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Long-term outcomes of interventions for radiation-induced xerostomia: A review

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Abstract

Xerostomia, or dry mouth, is a significant problem affecting quality of life in patients treated with radiation therapy for head and neck cancer. Strategies for reduction of xerostomia burden vary widely, with options including: sialagogue medications, saliva substitutes, acupuncture, vitamins, hyperbaric oxygen, submandibular gland transfer, and acupuncture or associated treatments. In this review, we sought to evaluate long-term outcomes of patients treated with various interventions for radiation-induced xerostomia. A literature search was performed using the terms “xerostomia” and “radiation” or “radiotherapy”; all prospective clinical trials were evaluated, and only studies that reported 1 year follow up were included. The search results yielded 2193 studies, 1977 of which were in English. Of those, 304 were clinical trials or clinical studies. After abstract review, 23 trials were included in the review evaluating the following treatment modalities: pilocarpine (three); cevimeline (one); amifostine (eleven); submandibular gland transfer (five); acupuncture like transcutaneous electrical nerve stimulation (ALTENS) (one); hyperbaric oxygen (one); and acupuncture (one). Pilocarpine, cevimeline, and amifostine have been shown in some studies to improve xerostomia outcomes, at the cost of toxicity. ALTENS has similar efficacy with fewer side effects. Submandibular gland transfer is effective but requires an elective surgery, and thus may not always be appropriate or practical. The use of intensity-modulated radiation therapy, in addition to dose de-escalation in select patients, may result in fewer patients with late xerostomia, reducing the need for additional interventions.

Key words: Xerostomia; Radiation therapy; Radiotherapy; Head and neck cancer; Quality of life

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Core tip: Xerostomia is a common side effect of radiation for head and neck cancer, and can impact patient quality of life even years after treatment. In this review, we sought to evaluate the current literature regarding long-term outcomes of interventions for radiation-induced xerostomia, including medical management, submandibular gland transfer, acupuncture, acupuncture like transcutaneous electrical nerve stimulation, and hyperbaric oxygen.

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INTRODUCTION

Head and neck cancer patients treated with radiation experience changes in their quality of life due to radiation-induced dry mouth or xerostomia^[1]. Complications include trouble eating, speaking, and swallowing, which can lead to depression and limited social activities^[2,3]. Xerostomia can be avoided by reducing the mean radiation dose delivered to parotid and submandibular glands^[4-9]. Intensity-modulated radiation therapy (IMRT) to spare parotid glands has been shown to reduce the incidence of xerostomia and improve quality of life^[10-16]. However, despite the improvements seen in quality of life, select patients report persistent xerostomia after IMRT^[17,18].

Standard care for radiation-induced xerostomia in head and neck cancer patients remains sialogogue medications, such as pilocarpine and cevimeline^[19]. However, these medications have been shown to cause complications such as nausea and sweating^[20], in some cases leading to patients withdrawing from the study^[21,22]. Numerous alternatives have been studied for xerostomia treatment, including amifostine^[23], bethanechol^[24], saliva substitutes^[25], palifermin^[26], alpha-tocopherol^[27], vitamin C/E^[28], thyme honey^[29], herbal products, acupuncture^[30], transcutaneous electrical nerve stimulations, submandibular gland transfer surgery^[31], gene therapy^[32], hyperbaric oxygen^[33], and hyperthermic, supersaturated humidification—many of which have been reviewed previously in a meta-analysis by Mercadante *et al*^[19]. However, few studies have long-term follow up data for interventions. We performed this review to evaluate various interventions for the long-term management of radiation-induced xerostomia.

LITERATURA RESEARCH

We performed a review of journal articles in English in July 2018. Our inclusion criterion was any prospective clinical trial reporting clinical outcomes of interventions for radiation-induced xerostomia, with evaluation for late xerostomia at least 1 year after the radiation or intervention. The exclusion criteria were: (1) review articles, retrospective studies, letters, or case reports; (2) studies that did not show the most updated results when multiple journal articles published from the same patient cohort; (3) xerostomia unrelated to prior radiation therapy; and (4) the use of radioiodine or radionucleotide as a treatment.

PubMed electronic databases were queried in July 2018 for search terms such as “xerostomia”, “radiotherapy”, and “radiation”. This database query initially resulted in 2193 studies. Of these, 304 studies were prospective trials written in English. With our exclusion criteria, these studies and their reference lists were reviewed to be considered for inclusion (Figure 1).

Twenty-three studies are selected for analysis (Tables 1-6). Of these, three studies evaluated pilocarpine; one evaluated cevimeline; eleven studies evaluated amifostine; five evaluated submandibular transfer; one evaluated ALTENS; one evaluated hyperbaric oxygen; and one evaluated acupuncture. Below we review the results of the studies.

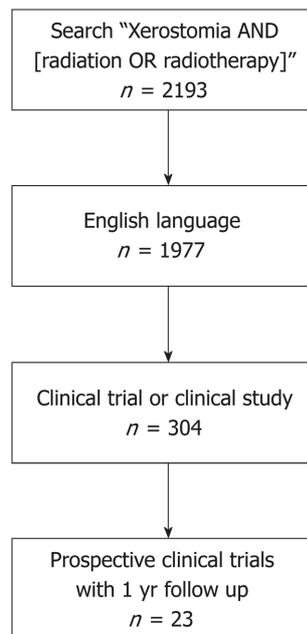


Figure 1 Literature research flowchart.

PILOCARPINE AND CEVIMELINE

Pilocarpine, a cholinergic agonist, has shown mixed results in the treatment of radiation related xerostomia. Burlage *et al*^[34] evaluated 170 patients randomized to either oral pilocarpine or placebo during radiation therapy. Based on LENT SOMA score, there was no statistical difference between the two arms at one year. However, based on patient reported xerostomia, pilocarpine significantly reduced symptoms in patients who received > 40 Gy mean dose to the parotid. Toxicity was relatively low in this, with 2 patients withdrawing from the study—one in the pilocarpine group (due to sweating) and one in the placebo group due to a suspected adverse event. The only grade 2 reported toxicity was excessive sweating in one patient. In study by Mateos *et al*^[35], 49 patients were divided into two groups. One group received pilocarpine during RT and throughout the year that followed, while the other received radiation alone. Visual analogue scale (VAS) revealed no subjective difference between the two groups. Dynamic salivary scintigraphy also showed no statistically significant advantage to pilocarpine. In contrast, Valdez *et al*^[36] reported a series of 9 patients receiving either pilocarpine for 3 mo or placebo. Based on patient reports surveys, there were significantly fewer symptoms of xerostomia in the pilocarpine group. Interestingly, in this small number of patients, there was a statistically significant difference between the groups in stimulated parotid salivary function at 3 mo. No pilocarpine related toxicities were reported.

Cevimeline has also been studied as an oral agent for treatment of xerostomia. Chambers *et al*^[37] reported a single arm trial of 255 patients taking cevimeline for 1 year. At final evaluation, 59.2% of patients had improved symptoms based on mean global evaluation score, with 37.3% showing no change, and 3.5% with worsening symptoms compared to initial visit. The rate of grade 3 toxicity was 20.4% and consisted mostly of sweating; 7.1% of patients experienced a severe adverse event, one of which (miscarriage) was possibly attributed to the study drug. Overall the authors conclude that cevimeline was well tolerated and may provide relief of xerostomia in head and neck cancer patients.

AMIFOSTINE

Eleven papers studying amifostine met inclusion criteria. Büntzel *et al*^[38] reported on 39 patients randomized to either IV amifostine 500 mg with carboplatin (days 1-5 and days 21-25) during concurrent chemoradiation, or to chemoradiation alone. The authors report that grade 3 mucositis, grade 2 xerostomia, and grade 3 thrombocytopenia were all significantly decreased in the amifostine group. Brizel *et al*^[39] also found an advantage with amifostine, reporting on 303 patients treated with either radiation along or amifostine 200 mg/m² 15-30 min prior to each RT dose.

Table 1 Pilocarpine and Cevimeline

Author	Type of study	n	Intervention	Xerostomia symptoms	Salivary Function	Toxicity
Burlage <i>et al</i> ^[34] , 2008	Double-blind, randomized, placebo-controlled trial	170	PC during RT <i>vs</i> placebo	LENT SOMA: no difference at 1 yr; Patient-reported xero: significantly lower scores in pilocarpine group at 12 mo only if mean parotid dose > 40 Gy	Parotid flow rate complication probability (PFCP): at 1 yr, no diff between arms (except in subset of pts with > 40 Gy mean parotid dose-reduced loss of flow in pilocarpine group)	2 patients didn't complete treatment, excessive sweating for PC and suspected AE for placebo pt; 1 G2 excessive sweating
Mateos <i>et al</i> ^[35] , 2001	Prospective non-randomized study	49	PC 5 mg TID during RT and for 1 yr <i>vs</i> no PC	No significant difference in visual analogue scale between groups	Dynamic salivary scintigraphy: no SS differences between groups	NA
Valdez <i>et al</i> ^[36] , 1993	Double-blind, randomized, placebo-controlled trial	9	PC 5 mg four times daily for 3 mo during RT <i>vs</i> placebo	Significantly fewer subjective oral symptoms in pilocarpine group on survey during treatment; no difference at 1 yr (25% in both arms)	Salivary flow rate (resting and stimulated): smaller losses in stim function in PC group at 3 mo (SS)	none reported
Chambers <i>et al</i> ^[37] , 2007	Open-label prospective single-arm study	255	Cevimeline for 1 yr 45 mg TID orally	Used mean global eval. score (0-3), at final eval. 59.2% improved, 37.3% no change, 3.5% worse compared with first visit ($P < 0.0001$ change from baseline to visit 8)	NA	20.4% G3 AE, most common was sweating; 7.1% severe AE, one possibly attributed to study drug (miscarriage)

PC: Pilocarpine; G: Grade; AE: Adverse event; xero: Xerostomia; pts: Patients.

Grade 2 xerostomia was significantly improved in the amifostine group compared with control (51% *vs* 78%, $P < 0.0001$); in addition, a higher threshold dose of radiation was required to cause grade 2 xerostomia in the amifostine group. This study also quantified whole saliva production (WSP) during RT and at follow up; there was significantly higher saliva production in the amifostine patients at 1 year. In terms of amifostine toxicities, 53% of patients experienced nausea and vomiting (5% of total amifostine administrations, with 3% grade3 nausea and 5% grade3 vomiting). Other complications included hypotension, venous catheter complications, infections, and clotting/vascular disorders. Many of these were related to the IV method of administration. The authors concluded that amifostine reduces xerostomia, although alternative delivery methods should be evaluated. In contrast, a separate study did not report significant administration-related toxicities with the use of IV amifostine 300 mg/m² prior to RT^[40]. This randomized trial assigned patients to either chemoradiation alone or chemoradiation with prophylactic amifostine. Toxicities reported included nausea/vomiting (1 patient) and transient hypotension (13.6%). By week 3 of radiation treatment, 100% of the control group and 9.1% of the study group had grade 2 mucositis; by week 5, 97.5% of control group was reported to have moderate to severe mucositis, and 63.6% of the study group. Additionally, treatment duration was significantly shorter in the amifostine group, due to more treatment interruptions from grade 4 mucositis.

Two additional studies evaluated the efficacy and safety of IV amifostine. A randomized trial by Buentzel *et al*^[41] included 132 patients randomized to either IV amifostine 300 mg/m² on days 1-5 and 200 mg/m² on other days of RT, or placebo. In contrast to prior studies mentioned, there was no difference in acute or late xerostomia based on RTOG criteria. There was, however, a difference in toxicity, with a 43% *vs* 20% grade 3 toxicity rate (amifostine and placebo groups, respectively). Of note, less than 1/3 of patients were evaluated at the 1 year time point. Wasserman *et al*^[42] included 303 patients randomized to either amifostine 200 mg/m² prior to each radiation fraction, or radiation alone. With 2 years of follow up, the amifostine group had: lower grade 2-4 chronic xerostomia, increased unstimulated saliva scores, and

Table 2 Amifostine: Xerostomia

Author	Type of study	n	Intervention	Xerostomia symptoms	Effect Size
Bardet <i>et al</i> ^[46] , 2011	Phase III randomized trial	291	Amifostine IV vs SC	RTOG grading: G2+ xero significantly higher in SC at 1 yr, but not at 2-3 yr	37% IV vs 62% SC
Haddad <i>et al</i> ^[45] , 2009	Phase II randomized trial	58	SC amifostine 500 mg daily (for median 28 doses) no amifostine	CTCAE: no significant difference in Gr2+ xero (minimum follow up 26 mo)	41% both arms
Law <i>et al</i> ^[44] , 2007	Phase II prospective nonrandomized trial	20	SC 500 mg amifostine 30-60 min before RT	G2 xero 42% at 12 mo, 29% at 18 mo; no G3+ xero. G3+ mucositis in 30% of pts.	
Anné <i>et al</i> ^[43] , 2007	Phase II single arm multicenter trial	54	SC amifostine	RTOG scoring: G2+ xero = 56%; late G2+ in 45% ; G3+ acute 33%	
Jellema <i>et al</i> ^[23] , 2006	Phase II randomized trial	91	No amifostine vs 200 mg/m ² IV daily (3 wk) vs 5 wk	RTOG scoring: significant difference in late G2+ xero at 6 mo between arms; no difference in xero at 12 mo or 24 mo; no dif in acute xero EORTC QLQ-H and N35: significantly higher mean xerostomia score in no amifostine group	Late G2+ xero 74% vs 67% vs 52%
Buentzel <i>et al</i> ^[41] , 2006	Phase III randomized placebo-controlled trial	132	IV amifostine 300 mg/m ² days 1-5 and 21-25, 200 mg/m ² on other days vs placebo	RTOG criteria: no significant difference in G2+ acute or late xero	39% amifostine vs 34% placebo (acute); 39% amifostine vs 24% placebo (late)
Wasserman <i>et al</i> ^[42] , 2005	Phase III randomized trial	303	IV amifostine 200 mg/m ² 15-30 prior to each RT fraction vs no amifostine	RTOG scoring: significantly lower G2+ xero in amifostine group on longitudinal analysis	20% vs 36% at 24 mo
Thorstad <i>et al</i> ^[47] , 2004	Pilot clinical trial	27	Amifostine concurrent with RT (500 mg SC daily)	not reported	NA
Antonadou <i>et al</i> ^[40] , 2002	Randomized controlled trial	50	Amifostine 300 mg/m ² 15-30 min prior to RT (daily) vs no amifostine	RTOG/EORTC scoring: significantly lower xero in amifostine group at 18 mo (G1+)	30.4% vs 4.5%
Brizel <i>et al</i> ^[39] , 2000	Phase III multiinstitutional randomized trial	303	Amifostine 200 mg/m ² 15-30 min prior to each RT tx vs no amifostine	RTOG scoring: significantly higher G2+ xero (acute and late) in control vs amifostine; higher dose required to cause G2 xero in amifostine pts (60 Gy vs 42 Gy);	78% vs 51% (acute); 57% vs 43% (1 yr)
Büntzel <i>et al</i> ^[38] , 1998	Phase II randomized trial	39	Amifostine IV 500mg prior to carboplatin (days 1-5 and 21-25) vs no amifostine	Acute G2 xero, G3 mucositis, and G3 thrombocytopenia all significantly decreased with amifostine; at 12 mo, trend toward xero improvement with amifostine	Xero: G2 100% vs 12% (acute); 55% vs 17% (late; P = 0.05)

SC: Subcutaneous; G: Grade; xero: Xerostomia; pts: Patients.

better patient reported mouth dryness.

As an alternative delivery method, subcutaneous administration of amifostine has been evaluated in four trials with mixed results. Two phase II single arm trials, with 54 and 20 patients each, treated patients with subcutaneous amifostine and compared results to prior studies using IV, and showed similar results in terms of efficacy^[43,44]. One phase II randomized study of 58 patients compared subcutaneous amifostine with no amifostine, and found no significant difference between the two arms^[45]. A phase III randomized controlled trial assigned 291 patients to either IV or subcutaneous amifostine^[46]. The authors found no significant benefit in terms of

Table 3 Amifostine: Salivary function, quality of life, toxicity

Author	Salivary Production	QOL	Toxicity
Bardet <i>et al</i> ^[46] , 2011	No difference in unstimulated and stimulated salivary flow rate =	No difference in patient-reported salivary function or Gr 2+ xero	No difference in compliance between arms (69% IV <i>vs</i> 71% SC). Acute toxicity 25% IV <i>vs</i> 27% SC (NS). SS higher rate of hypotension in IV arm; significantly higher skin rash and local pain in SC arm.
Haddad <i>et al</i> ^[45] , 2009	No difference in unstimulated or stimulated saliva at all endpoints (up to 1 yr)	No difference in penetration, aspiration, and pharyngeal residue on swallow eval.	G3 mucositis in 75% (amifostine) and 70% (no amifostine); Gr3 skin toxicity in 12 patients in amifostine group (main reason for withholding amifostine)
Law <i>et al</i> ^[44] , 2007	NA	NA	G2 weight loss for all pts, Gr2 or less N/V in 7 pts (35%). No grade 3+ amifostine-related AEs.
Anné <i>et al</i> ^[43] , 2007	NA	PBQ: mean score 8.5 baseline, 6.1 at 4 wk, 7.5 at 1 yr	Nausea, emesis, injection site reaction most common G1-2; G3 dehydration 11%, rash 6%, weight decrease, mucositis, dyspnea, allergic reaction 4% each; one G4 anaphylaxis
Jellema <i>et al</i> ^[23] , 2006	NA	QLQ-C30, QLQ-H and N35: no differences in sticky saliva or other QOL data	Significantly higher N/V in amifostine groups; 28% of patients discontinued amifostine early
Buentzel <i>et al</i> ^[41] , 2006	not assessed: fewer than one-third in each arm had salivary assessment at 1 yr	NA	42% G3+ toxicity (amifostine) <i>vs</i> 20% (placebo) (SS)
Wasserman <i>et al</i> ^[42] , 2005	no dif. in stimulated; unstimulated higher in amifostine group at 12 mo (SS)	PBQ: amifostine group had SS better mouth dryness at 12, 18, and 24 mo; better score for "use of oral comfort aids" with amifostine at 24 mo	not enough to analyze
Thorstad <i>et al</i> ^[47] , 2004	not reported	not reported	reasons for discontinuing amifostine: nausea (33%), rash (15%), fever (7%), other (11%)
Antonadou <i>et al</i> ^[40] , 2002	NA	NA	SS lower acute mucositis and acute dysphagia in amifostine group; in amifostine group, 1 pt had N/V, 3 pts had transient hypotension
Brizel <i>et al</i> ^[39] , 2000	Whole saliva production higher in amifostine pts at 1 yr (SS)	PBQ: overall score favored amifostine at 1 yr (SS)	53% nausea and vomiting (5% of total administrations; 3% G3 N, 5% G3 V); G3 N/V in 7% of pts; median weight loss higher in control group (SS); hypotension 15% (3% G3; < 1% of all doses); venous catheter complications 5%; infections 14%; clotting/vascular 3% (1 pt G4); allergic reaction 5%
Büntzel <i>et al</i> ^[38] , 1998	NA	NA	No significant difference in N/V between groups; hypotension 40% amifostine arm (max drop 20 mmHg)

QOL: Quality of life; SC: Subcutaneous; G: Grade; AE: Adverse event; xero: Xerostomia; NA: Not available; PBQ: Patient benefit questionnaire; pts: Patients.

patient compliance or efficacy with subcutaneous administration, suggesting that IV should remain the standard treatment. Thorstad *et al*^[47] report toxicity results of a pilot study of 27 patients assessing subcutaneous amifostine delivered concurrently with IMRT. Although compliance rate was not reported, the authors report that not all patients tolerated the treatment, with nausea, rash, and fever being the main complaints that caused discontinuation of amifostine.

SALIVARY GLAND TRANSFER

Five studies evaluating salivary gland transfer met criteria for inclusion. In a phase II single arm study of 57 patients, Jha *et al*^[48] reported that submandibular salivary gland transfer to the submental space is feasible and safe, with 81% of patients reporting none or minimal xerostomia with median follow up of 14 mo. One phase II prospective non-randomized trial of 38 patients showed improved stimulated and

Table 4 Submandibular gland transfer: Xerostomia

Author	Study design	n	Intervention	Xerostomia symptoms	Effect size
Zhang <i>et al</i> ^[51] , 2014	Randomized controlled trial	65	Submandibular transfer <i>vs</i> control	Significantly lower incidence of xerostomia (RTOG/EORTC staging criteria) at 1 yr and 5 yr in transfer group <i>vs</i> control. Significantly lower VAS at 5 yr for transfer group	Xerostomia 18.7% <i>vs</i> 81.8% at 1 yr; 15.4% for transfer <i>vs</i> 76.9% at 5 yr; VAS 3.7 for transfer <i>vs</i> 5.8 for control
Rieger <i>et al</i> ^[51] , 2012	Phase III randomized controlled trial	69	Submandibular transfer <i>vs</i> oral PC	EORTC QLQ H and N35: significantly worse dry mouth and sticky saliva at 1 yr in PC group <i>vs</i> submandibular transfer at 1 yr	Dry mouth score 42.6 <i>vs</i> 85.8; sticky saliva score 37.2 <i>vs</i> 66.7
Liu <i>et al</i> ^[50] , 2011	Prospective non-randomized controlled trial	70	Submandibular transfer <i>vs</i> control	At 5 yr, significantly higher mod-to-severe xerostomia in control group; significantly better VAS in transfer group <i>vs</i> control	Mod-to-severe xerostomia 78.6% <i>vs</i> 12.9%
Seikaly <i>et al</i> ^[49] , 2004	Phase II prospective non-randomized	38	Submandibular gland transfer <i>vs</i> control	UW-QOL: significantly better xerostomia symptoms (amount and consistency) at 2 yr	83% <i>vs</i> 0% reporting normal amount of saliva
Jha <i>et al</i> ^[48] , 2003	Phase II prospective single arm	76	submandibular gland transfer	UW-QOL: 81% minimal or no xero at end of RT; 65% at 2 mo; 71% at 6 mo (in unshielded pts, 71% had severe xero at 6 mo)	-

VAS: Visual analogue scale; PC: Pilocarpine; xero: Xerostomia; UW-QOL: University of Washington quality of life scale; pts: Patients.

unstimulated saliva as well as improved patient reported xerostomia in the transfer group compared to patients who did not receive transfer^[49]. Similarly, in another study including 70 patients, those treated with salivary gland transfer had an incidence of 12.9% of moderate-to-severe xerostomia compared with 78.6% in the control group^[50]. Two randomized controlled trials, of 65 and 69 patients each, evaluated submandibular transfer, one comparing to a control group, and the other to oral pilocarpine^[31,51]. The first showed a significant reduction in the incidence of xerostomia with salivary gland transfer; the second also showed a significant advantage for salivary gland transfer over pilocarpine with respect to dry mouth and sticky saliva. In all of the above studies, surgery was well tolerated, with no reported complications.

OTHER MODALITIES

Other studies include treatment with hyperbaric oxygen, which was shown in a randomized trial to improve patient reported dry mouth and sticky saliva^[52]. In a sham-controlled study of acupuncture for xerostomia, Blom *et al*^[53] treated patients either with acupuncture or superficial acupuncture, and found no difference in xerostomia outcomes or salivary flow rate between the two groups. Finally, Wong *et al*^[54], in a 148 patient phase III study, reported on the use of acupuncture-like transcutaneous electrical nerve stimulation (ALTENS) compared to oral pilocarpine. While there was no difference in whole salivary production, there was a significantly higher proportion of patients in the ALTENS group that responded positively to treatment. In addition, the rate of adverse events was 61.6% in the pilocarpine group compared with 20.9% in the ALTENS group, although the difference in adverse events was not significant at 9 mo ($P = 0.67$). There were three grade 3 toxicities overall (dry mouth and blurred vision in the pilocarpine group, headache in the ALTENS group).

Table 5 Submandibular gland transfer: Salivary function, quality of life, toxicity

Author	Salivary function	Quality of life	Toxicity
Zhang <i>et al</i> ^[31] , 2004	Transfer 1.39 g and 1.6 g saliva <i>vs</i> 0.66 and 0.68 g control at 1 yr and 5 yr, respectively. Significantly higher submandibular gland secretion in transfer group at 5 yr (radionuclide scintigraphy).	Significantly improved speech, chewing, swallowing, changes in eating habits, nighttime xero, need to wake up to drink frequently, sleep quality in transfer group	No surgical death or complications occurred in transfer group
Rieger <i>et al</i> ^[51] , 2012	NA	NA	Not reported
Liu <i>et al</i> ^[50] , 2011	Significantly better trapping and excretion (scintigraphy) in transfer group at 5 yr; Significantly higher mean weight of unstimulated saliva in transfer group at 5 yr	Transfer group improved significantly <i>vs</i> control in dry mouth, night rest, drink to speech, drink to eat, water intake, change in feeding pattern, tooth decay, and visual analogue scale	No major complications of surgery (one pt taken back 2 yr later for removal of wire used to mark borders of transferred gland due to pain)
Seikaly <i>et al</i> ^[49] , 2004	Significantly higher stimulated and unstimulated saliva in transfer group at 16 mo	NA	No surgical complications from submandibular transfer
Jha <i>et al</i> ^[48] , 2003	stimulated and unstimulated saliva decrease gradually, then increase at 16 mo (graphical)	NA	No surgical complications

xero: Xerostomia; NA: Not available.

DISCUSSION

Although there have been prior reviews on the management of radiotherapy-induced xerostomia, to our knowledge there has been no review of the current literature with a focus on late xerostomia following radiotherapy for head and neck cancer^[19,55,56]. We found a very heterogeneous group of studies in this review, with many different modalities, doses, routes of administration, timing with respect to treatment, and differing quality of life (QOL) endpoints as well as different objective saliva measurements.

In most of the studies reviewed above, amifostine appears to be beneficial in reducing the risk of long term xerostomia, although it likely requires IV administration. Severely limiting clinical utilization, however, toxicity was noted in close to half of the patients treated^[39,41]. Similarly toxicity limits the clinical utilization of pilocarpine and cevimeline, which have been shown to improve xerostomia, with treatment related adverse events exceeding 91.4% (20.4% grade 3) with cevimeline^[37].

In contrast, ALTENS treatment was shown to be as effective as pilocarpine, with fewer adverse events (20.8% in ALTENS group *vs* 61.6% in pilocarpine group)^[54]. At 15 mo, the treatment response rate was significantly higher in the ALTENS group. ALTENS represents a non-invasive, well tolerated option for treatment of late xerostomia. However, ALTENS devices are not widely available and when offered in a clinical setting, require patients to travel to the clinic twice weekly for 12 wk. Both of these issues limit availability. To address this issue, Iovoli *et al*^[57] have described a case report of excellent improvement in dry mouth with home use of a new, cheap, commercially available device.

Submandibular gland transfer has shown promise in several studies as mentioned above. The use of salivary gland transfer in select patients appears to be effective with regard to xerostomia prevention. Additionally, none of the studies evaluated here reported complications from surgery. However, the use of this procedure is somewhat limited based on several factors including patient selection criteria (for example, it would not be feasible in patients with bilateral positive neck nodes), experience of each surgeon and willingness to perform the procedure, as well as time constraints and potential delay of definitive treatment for an elective procedure.

With the advancement of radiation delivery techniques, the use of IMRT has been shown to reduce dose to selected salivary glands, therefore sparing salivary function. It is generally thought that damage to major salivary glands (submandibular and parotid) is the major cause of xerostomia following radiation therapy, as evaluated with MRI, CT, and ultrasound^[58-62]. Pacholke *et al*^[63] retrospectively reviewed 210 patients with xerostomia at least one year following completion of radiation therapy, as measured by the University of Michigan xerostomia QOL score. Higher xerostomia scores were associated with higher salivary gland dose. On multivariate analysis, radiation technique was an independent predictor of xerostomia, favoring IMRT. The PARSPORT trial was a randomized phase III randomized controlled trial that

Table 6 Other

Author	Type of study	Sample size	Intervention	Xerostomia symptoms	Salivary function	Quality of life	Toxicity
Wong <i>et al</i> ^[54] , 2015	Phase III randomized controlled trial	148	ALTENS <i>vs</i> oral PC (5 mg TID for 12 wk)	NA	Basal WSP and stimulated WSP: no sig difference	XeQOLs: no difference at 15 mo. 83% ALTENS positive responders <i>vs</i> 62.8% PC, SS at 15 mo.	2 G3 events in PC (dry mouth, blurry vision) <i>vs</i> 1 G3 event in ALTENS (headache). 61.6% of PC had Grade 3 or less non-hematologic AEs <i>vs</i> 20.9% of ALTENS
Teguh <i>et al</i> ^[52] , 2009	randomized controlled trial	19	Hyperbaric O2 (30 sessions at 2.5 ATA with O2 breathing for 90 min daily, 5 d a week) <i>vs</i> control	Visual analogue scale dry mo better on O2 (SS)	NA	EORTC QLQ-C30 and H and N35; Sticky saliva better on O2 (SS) and less dry mouth on O2 (SS)	NA
Blom <i>et al</i> ^[53] , 1996	randomized placebo-controlled trial	38	acupuncture <i>vs</i> placebo (superficial acupuncture)	NA	salivary flow rate: no dif. between groups; both groups showed increased flow rates after treatment	No specific endpoints	Tiredness, small haematomas at acupuncture sites

ALTENS: Acupuncture like transcutaneous electrical nerve stimulation; NA: Not available; G: Grade; PC: Pilocarpine; AE: Adverse event; WSP: Whole salivary production; XeQOLs: Xerostomia quality of life scale.

assigned patients with pharyngeal squamous cell carcinoma to either conventional radiotherapy or parotid-sparing IMRT, and found a significant reduction in xerostomia in the IMRT group^[60]. In addition to IMRT, the use of intensity modulated proton beam therapy (IMPT) has also been studied in a 150 patient case-matched analysis comparing IMPT to IMRT^[64]. With respect to xerostomia, the authors found improved patient-reported symptoms at 3 mo, but no difference at 1 year.

In many cases, however, complete sparing of the parotid or submandibular glands is not possible due to proximity of primary tumor or grossly involved lymph nodes. Recently, there is new evidence that sparing even a portion of the parotid gland may be helpful in preventing xerostomia. Parotid stem cells are thought to be capable of regenerating salivary function, and are located in a concentrated area in the parotid gland around the main salivary ducts, as demonstrated in a study in rats^[65]. In this same study, the authors identified a volume in the human parotid gland posterior to the mandible that was most associated with saliva production one year following radiation therapy, and demonstrated that it is possible to spare this area in some patients where sparing the entire parotid is not feasible^[65].

Because of the increasing incidence of HPV positive head and neck cancer, there has been interest in de-escalating therapy for this subset of patients^[66-68]. By reducing the total radiation dose, xerostomia may become less prevalent in this population, thus reducing the need for alternative treatment of salivary dysfunction.

While pilocarpine, cevimeline and amifostine have been shown to improve late xerostomia outcomes, these treatments often cause side effects that are not tolerable for patients. ALTENS represents a less toxic alternative therapy for prevention of late xerostomia, but has not been widely available until recently^[57]. Similarly, submandibular gland transfer is effective, but may not be appropriate for all patients. Salivary gland sparing with improved radiation techniques (IMRT) – in particular sparing of parotid stem cells – is a practical way to reduce late salivary dysfunction. As IMRT becomes more widely available, in conjunction with potential dose de-escalation, the need for alternative xerostomia treatments may become less relevant.

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