Original Article

JRAD Journal of Research and Advancement in Dentistry

J Res Adv Dent 2023;14:6:1-8.

Xerostomia after Radiotherapy for Oral and Oropharyngeal Cancer: Increasing Salivary Flow with Tasteless Sugar-free Chewing Gum

Diwakar Mishra[1]

[1] Department of Oral Medicine and Radiology, Mansarovar Dental College and Research Centre, Bhopal, Madhya Pradesh, India,

ABSTRACT

Background: Radiation-induced xerostomia is a common late side effect following treatment for oral and oropharyngeal cancers. This condition can lead to difficulties in swallowing, compromised oral health, decreased nutritional intake, or speech problems. As a result, the quality of life for these patients is often diminished. The purpose of this study was to explore the possibility of mechanically stimulating residual saliva function using tasteless and sugar-free chewing gum. It was hypothesized that tasteless and sugar-free chewing gum could immediately enhance salivary flow and possibly improve oral health when used regularly basis.

Materials and Methods: From January to November 2023, 24 consecutive patients treated with primary radiotherapy (RT) and concomitant cisplatin (for locally advanced cases) for oral or oropharyngeal cancer consented to participate. All patients had completed RT 2–8 months prior to participation and suffered from xerostomia. Samples of unstimulated and chewing gum-stimulated saliva were obtained upon entry into the study (Visit 1). For 2 weeks, patients regularly used chewing gum, and saliva measurements were repeated to verify the changes (Visit 2). An abbreviated EORTC H&N35 questionnaire was completed for both visits. A small control group consisting of young and healthy individuals also tested the chewing gum.

Results: Twenty patients completed the study and an increase in saliva flow was observed for 14 patients. Before and after intervention with chewing gum, an increase in mean saliva output was seen between unstimulated and stimulated saliva for both Visit 1 and 2 ($p = 0.008$ and $p = 0.05$, respectively). No change in saliva output was seen in the control group.

Conclusion: The chewing gum was able to stimulate saliva output, which was seen at the beginning and at the end of the intervention. No improvement in baseline saliva was seen. Relevant changes in subjective measures of xerostomia were seen after 2 weeks of chewing the gum

Keywords: Xerostomia, chewing gum, radiotherapy, oral cancer, oropharyngeal cancer.

INTRODUCTION

Xerostomia is a common acute and late side effect when treating head and neck cancer (HNC) patients with curative intended radiotherapy (RT) (1–3). Xerostomia is the subjective feeling of oraldryness, whereas hyposalivation is the physiological reduction in salivary flow (4). Hyposalivation is defined as unstimulated whole saliva flow of ≤0.2 mL/min, and symptoms of xerostomia often become evident when saliva flow is below 0.1–0.2 mL/min (5, 6). Xerostomia is not necessarily correlated to a reduction in saliva flow and may also be present independent of hyposalivation. Healthy individuals produce between 0.5 and 1.5 L of saliva daily, with saliva being secreted by the three paired major

Received: July. 19, 2023**: Accepted**: Aug. 28, 2023

***Correspondence Dr. Diwakar Mishra.**
Department of Oral Medicine and Radiology, Mansarovar Dental College and Research Centre, Bhopal, Madhya Pradesh, India.
Email: Not Disclosed

Copyright ©2023

pISSN 2278-0076
eISSN 2321-9270

salivary glands. It consists of approximately 99% water and 1% proteins and salt, and normal daily secretion of saliva is vital for main- taining good oral health, nutritional intake, and communication skills (7, 8).

The severity of xerostomia caused by RT is influenced by the total dose and dose per fraction and is often irreversible (9, 10). To assess the severity of xerostomia in the clinic, a good approach is to utilize an observer-based scoring system, a validated quality of life measurement tool, and to measure salivary flow (11). Various treatments are available to alleviate the discomfort of xerostomia, including symptomatic relief through oral lubricants and saliva substitutes. Salivary stimulants may be considered where residual salivary gland function remains (12).The purpose of this study was to investigate the possibility of mechanically stimulating residual saliva function. It was hypothesized that by using a tasteless and sugar-free chewing gum, an immediate increase in saliva flow would be obtained and potentially improve oral well-being when used on a regular basic.

MATERIALS AND METHODS

This non-randomized cohort study was conducted at the Department of Oncology at Setha Cancer Hospital from January to November 2023. HNC patients diagnosed with oral or oropharyngeal carcinomas were eligible for participation after completing either curative-intended treatment with EBRT or postoperative EBRT with or without concomitant cisplatin. Patients were recruited during follow-up visits to the department 2–12 months after completing treatment. Furthermore, all patients had to suffer from xerostomia (slight/moderate/severe) as graded by the attending physician according to the Danish Head and Neck Cancer Group (DAHANCA) follow-up guidelines. Medical records for all consenting patients were reviewed concerning medication-induced xerostomia. For each patient, the study consisted of two visits to the department separated by 14 days. All oral intakes one hour before the onset of the test that potentially could influence the test results were not recommended. Visit 1 consisted of four elements:

(1) An unstimulated saliva sample.
(2) An abbreviated version of the EORTC H&N35 questionnaire.
(3) Testing the chewing gum.
(4) A stimulated saliva sample.

First, the unstimulated saliva sample was obtained by the patient spitting into a test tube for 5 minutes. No sipping of water or saliva stimulant was allowed 1 hour before and during the collection of the saliva sample. Second, an abbreviated version of the EORTC H&N35 questionnaire (including only the oral and food-related questions, plus two additional questions added for the purpose of the study) (Table 2) was completed to assess xerostomia grade, quality of life, and difficulties associated with xerostomia (13, 14). Afterward, a saliva stimulant in the form of tasteless, sugar-free chewing gum was tested and chewed for 5 minutes, supported by a metronome set to 60 beats per minute. After depositing the chewing gum, the stimulated saliva sample was obtained by the patient spitting into a second test tube for 5 min.

The study chewing gum was distributed for use at home between visits, and patients were instructed to use it three to five times a day, including before regular meals. At Visit 2, the patient repeated all tests conducted during Visit 1. A second unstimulated and stimulated saliva sample was obtained, and the EORTC H&N35 abbreviated questionnaire was completed again.

Chewing Gum

For this study, a specially designed chewing gum was used to stimulate whole saliva flow. The chewing gum contained neither taste nor sugar, had no hard coating, and consisted of a basic gum base with added mannitol. The chewing gum conformed to the relevant European Union legislation on foods. For practical use, it was reduced in size to accommodate any inconvenience for the recruited patients dealing with pain in the mouth or having trouble with large food objects.

Control Group

To compare and evaluate the saliva stimulating effects of the chewing gum, the product was tested on a small control group(n = 10) consisting of young, healthy, non-smoking, and non- medicated students/health-care professionals. None reported problems regarding xerostomia. All participants

were instructed in the spitting and chewing procedures and provided salivasamples. One unstimulated and stimulated saliva sample was obtained from each participant.

Characteristic	Total (n = 62)	Non-participants (n = 31)	Participants (n = 31)	p	Study group (n = 26)	p*
Men	42 (68%)	18 (58%)	24 (77%)	NS	15 (75%)	NS
Age (median) (range, years)	63 (39-78)	64 (39-78)	62 (46-73)	NS	62 (46-73)	NS
Smoking after RT	10 (16%)	9 (29%)	1 (3%)	0.01	0	NS
Follow-up after RT	34 (55%)	18 (58%)	16 (52%)	NS	10 (50%)	NS
2-5 months	5 (25%)	-	-	-	5 (25%)	-
6-9 months	13 (21%)	7 (23%)	6 (19%)	-	5 (25%)	-
10-12 months	14 (23%)	7 (23%)	7 (23%)	-	5 (25%)	-
>12 months	1 (2%)	-	1 (3%)	-	-	-
Site	48 (77%)	25 (81%)	23 (79%)	NS	15 (75%)	NS
Pharynx	5 (16%)	-	5 (16%)	-	3 (15%)	-
Oral cavity	10 (16%)	5 (16%)	1 (3%)	-	5 (16%)	-
Saliva gland	1 (2%)	-	1 (3%)	-	-	-
Unknown primary tumor	3 (5%)	1 (3%)	2 (7%)	NS	16 (80%)	2 (10%)
Clinical stage III-IV	51 (82%)	27 (87%)	24 (77%)	-	-	-
Concomitant chemotherapy	32 (52%)	13 (31%)	19 (61%)	NS	10 (50%)	0.05
Distance to hospital	24 (39%)	12 (36%)	12 (41%)	NS	10 (50%)	NS
>50 km	38 (61%)	20 (65%)	18 (58%)	-	10 (50%)	-
<50 km	-	-	-	-	-	-

Table 2: Responses to the abbreviated EORTC H&N35 questionnaire from participants completing the study (n = 20).

In the past week	have you had...	None	A little	Quite a bit	A lot	None	A little	Quite a bit	A lot	
Oral cavity										
Q1	Pain in your month?	13(65%)	4(20%)	2(10%)	1(5%)	17(85%)	2(10%)	1(5%)		0.05
Q2	Pain in your jaw?	14(70%)	4(20%)	1(5%)	1(5%)	18(90%)	1(5%)	1(5%)		0.01
Q4	A dry month?	1(5%)	1(5%)	8(40%)	10(50%)	7(35%)	7(35%)	6(35%)		NS
Q5	Sticky saliva?	4(20%)	8(40%)	5(25%)	3(15%)	5(25%)	7(35%)	7(35%)	1(5%)	NS
Q6	Less saliva?	7(35%)	2(10%)	5(25%)	6(30%)	13(65%)	3(15%)	3(15%)	1(5%)	0.007
Eating difficulties Q7	Problems swallowing liquid?	13(65%)	6(30%)	1(5%)		15(75%)	4(20%)	1(5%)		NS
Q8	Problems swallowing solid food?	7(35%)	5(25%)	4(20%)	3(15%)	6(30%)	8(40%)	5(25%)	1(5%)	NS
Q11	Decreased sense of taste?	8(40%)	4(20%)	3(15%)	5(25%)	12(60%)	4(20%)	3(15%)	1(5%)	0.01
Q13	Trouble enjoying your meals?	5(25%)	3(15%)	7(35%)	5(25%)	6(30%)	9(45%)	4(20%)	1(5%)	0.004
Q14	Trouble eating with other people?	12(60%)	4(20%)	3(15%)	1(5%)	10(50%)	6(30%)	4(20%)		NS
Q19	Increased saliva flow after using the chewing gum?	-	-	-	-	"Yes"	"No"			NS
						19(95%)	1(5%)			

Saliva Measurement

Saliva samples were weighed, and the salivary flow rate was calculated in grams per minute (7). For all sample tubes, pre- and post-weight measurements were taken on a Mettler Toledo (Columbus, OH, USA) scale. To determine the exact weight of saliva, the scale was calibrated with 500g, 100g, and 1g weights before use. After weighing, all samples were centrifuged at 2000 × g and 20°C for 5 minutes

before the volume was determined using 3 mL pipettes. For this study, the weight of the saliva output was considered the most accurate.

Ethics

Written informed consent was obtained from all patients agreeing to participate. The study was approved by the Regional Scientific Ethical Committees for Southern Denmark. The study was conducted, and the data were analyzed without involvement from Fertin Pharma, which produced the chewing gum.

Statistics

The primary endpoint was the immediate increase in saliva output after stimulation with tasteless sugar-free chewing gum at Visit 1. The secondary endpoints included oral well-being estimated by the abbreviated EORTC H&N35 questionnaire. Saliva output was expected to be normally distributed. The correlations between measurements of the saliva output were tested using a paired t-test. Patient and tumour characteristics for all eligible patients and responses to the questionnaires were tested by Spearman's correlation for categorical values. A two-sided p-value <0.05 was regarded as significant. Data were analyzed using SPSS version 22 for Windows.

RESULTS

A total of 32 consecutive HNC patients were assessed for eligibility. Seven patients declined to participate. Among the 24 included patients, 11 did not complete the study due to issues with prosthetic teeth (n = 2), distance to the hospital (n = 2), withdrawal of consent without explanation (n = 5), or screening failure (n = 2). In total, 13 patients completed the study and underwent saliva collection four times while testing the chewing gum during the two-week study period.

The study group consisted entirely of current non-smokers. Regarding the follow-up period after RT, 10 patients completed treatment within 2–5 months, while 10 patients finished within 6–12 months. The patients who declined participation did not differ from those consenting to participate in terms of gender, age, follow-up after RT, tumor site, clinical stage, or distance to the hospital. Only smoking appeared to be more prevalent among patients who did not enter the study (p = 0.01) (Table 1).

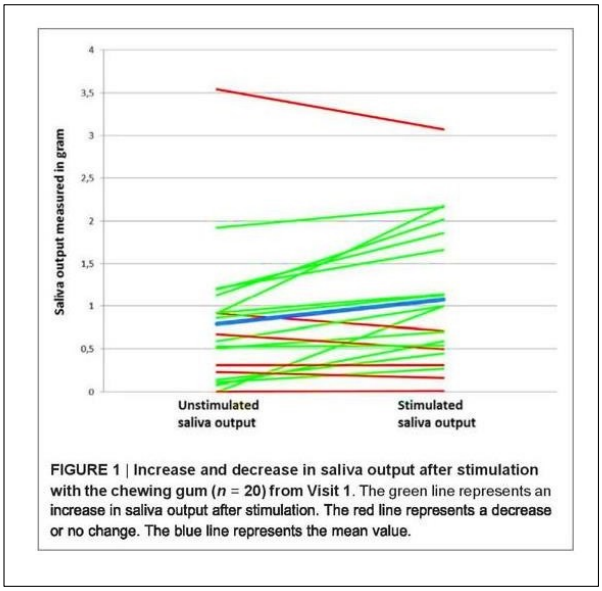


FIGURE 1 | Increase and decrease in saliva output after stimulation with the chewing gum (*n* = 20) from Visit 1. The green line represents an increase in saliva output after stimulation. The red line represents a decrease or no change. The blue line represents the mean value.

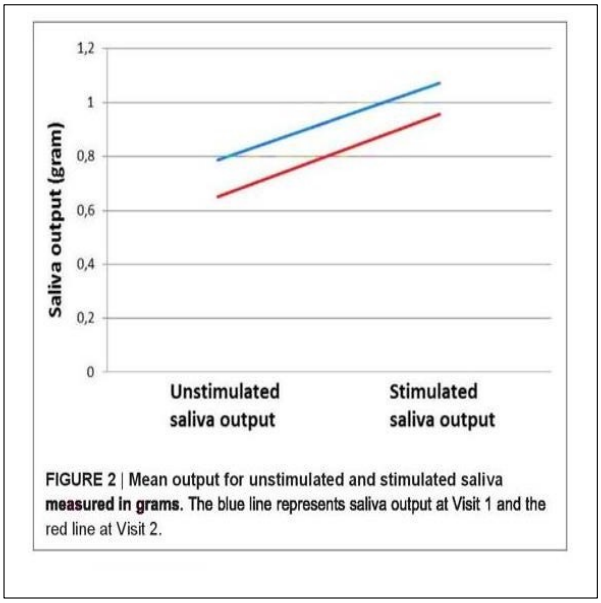


FIGURE 2 | Mean output for unstimulated and stimulated saliva measured in grams. The blue line represents saliva output at Visit 1 and the red line at Visit 2.

Xerostomia

All study patients reported xerostomia before testing the chewing gum. Responses to the abbreviated EORTC H&N35 questionnaire at Visit 1 showed that xerostomia was a major complaint, with 90% of the patients rating it as "quite a bit" or "a lot" (Table 2). At Visit 2, only 30% of the patients rated xerostomia as "quite a bit," and none experienced complaints corresponding to "a lot." No significant difference was found in the patient-reported evaluations of xerostomia. Medical records revealed that five patients were prescribed opioids, antidepressants, and antiepileptic medication, and

all five patients had pronounced xerostomia complaints ("quite a bit" or "a lot").

Oral Complaints

Pain in the mouth or jaw and difficulties with eating were evaluated using the abbreviated EORTC H&N35 questionnaire both before and after the intervention with the chewing gum (Table 2). Results showed a significant reduction in these issues after 2 weeks of intervention ($p = 0.05$ and $p = 0.01$, respectively). Additionally, a subjective increase in the total amount of saliva in the mouth was reported ($p = 0.007$). Out of 19 patients, 95% noted a perceived increase in saliva flow following the chewing gum intervention. While no significant differences were observed regarding swallowing difficulties, patients indicated less trouble enjoying their meals after Visit 2 ($p = 0.004$).

Salivary Output

The mean distribution and individual data of saliva output for patients at Visit 1 are illustrated in Figure 1. At Visit 1, the mean unstimulated saliva output and stimulated saliva output were 0.79 and 1.07 g, respectively, compared to 0.62 and 0.82 g at Visit 2 after intervention with chewing gum (Figure 2). The increase in saliva output was significant for both Visits 1 and 2 when tested using the two-sided t-test ($p = 0.008$ and $p = 0.05$, respectively). No significant difference in stimulated output between Visits 1 and 2 was found ($p = 0.2$). When testing the mean saliva flow rate in grams per minute ($p = 0.05$ and $p = 0.04$) and saliva volume ($p = 0.02$ and $p = 0.05$), the increase in saliva was also found to be significant.

The mean flow rate for unstimulated saliva was 0.09 mL/min after using chewing gum for two weeks. The definition of a very low unstimulated whole saliva flow rate is <0.1 mL/min, which corresponds to hyposalivation (6). Reviewing all measurements of the unstimulated flow rate (milliliters per minute), nine patients exhibited a very low flow rate below 0.1 mL/min, while seven patients had a low flow rate between 0.1 and 0.2 mL/min.

Saliva output for patients prescribed xerostomia-induced medication ($n = 5$) did not appear to influence the results of the chewing gum intervention. The mean unstimulated and stimulated saliva outputs were 1.25 g and 1.52 g at Visit 1. When comparing the mean saliva output from the study group at Visit 1 and Visit 2 to the mean saliva output of the control group, no increase in saliva production was observed in the control group. For the control group, both mean unstimulated and stimulated saliva outputs were significantly higher than those in the study group, measuring 4.01 g and 3.96 g, respectively. No significant difference was noted between the mean unstimulated and stimulated saliva outputs for the control group.

DISCUSSION

In this study, HNC patients treated with curative-intent RT and concomitant chemotherapy experienced an increase of at least 0.2 g in saliva output after using the tasteless, sugar-free chewing gum. For both Visit 1 and Visit 2, saliva output increased when stimulated by the chewing gum ($p = 0.008$ and $p = 0.05$, respectively). This increase corresponded well with the patients reporting a positive subjective change regarding their xerostomia complaint. No special parotid-sparing techniques were used for the patients included in the study. However, dose constraints to the parotid glands [Dmean ≤ 20 Gy (contralateral) or Dmean ≤ 26 Gy (both)], submandibular glands (Dmean ≤ 35 Gy), and oral cavity (Dmean ≤ 30 Gy) were intended to be met for every single patient in the study case.

With xerostomia being both an early and late side effect of the primary curative intended radiotherapy for oral and oropharyngeal carcinomas, it is common for many patients to experience a permanent subjective feeling of dry mouth. Xerostomia is not a life-threatening complication; however, decreased saliva flow and changes in saliva composition can be distressing. Saliva often becomes sticky and unmanageable, compromising oral well-being and resulting in eating difficulties, an increased risk of caries, and impaired speaking abilities. Living with xerostomia may cause emotional strain, such as worry, tension, and depression, and limit social activities. (10, 12, 15).

Various salivary substitutes and stimulants are available on the market to relieve discomfort associated with xerostomia. Substitutes, such as sprays, gels, mouthwashes, and special toothpaste, are designed to keep soft tissue moist and increase the viscosity of liquids (16). These substitutes are

limited by their short duration of effect, often unpleasant taste, and high cost but can be useful during the night (17). Saliva stimulants include sugar-free chewing gum, ascorbic acid (vitamin C tablets), malic acid, and pilocarpine (18). There is a low level of evidence concerning the effectiveness of the various products available.

For HNC patients, finding suitable products to increase salivary flow remains a challenge. After completing RT, the oral cavity becomes highly sensitive due to a decreased salivary flow rate and alterations in the sense of taste. Strong flavors, such as peppermint or lemon, are often not preferred in the early phase of recovery (19). Sugar may contribute to or exacerbate xerostomia and increase the risk of caries. The chewing muscles may be restricted due to radiation sequelae, and some patients may struggle with processing small food items.

The chewing gum developed for this study aims to meet the needs of HNC patients. The lack of taste is intended to stimulate saliva production through physical and mechanical means, while the soft texture and small size make it easy to chew, regardless of muscle rigidity or oral sensitivity. This aligns with others who suggest that saliva stimulants in the form of sugar-free chewing gum can help promote salivation when residual salivary gland function is present (20). The gum increases salivary flow by stimulating the taste receptors and physically stimulating the salivary glands. (12, 18, 21).

When comparing the mean unstimulated and stimulated saliva output for both Visit 1 and Visit 2, a relatively similar increase in salivary output was observed at both visits (Figure 2). The study was unable to find an absolute increase in whole unstimulated saliva output after the second visit, indicating that two weeks of regular chewing gum use did not enhance unstimulated saliva output. The decline may be attributed to the brief duration allowed for the patient to adapt to chewing gum, failure to use it consistently, or worsening xerostomia after RT. Furthermore, the study by Flink et al. suggests that circadian rhythm and fasting may negatively affect saliva secretion in patients with hyposalivation (6). In this study, measurements of saliva flow occurred throughout the daytime without considering the circadian rhythm of saliva secretion. Due to scheduling difficulties, it was not feasible to conduct Visit 2 at the exact same time slot or location for all study participants patients.

Despite including 31 eligible HNC patients, only 20 completed the study. After finishing treatment for HNC, the patients visit the department for scheduled checkups every 3 to 6 months. Participation in this study required an extra visit to the hospital for saliva collection and evaluation of the chewing gum alone. Some patients lost to follow-up were unable to attend an additional visit due to long travel distances or work conflicts. The study did not examine changes in saliva composition, and further studies should test variations in saliva composition. The chewing gum used in this study did not contain any lubricating or fluoride additives. Further testing should include chewing gum with emollient additives to determine whether it is possible to alter saliva composition and further improve oral health well-being.

CONCLUSION

Using chewing gum as a saliva stimulant, the study was able to stim- ulate and increase mean salivary output for 14 out of 20 consecutive HNC patients. The majority of the patients reported a self-rated improvement regarding xerostomia complaints and improved oral well-being after being subjected to the study chewing gum.

REFERENCES

1. Mira JG, Fullerton GD, Wescott WB. Correlation between initial salivary flow rate and radiation dose in the production of xerostomia. Acta Radiol Oncol (1982) 21(3):151–4. doi:10.3109/02841868209133999

2. Jellema AP, Doornaert P, Slotman BJ, Leemans CR, Langendijk JA. Does radiation dose to the salivary glands and oral cavity predict patient-rated xerostomia and sticky saliva in head and neck cancer patients treated with curative radiotherapy? Radiother Oncol (2005) 77(2):164–71. doi:10.1016/j. radonc.2005.10.002

3. Porter SR, Fedele S, Habbab KM. Xerostomia in head and neck malignancy. Oral Oncol (2010) 46(6):460–3. doi:10.1016/j.oraloncology.2010.03.008

4. Nieuw Amerongen AV, Veerman EC. Current therapies for xerostomia and salivary gland hypofunction associated with cancer therapies. Support Care Cancer (2003) 11(4):226–31. doi:10.1007/s00520-002-0409-5

5. Wolff M, Kleinberg I. Oral mucosal wetness in hypo- and normosalivators. Arch Oral Biol (1998) 43(6):455–62. doi:10.1016/S0003-9969(98)00022-3

6.Flink H, Tegelberg A, Lagerlof F. Influence of the time of measurement of unstimulated human whole saliva on the diagnosis of hyposalivation. Arch Oral Biol (2005) 50(6):553–9. doi:10.1016/j.archoralbio.2004.10.015

7. Navazesh M, Kumar SK. Measuring salivary flow: challenges and oppor- tunities. J Am Dent Assoc (2008) 139(Suppl):35s–40s. doi:10.14219/jada. archive.2008.0353

8. Saleh J, Figueiredo MA, Cherubini K, Salum FG. Salivary hypofunction: an update on aetiology, diagnosis and therapeutics. Arch Oral Biol (2014) 60(2):242–55. doi:10.1016/j.archoralbio.2014.10.004

9. Mortensen HR, Overgaard J, Specht L, Overgaard M, Johansen J, Evensen JF, et al. Prevalence and peak incidence of acute and late normal tissue morbidity in the DAHANCA 6&7 randomised trial with accelerated radiotherapy for head and neck cancer. Radiother Oncol (2012) 103(1):69–75. doi:10.1016/j. radonc.2012.01.002

10. Jensen AB, Hansen O, Jorgensen K, Bastholt L. Influence of late side-effects upon daily life after radiotherapy for laryngeal and pharyngeal cancer. Acta Oncol (1994) 33(5):487–91. doi:10.3109/02841869409083923

11. Deasy JO, Moiseenko V, Marks L, Chao KS, Nam J, Eisbruch A. Radiotherapy dose-volume effects on salivary gland function. Int J Radiat Oncol Biol Phys (2010) 76(3 Suppl):S58–63. doi:10.1016/j.ijrobp.2009.06.090

12. Dirix P, Nuyts S, Vander Poorten V, Delaere P, Van den Bogaert W. The influence of xerostomia after radiotherapy on quality of life: results of a ques- tionnaire in head and neck cancer. Support Care Cancer (2008) 16(2):171–9. doi:10.1007/s00520-007-0300-5

13. Bjordal K, Hammerlid E, Ahlner-Elmqvist M, de Graeff A, Boysen M, Evensen JF, et al. Quality of life in head and neck cancer patients: validation of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-H&N35. J Clin Oncol (1999) 17(3):1008–19.

14. Bjordal K, de Graeff A, Fayers PM, Hammerlid E, van Pottelsberghe C, Curran D, et al. A 12 country field study of the EORTC QLQ-C30 (version 3.0) and the head and neck cancer specific module (EORTC QLQ-H&N35) in head and neck patients. EORTC Quality of Life Group. Eur J Cancer (2000) 36(14):1796–807. doi:10.1016/S0959-8049(00)00186-6

15. Jensen K, Jensen AB, Grau C. A cross sectional quality of life study of 116 recurrence free head and neck cancer patients. The first use of EORTC H&N35 in Danish. Acta Oncol (2006) 45(1):28–37. doi:10.1080/02841860500417536

16. Vissink A, Mitchell JB, Baum BJ, Limesand KH, Jensen SB, Fox PC, et al. Clinical management of salivary gland hypofunction and xerostomia in head- and-neck cancer patients: successes and barriers. Int J Radiat Oncol Biol Phys (2010) 78(4):983–91. doi:10.1016/j.ijrobp.2010.06.052

17. Chambers MS, Rosenthal DI, Weber RS. Radiation-induced xerostomia. Head Neck (2007) 29(1):58–63. doi:10.1002/hed.20456

18. Visvanathan V, Nix P. Managing the patient presenting with xerostomia: are view. Int J Clin Pract (2010) 64(3):404–7. doi:10.1111/j.1742-1241.2009.02132.x

19. Tribius S, Raguse M, Voigt C, Munscher A, Grobe A, Petersen C, et al. Residual deficits in quality of life one year after intensity-modulated radiotherapy for patients with locally advanced head and neck cancer: results of a prospective study. Strahlenther Onkol (2015) 191(6):501–10. doi:10.1007/s00066-015-0824-4

20. Dost F, Farah CS. Stimulating the discussion on saliva substitutes: a clinical perspective. Aust Dent J (2013) 58(1):11–7. doi:10.1111/adj.12023

21. Plemons JM, Al-Hashimi I, Marek CL. Managing xerostomia and salivary gland hypofunction: executive summary of a report from the American Dental Association Council on Scientific Affairs. J Am Dent Assoc (2014) 145(8):867–73. doi:10.14219/jada.2014.44.