect of the dose to the superior constrictor remained stable, suggesting time dependence of these parameters [9,100]. In certain clinical situations, e.g. in patients with deep posterior wall pharyngeal primaries or in those with extensive base of tongue and supraglottic tumors, injury to the important swallowing structures with resulting high-grade dysphagia is unavoidable, diminishing the potentially positive effects of prophylactic measures for improving swallowing outcome in these subgroups of patients [101]. The risk of tube feeding dependence was found to depend on a variety of dose-volume histogram (DVH) parameters, including the superior and inferior pharyngeal constrictors and the contralateral parotid gland mean dose [102]. Recently, Christianen, et al. [103] showed that when the dose to the superior pharyngeal constrictor and supraglottic area was reduced by adding dose constraints to these structures, the risk of grade II–IV dysphagia could be reduced significantly as well.

Behavioral and exercise-based swallowing rehabilitation

The exercises, maneuvers and postures aimed at improving swallowing efficiency and safety include motor exercises (to increase the strength, mobility, and endurance of the swallowing structures); patterning and postural patterning and techniques (to minimize aspiration/ maximize swallowing efficiency with changes in body position or motor patterns of swallowing); and sensory techniques (to increase sensory response by stimulation, employing alterations in temperature, taste, pressure, or bolus – its consistency, placement, or size) [104]. Neuromuscular electrical stimulation coupling surface electrodes placed overlying neck or submental muscles during exercise and respiratory-swallowing training using visual feedback for the optimization of respiratory/swallowing patterning also belong

to this group of behavioral interventions, often directed by speech pathologists for patients in North America [105,106].

Precious few studies have examined rehabilitation interventions introduced after HNC (chemo)RT (with or without surgery) to alleviate dysphagia [104–117]. In six randomized studies, two different swallowing strategies were compared rather than to the non-interventional control group [111–117]. While there is single-institution evidence supporting modest effect achieved after non-preventive behavioral or exercise based swallowing interventions after (chemo)RT, they are of limited quality [118]. Major and recurrent limitations include the small sample size and methodological issues, including a lack of standardization in the evaluation methods and the absence of a core set of dysphagia parameters for reporting, and almost universal short-term follow-up of patients. These issues are summarized in a recent inconclusive Cochrane review on the topic [119].

On the contrary, a recently published double–blinded, randomized controlled trial comparing a combination of neuromuscular electrical stimulation and swallowing exercises to exercise with sham stimulation in 170 post-RT dysphagia patients reported no benefit of electrical stimulation, and swallowing exercises alone (with sham stimulation) were found to have modest effect on diet and QOL and no improvement on radiographic measures of swallowing function [116,117]. The authors concluded that traditional swallowing exercises may not be effective in HNC patients with moderate-to severe chronic RAD, perhaps due to progressive fibrotic changes and entrapment of the swallowing apparatus induced by RT. Contrary to these disappointing objective results, the patients from the trial reported significantly better diet and QOL outcomes, as is often the case with conflicting patient-reported and physical measures. In RTOG 9003 study, the 1- and 5-year feeding tube rates in disease-free patients were 12.1% and 7.8%, reflecting that patients can adapt and force themselves to some extent to eat with impaired pharynx [7].

Novel, systematic efforts are under study to offer more for complex dysphagia. These include bolus-driven "boot camp" style therapies such as McNeil Dysphagia Therapy Program and biofeedback swallow pattern training [120–123]. These therapy models focus on standardized, clinician-directed training to adjust the swallow pattern during bolus swallows rather than focusing on strengthening exercise outside of mealtime. Small, single institution case series report functional gains (better diet or less frequent aspiration) but persistent physiologic dysphagia on videofluoroscopy that can be interpreted at helping compensation rather than reversing dysphagia [120–123]. These results, together with perceived non-uniformity in usual dysphagia therapy practices, call for the development and refinement of novel dysphagia interventions tailored to unique pathophysiology in HNC patients on one hand and to the development of evidence-based algorithms for personalized HNC dysphagia treatment guidelines [124–126].

Acupuncture

While acupuncture appears have some efficacy as a therapy for post-stroke dysphagia, its role in RAD is yet to be determined [127]. Although the etiology of dysphagia in stroke and HNC differ, the two share many aspects of the needling technique [128]. In the literature, 3 reports were published, 2 of them from China, that evaluated the efficacy of acupuncture in

HNC patients with dysphagia [129–131]. In the Dana-Faber Cancer Institute study, a subjective improvement of various degrees in patient-reported swallowing functions, xerostomia, pain, and fatigue levels was reported in 9 of 10 treated patients [131]. Of 7 PEG tube-dependent patients, 6 had their feeding tube removed after acupuncture. Building on these observations, a pilot randomized sham-controlled trial has been conducted, showing that both active acupuncture and sham acupuncture during and after head and neck RT are feasible and safe [128,132]. An improvement in the dysphagia-related QOL from the baseline to 12 months post-RT was observed in both treatment arms, though with no difference between the two.

Current clinical standards

Level 1 evidence is lacking as a basis for evidence-based management of late dysphagia. Late dysphagia is complex and a comprehensive assessment is the first step in personalized management. Assessment ideally should include imaging studies (videofluoroscopy and/or endoscopy) with consideration of rapidly emerging technologies like pharyngeal high resolution manometry to characterize pathophysiology and pattern of dysphagia. Modest effect sizes of current strategies may reflect low or static intensity of therapy programs where a patient practices the same tasks at the same intensity on their own rather than varying performance with progressive resistance or progressive complexity to enhance gains. Personalized, intensive therapies are likely ideal. Published work also suggests impetus to avoid pharyngeal disuse that likely hastens or exacerbates the problem [87]. Preventive efforts are paramount that should couple dose-optimization strategies with supportive care to help patients avoid pharyngeal disuse. Despite the uncertainty of the evidence, patients with dysphagia might still be encouraged to practice swallowing exercises as the inhibitory potential of such exercises on the progression of swallowing dysfunction cannot be ruled out. An additional justification for maintenance exercise regimens draws from the possible positive effect of the simple act of practicing swallowing over and above the meal time effort which could impact the patient's skill, ease and rate of eating [116,117]. Emerging methods such as acupuncture and manual therapies are much less integrated in routine practice, but hold promise in small clinical studies. Novel strategies and interdisciplinary trials are desperately needed to improve options for late dysphagia in HNC.

Mandible osteoradionecrosis

ORN is defined as a necrotic process in the bone that results from a high-dose RT and persists for 3 months or longer, worsens slowly and does not heal spontaneously [133]. In addition to dosimetric factors, poor dental health before RT, post-radiation extraction of teeth and trauma (by prosthesis, bone biopsy, salvage surgery) in bone regions exposed to a high RT dose, are the main risk factors for ORN development. Xerostomia and trismus are well recognized contributing factors, as they impair oral hygiene and promote caries [133,134]. ORN presents clinically as a painful and denuded bony region, with purulent drainage and sometimes progresses to fistula formation (to the mucosal or skin surface). On a panoramic radiograph, loss of trabecular architecture usually seen though the appearance of the affected bone may be normal. In a historical RT series, the incidence of ORN ranged from 2% to 22%: this wide range reflects not only the differences in RT techniques

employed but also ambiguity in definition and difficulties in the diagnosis of ORN [133,134]. In an extensive review of 31 studies published between 1990 and 2008 by Peterson et al. [135], the weighted prevalence for ORN in patients with different types of HNC treated with conventional RT was 7.4%, with IMRT 5.2%, with (chemo)RT 6.8%, and with brachytherapy 5.3%. Recently, De Felice et al. [136] reviewed 10 studies with over 3,000 patients included, employing exclusively IMRT: the ORN incidence rates ranged from 0% to 6.3% (median 1.4%). In a detailed analysis of 531 oral cavity, oropharyngeal and salivary gland cancer patients treated with IMRT and doses to the mandible 60 Gy, Studer et al. [137] reported the overall incidence of ORN as 7%; in oral cavity cancer patients with mandibular surgery the rate was 29% (when no mandibular surgery was done 7%) and when marginal or periostal bone was resected it was 39% (segmental resection or no resection, 7%). The importance of reduced mandibular volumes receiving high doses and improved salivary flow with associated improved oral health when IMRT was used, together with meticulous dental prophylactic care, was stressed by Ben-David et al. [138], who reported no case of ORN among 176 patients after IMRT.

Available therapeutic options in ORN are complementary to its complex pathophysiology and both currently accepted theories of ORN development. The Marx's "3Hs paradigm" or "hypovascular-hypoxic-hypocellular" theory, with persistent hypoxia as one of the main features of ORN, provides the grounds for the use of HBOT [139]. Later, Delanian and Lefaix [140] introduced the "fibroantropic" theory, proposing the activation and dysregulation of fibroblast activity and resulting fibrosis of tissue that is prone to traumatic breakdown as the main mechanism of ORN. Several drugs that counteract various aspects of the latter theory have been studied [140].

The range of possible intervention in patient with ORN starts from non-invasive measures with optimization of oral hygiene and antibiotic coverage, and escalates through sequestrectomy and debridement to major and more mutilating surgical procedures. Surgery employing resection of involved bone and free-flap reconstructions are indicated in advanced-stage ORN cases with fractures and/or fistulas [133,134]. According to a systematic review of the pertinent literature by Lee et al. [141], the fibula is the workhorse free flap for reconstruction in mandibular ORN, with the risk of flap failure and postoperative complications being significantly increased compared to reconstruction of the primary tumor in unirradiated patients. Thus, it seems appropriate to defer resection and reconstruction in patients whose symptoms can be managed without an operation. A conservative approach also gained confirmation in health-related QOL analyses where the scores were disappointingly poor after mandibular surgery [142,143].

Hyperbaric oxygen therapy

Inhalation of pure oxygen (100%) at pressures greater than 1 atmosphere absolute in an airtight chamber promotes healing by stimulating angiogenesis, epithelization, osteoblastic proliferation, collagen synthesis, and has antibacterial properties. In healthy tissues, it results in hyperoxic vasoconstriction which is followed by the redistribution of peripheral blood volume toward the hypoxic tissues (the Robin-Hood effect) [144]. Lung, brain, and ocular

(progression of cataract, transitory myopia) toxicities may occur due to hyperoxia and increased air pressure but are rarely observed when HBOT follows accepted protocols [144].

In 2010, Peterson et al. [135] reviewed seven studies employing HBOT, alone or with a varying degree of surgical management, for the treatment of ORN. ORN resolution rates in these studies varied from 19% to 93% showing no advantage of HBOT over surgery but rather a synergistic effect when both therapies were combined. This conclusion was recently confirmed in a series of 27 patients reported by Dieleman et al. [145] who observed a beneficial effect of HBOT alone in early-stage disease (improved/healed cases: stage I – 54%, stage II – 25%) but in stage III ORN cases healing was achieved only after a HBOT-surgery combination. In the latter group, HBOT seemed to be ineffective for bone healing but may have resulted in improvement of the surrounding soft tissues which positively affected the healing of the surgical wound. In addition, a better prospect for successful healing after tooth extraction (compared to antibiotic cover) and for complete mucosal cover of exposed bone in patients with ORN when using HBOT was confirmed in Cochrane's review, though the quality of evidence was only found to be moderate [146]. The only randomized trial was reported by Annane et al. [147] who compared HBOT with a placebo, with (more advanced cases) or without (less advanced cases) surgery. The trial was prematurely stopped after enrolling 68 patients with overt ORN due to a potentially worse outcome in the HBOT arm. This study was severely criticized due to several methodological and performance issues [146]. Wide variability in HBOT regimens used in the UK and Europe concerning the actual pressure, duration and number of dives was reported [148,149]. To overcome these shortcomings, the role of HBOT in the prevention and treatment of ORN is currently being investigated in three prospective multicenter randomized trials: the UK's HOPON trial, the Danish DAHNCA21 trial, and the Portuguese phase II trial on HBOT therapy with or without antifibrotic agents [150,151].

Medical management

The following agents that cause a blockade at specific points/levels in the fibroantropic model of ORN development were used in the management of ORN: pentoxifylline, tocopherol and clodronate. Pentoxifylline is a methylxanthine derivative with an *in vivo* established inhibitory effect on fibroblast proliferation and extracellular matrix production, as well as collagenase activity stimulation. Due to toxicity induced by the drug concentration needed for the effective suppression of collagen synthesis, the isolated administration of pentoxifylline is not indicated. Antioxidant tocopherol (vitamin E) is the free radial scavenger, acting as a protector of cell membranes against lipid peroxidation; its antifibrotic activity is based on downregulation of procollagen gene expression. Both agents exhibit anti-inflammatory actions by inhibiting TNF-α,TGF-β and other mediators. The third agent, clodronate, is a first-generation bisphosphonate that inhibits bone resorption by reducing osteoclast activity through direct activation of osteoblasts it increases bone synthesis and decreases proliferation of fibroblast [152].

Promising early results on the use of a pentoxifylline-tocopherol combination in a mixed patient population with symptomatic RT-induced fibrosis [153] resulted in the phase II trial in patients with refractory mandible ORN [154]. A total of 18 patients were treated with a

daily oral combination of 800 mg of pentoxifylline and 1000 IU of tocopherol for 6 to 24 months; the worst 8 cases also received clodronate 1600 mg/day, 5 days a week. Treatment was well tolerated and complete recovery was observed in a median time of 6 months. The favorable clinical outcome and the toxicity profile of the medical ORN treatment were duplicated by the same group in a larger prospective cohort of 54 HNC patients with refractory mandibular ORN, mainly after surgery and HBOT [155], and was confirmed by several other groups [152,156,157]. However, the true value of this strategy is yet to be confirmed in a randomized clinical trial setting [151].

Current clinical standards

Currently, there is no gold standard treatment of ORN and no widely accepted guidelines exist. It seems that maximal benefit is gained by combining several therapeutic strategies directed against different targets in the ORN pathophysiology chain, taking into consideration the stage of the condition and characteristic of the patient and her/his malignant disease. Whereas early-stage ORN in patients who are symptom-free or mildly symptomatic needs only conservative measures (a wait-and-see policy: optimal oral hygiene, antibiotics), any sign of progression requires early surgical intervention in the form of sequestrectomy and debridement with local mucosal flaps to cover bone defect. The role of HBOT and medical management, however, is yet to be defined with consensus guidelines and robust clinical trials.

Trismus

RT-associated trismus infers fibrotic changes with contracture in mastication structures, including the masseter and pterygoid muscles, damage to their neural innervation and temporomandibular joint degeneration [158]. These changes can result in a considerable reduction in mouth opening (with a maximum inter-incisor opening <35 mm, i.e. the distance usually used as the cutoff point) compared to pre-irradiation status with about two-thirds of the total reduction in mouth opening observed in the first 9 months after RT [159]. Then, the process becomes slower but may continue over later years. Dosimetric studies showed an increase in the probability of trismus of 24% per every additional 10 Gy delivered to the pterygoid muscles, with doses as low as 15 Gy resulting in functional impairment [160,161]. The prevalence of trismus primarily depends on tumor site and size, being the highest in patients with tumors close to the mastication apparatus, i.e. parotid lesions, nasopharyngeal and lateralized oropharyngeal or posterior oral cavity primaries [162–164]. The wide prevalence range reported in the literature reflects the differences in the studied populations and, consequently, the dose burden across the studies. With improved control over spatial radiation dose distribution, IMRT may lessen the problem with trismus, though not in cases with a target lesion sited in or next to structures important for mastication. In a systematic review of 22 studies, Bensadoun et al. [165] reported the weighted prevalence of trismus following RT of 25.4% for conventional RT, 5% for IMRT and 30.7% for a combination of RT (mainly conventional) and chemotherapy.

Trismus was recognized as the third most burdening side-effect of oncologic therapy [166]. It was found to be associated with poorer health-related QOL and a greater proportion of

HNC patients with trismus displayed depression compared to a control group without trismus [164,167]. Improper mastication mandates changes in food consistency and, in extreme cases, enteral tube feeding. Other negative consequences of trismus include difficulties maintaining oral hygiene with an associated increase in the risk of oral infections and dental problems, as well as impaired oral examination, dental care and intubation.

Conservative measures with HBOT and pentoxifylline did not show any convincing improvement of trismus [168,169]. The same was observed for injections of botulinum toxin into the mastication muscles, though they can effectively reduce local pain produced by muscle spasms associated with trismus [170]. Forced mouth opening under general anesthesia can improve trismus, but the effect is usually short-lived and the procedure is less controlled and at considerable risk of fracture and adjacent soft tissue rupture.

Exercise therapy employing different stretching techniques and devices is aimed at increasing the range of mouth opening by strengthening musculature, improving the mobility, flexibility, and elasticity of the temporomandibular joint and by improving blood circulation [158]. Recently, a systematic review by Kamstra et al. [171] identified 12 studies, ranging from chart reviews to randomized controlled trials that analyzed the effect of therapeutic measures on mouth opening after trismus occurred. The duration of the therapy in these studies ranged from 1 to 9 months, the number of exercise sessions per day varied from 2 to 10, with 3 to 8 repetitions, and the duration of stretch ranged from 6 seconds to 60 minutes. Meta-analysis was not possible due to significant heterogeneity in the clinical profile of the patients included, variety mechanical devices used (dynamic bite openers, a sledge hammer device, the TheraBite, Engstron Jaw mobilizing device, tongue depressors, rubber plugs, Dynasplint Trismus System), and inconsistent methodology. Collectively, the studies suggested some efficacy of therapeutic jaw mobility interventions. An increase in mouth opening was reported in the majority of studies, although, in many, the final mean mouth opening was still <35 mm suggesting that even after therapy, a proportion of patients still suffer from trismus. No exercise technique was found to be superior to others, and the results were influenced by compliance with the exercises and the time interval between oncologic treatment and the start of the exercises (the sooner, the better) [171]. A recently reported study using the Dynasplint Trismus System confirmed that early detection of trismus and the early start of exercise therapy ensure a better outcome of mouth opening [172].

Surgical treatment is an option for patients without known malignant disease with trismus refractory to physical therapy. Coronoidectomy proved effective, increasing inter-incisor distance at least 20 mm, in a series of 18 previously irradiated patients reported by Bhrany et al. [173]. Moreover, all maintained an inter-incisor distance equal to or greater than 35 mm for 6–12 months after the procedure. Similarly, Mardini et al. [174] used free flaps to reconstruct the defects created after surgical trismus release in 11 patients with previous intraoral reconstruction (8 patients had postoperative RT). The initial mean inter-incisor distance of 3.1 mm was increased to 33.4 mm immediately after the release and to 18.9 mm at a mean follow-up time of 22.7 months. The authors concluded that the procedure is a viable option in complex cases that yields a reasonable, long-lasting improvement in mouth opening, intraoral hygiene, and QOL.

Current clinical standard is exercise based therapy with the precise device and schedule still debated. Surgical management is reserved for extreme cases, and HBOT and pharmacological therapy have no strong evidence in published literature.

Hearing loss

Damage to the hearing apparatus with resultant sensorineural hearing loss (SNHL) is a common adverse event after RT [175–177], occurring in up to 43% of irradiated HNC patients. Its incidence is increased to 17–88% when RT is combined with cisplatin [178]. Traditionally, SNHL denotes a pure-tone audiometry confirmed, clinically significant increase in bone conduction threshold at the key human speech frequencies (0.5–4.0 kHz) [179]. Radiation-induced SNHL results from damage to the organ of Corti and stria vascularis of the cochlea, spiral ganglion and/or the acoustic nerve. The pathophysiology includes a small vessel endothelial reaction with vascular insufficiency and insult to the inner ear sensory structures, leading to their progressive degeneration and atrophy, fibrosis and even ossification of the inner ear fluid space. Furthermore, the cochlear nerve can be affected by edema and inflammation in the narrow space of the internal auditory bony canal [180]. Hearing deterioration is worse at higher frequencies compared to speech frequencies and commences soon after RT. Early changes in hearing could be reversible, though the probability of clinically relevant threshold deterioration of hearing increases over time, with the median latency period being 1.5 to 2 years [181,182]. In addition to a radiation dose of 47 Gy or more to the cochlea, the main factors affecting the risk of SNHL are the patient's age and baseline hearing level, cisplatin dose, post-RT otitis media, and follow-up time [178,179,183–185]. In addition, the deterioration in air conduction caused by RT-induced Eustachian tube dysfunction and middle air fibrosis may accompany persistent SNHL, indicating mixed hearing impairment [186].

There is no standard treatment of SNHL caused by RT. Different interventions were tested in uncontrolled and retrospective case series but not in a properly designed randomized trial. Conservative measures may include systemic steroids to improve inflammation and edema in the inner ear after radiation-induced damage and to reduce compression of the acoustic nerve due to inflammatory swelling. Chen et al. [187] reported that the use of systemic methylprednisolone during RT can reduce early SNHL caused by irradiation. In a post-RT setting, Sakamoto et al. [188] observed an improvement in hearing loss with oral prednisone, at least in young patients having a useful pretreatment hearing level, if the steroid treatment was administered immediately after the first detection of the hearing loss. The benefit of oral corticosteroid therapy in salvaging acute hearing deterioration was also suggested by Kim et al. [189]. In idiopathic sudden SNHL, however, the value of steroids was termed unclear in the Cochrane review of the evidence [190], though salvage intratympanic therapy has shown some positive effects in refractory cases [191].

The rationale for the use of HBOT is based on the role of vascular damage and ischemia in RT-induced SNHL development. A Cochrane review suggests that hearing improvement of 25% can be expected in one out of every five treated patients with acute idiopathic sudden SNHL but no beneficial effect of HBOT was found in chronic cases [192]. In another review

by the same source, no evidence of any important clinical effect of HBOT was found on neurological tissues, either peripheral or central [146].

In patients with RT-induced bilateral profound SNHL, cochlear implants are a viable rehabilitation option. As determined in nasopharyngeal cancer survivals, the retro-cochlear auditory pathways are not seriously damaged and remain functionally intact even in the longer term after RT [193]. Overall hearing outcomes after cochlear implantation for post-irradiated patients were found not to be worse than in patients who have had no prior RT to ear structures [194] and related complications are rare, though so far, no study has compared the incidence of complications of post-cochlear implantation in irradiated versus non-irradiated temporal bones [195,196]. Moreover, cochlear implant surgery and cochlear implant activity have not been seen to have harmful effects on vestibular function and balance [197].

Current clinical standard includes proactive ototoxicity monitoring and standard aural rehabilitation with hearing aids for the vast majority of cases with efficacy of cochlear implants supported for profound SNHL after RT.

Conclusions

RT undeniably contributes to favorable disease control in the great majority of HNC patients and will remain one of the integral components of a multidisciplinary treatment approach for this disease. Even with recent improvements in RT planning and delivery with enhanced control over spatial distribution of radiation dose, some damage to normal tissues cannot be avoided [198]. While the management of acute RT-induced toxicity is rather effective, the treatment options of late sequelae of RT are much more limited and of variable benefit which goes in line with the generally rather low quality level of available evidence (Table 4). Accordingly, there are no widely accepted clinical standards of management and treatment for these conditions, but only recommendations that could be used in clinic associated with variable degrees of benefit to the patients. The impact of late RT toxicity to the QOL in long-term HNC survivors cannot be overstated; indeed, they can also be life-threatening as suggested by long-term results of studies with mature follow-up [14,199]. Several new strategies are under development and/or extensive evaluation to improve the balance between efficacy and morbidity. Some of them refer to refinements in diagnostics (tumor identification) or RT techniques (e.g. guidelines for the delineation of target volumes and organ at risk, adaptive RT, biologically conformal RT/dose-painting, proton RT) [200]; other innovative approaches include a decrease in the treatment intensity for selected cases (e.g. HPV-associated oropharyngeal cancer), together with optimization in selection among different treatment options by using predictive tests in order to identify hypersensitive patients for RT-induced complications for a personalized strategy [201,202]. Enormous expansion in the field of innovative drug design offers a good prospect for the development of new preventive and therapeutic agents to counteract different RT-induced late sequelae.

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Table 1

Cholinergic agonists for radiotherapy-induced xerostomia in patients with head and neck cancer: randomized-controlled studies

Study	No. of patients			Doses & therapy duration	Results (drug vs. placebo)
	Total	Drug	Placebo		
Johnson et al., 1993 (31)	207	142	65	Pilocarpine, 5 mg t.i.d. for 12 weeks (73 patients) *or* 10 mg t.i.d. for 12 weeks (69 patients)	• improvement in overall condition of xerostomia: 53.5% vs. 42.9% vs. 25%, p=0.010 • improvement in saliva production at weeks 4 and 8; did not correlate with symptomatic relief • withdrawal from the study (adverse experience): 5.5% vs. 29% vs. 3.1% • no serious drug-related adverse events
LeVeque et al., 1993 (32)	162	75	87	Pilocarpine, Weeks 1–4: 2.5 mg t.i.d. Weeks 5–8: 5 mg t.i.d. Weeks 9–12: 10 mg t.i.d.	• improvement in overall condition of xerostomia: 48.7% vs. 28.1%, p=0.015 • improvement in whole saliva and unstimulated parotid saliva flow • withdrawal from the study (adverse experience, lack of efficacy): 14.67% vs. 13.75% • no serious drug-related adverse events • best results: doses >2.5 mg t.i.d., continuous treatment for 8–12 weeks
Chambers et al., 2007 (39)	284	139	145	Cevimeline, 30 mg t.i.t. for 12 weeks	• global xerostomia improvement: 47.4% vs. 33.3%, p=0.0162 • improvement in unstimulated saliva flow: p<0.0001 vs. p=0.942 • withdrawal from the study (adverse experience): 14.6% vs. 3.5% • treatment-related adverse effects: 41.6% vs. 17.4% (mild to moderate)
Study 004	286	139	147	If no improvement in dry mouth: escalation of dose to 45 mg t.i.d. at week 6	• global xerostomia improvement: 48.9% vs. 47.6%, p=0.9565 • improvement in unstimulated saliva flow: p=0.0002 vs. p=0.0928 • withdrawal from the study (adverse experience): 13.9% vs. 5.5% • treatment-related adverse effects: 38% vs. 18.6% (mild to moderate)

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Table 2

Acupuncture for radiotherapy-induced xerostomia in patients with head and neck cancer: randomized-controlled studies

Study	No. of patients		Interventions	Results (intervention vs. control)
	Total	Groups		
Blom et al., 1996 (48)	38	20	Real AP (2 series of 12 THs with 2-week pause 2 THs/week, 20 min/AP	• improvement in saliva flow rates: in 68% vs. 50% patients
		18	Control: superficial (sham) AP	• no significant difference between real AP and sham AP
				• improvement persists during the observation year in both groups
				• control group: improvement is smaller and appears later
Cho et al., 2008 (49)	12	6	Real AP (2 THs/week, 20 min/TH, for 6 weeks)	• real AP significantly increase unstimulated salivary flow rate and improve the score for dry mouth (at 6 weeks)
		6	Control: superficial AP	
Pfister et al., 2010 (50)	58	28	AP (1 TH/week, 30 min/TH, for 4 weeks)	• real AP produces a significantly greater improvement in reported
		30	Control: usual care	• xerostomia compared to "usual care"
Simcock et al., 2013 (51)	145	70	AP → oral care	• no significant changes in stimulated or unstimulated saliva flow by AP
		75	Oral care → AP	• AP provides significantly better reductions in patient reports of xerostomia-related symptoms compared to "oral care"
			AP: 1 TH/week, 20 min/TH, for 8 weeks	
			Oral care: 1 educational sessions of 1h, 1/month	
Wong et al., 2015 (52) [1]	148	75	ALTENS (2 TH/week, 20 min/TH, for 12 weeks)	• no significant difference in the change in xerostomia burden between the ALTENS a pilocarpine
		73	Pilocarpine (5 mg t.i.d., for 12 weeks)	• significantly less toxicity in ALTENS group

AP – Acupuncture; TH – Therapy; ALTENS – Acupuncture-like transcutaneous electrical nerve stimulation.

[1] Only 96 and 76 patients with all items completed were evaluable at 9 and 15 months from randomization.

Table 3

Recommendations for the use of oral lubricants and saliva substitutes to alleviate hyposalivation (adapted from Regelink et al., Ref.68)

Xerostomia	Recommendation
Severe	During the night:
	saliva substitute with gel-like properties or mucin-containing lozenges
	During the day:
	saliva substitute with properties resembling the viscoelasticity of natural saliva (e.g. polyacrylic acid, xanthan gum, or mucin based substitutes)
Moderate	During the night:
	gel
	During the day
	saliva substitute with a rather low viscoelasticity (e.g. carboxymethylcellulose, hydoxypropylmethylcellulose, mucin–based sububstitutes); or low concentrations of xanthan gum and polyacrylic acid
Slight	Little amelioration is expected from the use of saliva substitutes (gustatory or pharmacologic stimulation is the treatment of choice)

Table 4

Late sequeale after radiotherapy: recommended radiotherapy dose constrains, therapeutic options and their level of evidence (according to the American Society of Clinical Oncology Levels and Grades of Evidence)

Toxicity	RT dose constraints (198)	Treatment options	Level of evidence
Xerostomia	Parotid gland:	Muscarinic agonist stimulation	Level II, Grade B
	D_{mean} 26 Gy *or*	Acupuncture	Level II, Grade B
	$V_{30}{<}50\%$	Hyperbaric oxygen therapy	Level III, Grade B
	Submandibular gland:	Gustatory/masticatory stimulants, mucosal lubricants and saliva substitutes	Level II, Grade B
	$D_{mean}{<}35$ Gy		
Dysphagia	Pharyngeal constricto muscle:	Exercise-based swallowing rehabilitation	Level II, Grade C
	$D_{mean}{<}50$ Gy	Acupuncture	Level II, Grade B
Mandible osteoradionecrosis	Mandibular bone:	Hyperbaric oxygen therapy	Level II, grade B
	1 cc: D_{max} 70–73.5 Gy	Medical management	Level III, Grade B
Trismus	Temporomandibular joint:	Exercise therapy	Level II; Grade B
	0.1 cc <70 Gy	Surgery	Level III, Grade B
Hearing loss	Inner ear:	Systemic steroids therapy	Level III, Grade B
	$D_{mean}{<}50$ Gy	Cochlear implants	Level IV, Grade B

RT – Radiotherapy; D – Dose, VX – Volume that receives dose of X Gy.