Original Article

Determinants of Patient-Reported Xerostomia Among Long-Term Oropharyngeal Cancer Survivors

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BACKGROUND: This study was conducted to identify clinicodemographic risk factors for xerostomia among long-term oropharyngeal cancer (OPC) survivors. **METHODS:** This cross-sectional study included 906 disease-free, adult OPC survivors with a median survival duration at the time of survey of 6 years (range, 1-16 years); self-reported xerostomia scores were available for 877 participants. Study participants had completed curative treatment between January 2000 and December 2013 and responded to a survey administered from September 2015 to July 2016. The primary outcome variable was cancer patient–reported xerostomia measured with the MD Anderson Symptom Inventory Head and Neck Cancer Module. Clinicodemographic risk factors for moderate to severe xerostomia were identified via multivariable logistic regression. **RESULTS:** Moderate to severe xerostomia was reported by 343 of the respondents (39.1%). Female sex (odds ratio [OR], 1.82; 95% CI, 1.22-2.71; $P = .003$; Bayesian false-discovery probability [BFDP] = 0.568), high school or lower education (OR, 1.73; 95% CI, 1.19-2.52; $P = .004$; BFDP = 0.636), and current cigarette smoking at the time of survey (OR, 2.56; 95% CI, 1.19-5.47; $P = .016$; BFDP = 0.800) were risk factors for moderate to severe xerostomia, and bilateral intensity-modulated radiotherapy (IMRT) combined with proton therapy and ipsilateral IMRT were protective. **CONCLUSIONS:** In this large xerostomia study, modern radiotherapy was a protective factor, and continued cigarette smoking at the time of survey, female sex, and high school or lower education were identified as other contributing risk factors associated with moderate to severe xerostomia. Importantly, these findings need to be confirmed in prospective studies. These results can inform future research and targeted patient-centered interventions to monitor and manage radiation therapy–associated xerostomia and preserve quality of life among patients with OPC. ***Cancer* 2021;127:4470-4480**.

KEYWORDS: dry mouth, oropharyngeal cancer, survivorship, treatment-related effect, xerostomia.

INTRODUCTION

Xerostomia, also known as dry mouth, is a common acute and late treatment-associated symptom of radiotherapy (RT) and chemoradiotherapy (CRT). Xerostomia may develop because of salivary gland injury and reduced or absent salivary flow among patients with head and neck cancer (HNC).[1,2] Xerostomia may lead to oral problems, including pain, dysphagia, speech difficulty, a reduced or altered sense of taste, an increased risk of dental caries, infections, and osteoradionecrosis.[3] Xerostomia has been numbered among the top 5 most severely reported symptoms in patients with long-term oropharyngeal cancer (OPC).[4] Braam et al[5] demonstrated that 91.8% of patients with HNC (≥6 months after RT) reported xerostomia, and 64% of long-term (≥3 years after RT) HNC survivors reported moderate to severe xerostomia. Xerostomia has no effective treatment and can result in weight loss, reduced nutritional consumption, increased patient suffering, and poorer overall quality of life (QOL) among patients with HNC.[6]

Curative RT for HNC incorporates a high ionizing RT dose delivered to typically include the major salivary glands.[2] Such treatment may cause glandular injury and contribute to reduced salivary production and changes in saliva volume, consistency, and pH and thereby result in a sensation of dry mouth and thick, sticky saliva, which may be more acidic.[2,7-10] It is believed that a total RT dose > 52 Gy can contribute to a severe decline in saliva production,[6] although many patients can develop xerostomia with even lower doses.[11] As most patients with HNC receive a cumulative RT dose of 50 to 70 Gy to their tumors, the risk of developing xerostomia is exceptionally high if similar doses are delivered to the major salivary glands.[11] Modern RT techniques such as intensity-modulated radiotherapy (IMRT) attempt to minimize the salivary gland dose to reduce the severity of xerostomia, but it remains common after RT.[12] The RT dose, fraction,

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and fractionation schedule, the irradiated tissue volume, and the type of RT treatment can contribute to salivary tissue injury and xerostomia.[13] Furthermore, some chemotherapy drugs can also cause acute xerostomia during treatment by altering salivary composition and flow, and this may persist after treatment.[2]

In the United States, there has been a 5% annual increase in the incidence of human papillomavirus (HPV)–associated OPC in recent years.[14] This increase has contributed to a demographic of patients with OPC who are younger (often middle-aged) at diagnosis, have excellent prospects of a long-term cure, and are likely to survive decades after treatment.[14-17] It is important to note that HPV vaccination will contribute to lower numbers of patients with OPC in the future; however, it will take decades to realize such benefits. Notably, HPV vaccination rates are currently suboptimal in the United States.[18] Furthermore, projections suggest that by 2030, OPC will account for half of HNCs.[14] Therefore, there is a growing pool of younger patients with HNC at risk of xerostomia and other adverse effects after cancer treatment.[14]

Previous studies examining xerostomia have predominantly investigated RT regimens, RT dosimetric predictors, and QOL associations,[19-27] but few have comprehensively identified other clinical, demographic, non–RT-related risk factors of xerostomia easily accessible from electronic health records and have quantified their associations among OPC survivors. Therefore, the objective of this study was to identify risk factors for xerostomia among long-term OPC survivors. The identification of risk factors for xerostomia would allow the identification of high-risk populations that are most vulnerable and the future implementation of targeted risk-reduction strategies to alleviate xerostomia and improve QOL among OPC survivors.

MATERIALS AND METHODS

Materials and Methods: Study Population

This study included OPC survivors treated at The University of Texas MD Anderson Cancer Center from January 1, 2000, to December 31, 2013, who responded to a cross-sectional survivorship survey with a consent statement (n = 906; response rate = 56%) administered from September 9, 2015, to July 7, 2016. Eligible participants were at least 18 years old and had completed curative OPC treatment at least 1 year before survey administration. Patients who had a secondary primary malignancy or recurrent HNC before the survey's administration were excluded. Details are presented elsewhere.[4]

Survey Items

The MD Anderson Symptom Inventory Head and Neck Cancer Module (MDASI-HN) is a 28-item, multiple-symptom, validated, patient-reported outcome instrument that evaluates symptom severity and interference in patients with HNC.[28-32] The MDASI-HN includes 13 questions to assess core symptoms common across all cancers, 9 questions to assess HNC-specific symptoms, and 6 interference-specific questions to assess the impact of symptoms on daily function. Patients are asked to rate the severity of symptoms and interference on a scale of 0 to 10, with higher scores indicating more severe symptoms and limitations and lower QOL.[28-30,32] The MDASI-HN mean subscale scores have been shown to be internally consistent.[28-30,32]

Primary Outcome

The primary outcome variable for this study was cancer treatment–related xerostomia. Xerostomia was measured by a single question from the MDASI-HN:

> How severe are your symptoms? People with cancer frequently have symptoms that are caused by their disease or their treatment. We ask you to rate how severe the symptoms have been in the last 24 hours.

Patients were then asked to rate the severity of xerostomia via a question asking about their experience with "having dry mouth at its worst," with severity item scores ranging from 0 ("not present") to 10 ("as bad as you can imagine").[31] For clinical application and to identify predictors of moderate to severe xerostomia versus no to mild xerostomia, the primary outcome variable was dichotomized on the basis of the presence of moderate to severe symptoms, with scores from 0 to 4 indicating none to mild xerostomia symptoms and scores from 5 to 10 indicating moderate to severe xerostomia symptoms.[30,33-35]

Clinical and Sociodemographic Variables

The following clinical and treatment variables were abstracted from electronic medical records: T and N categories (American Joint Committee on Cancer, seventh edition); primary tumor subsite; treatment modality; RT dose, mode/type, and fractionation schedule; receipt of chemotherapy or surgery; solid food diet at the baseline (surrogate control for pretreatment oral dysfunction/symptoms); age at diagnosis; and HPV-positive or p16-positive status.

Primary head and neck tumor subsites included the tonsils, the base of tongue and glossopharyngeal sulcus, and others (including the soft palate, the pharyngeal wall, and an oropharynx site not otherwise specified). Primary

tumor T categories included T1 (including Tx), T2, T3, and T4 (including both T4a and T4b). Systemic therapy/chemotherapy included the use of any chemotherapy (induction, concurrent, and adjuvant) as a yes/no indicator. Any induction, any concurrent chemotherapy, and any induction in combination with concurrent chemotherapy was abstracted and coded as a yes/no variable. Concurrent chemotherapy drugs given concomitantly/at the same time with radiation treatment included high-dose cisplatin, weekly low-dose cisplatin, weekly carboplatin, weekly cetuximab, and other chemotherapy drugs (including treatment discontinuation, other drugs, and changes in treatment). Each of these drugs was coded into binary categories of receiving or not receiving the specific drug. Information on induction chemotherapy regimens, including paclitaxel, carboplatin, and cetuximab (PCC), docetaxel, cisplatin, and 5-flurouracil (TPF), cetuximab, docetaxel, cisplatin, and 5-flurouracil (CTPF), and other chemotherapy drugs, was also coded as a yes/no variable.

The survival time was defined as the number of years that a patient survived after his or her diagnosis and was calculated as the difference between the age at the time of survey and the age at the diagnosis of OPC. The cigarette smoking status was determined as follows: participants who had not smoked 100 cigarettes in their lifetime were classified as never smokers; those who had quit more than 6 months before their diagnosis were considered former smokers at the time of diagnosis[10,11]; and, finally, current smokers at the time of diagnosis were further categorized as those who quit subsequently and those who continued to smoke.[35]

The types of radiation regimens/modalities evaluated in our study included modern RT (bilateral IMRT with a split field or whole field, volumetric-modulated arc therapy, proton therapy, and ipsilateral IMRT regimens) and an older RT technique (3-dimensional conformal radiotherapy [3D-CRT]). The RT dose was the total radiation dose to the primary tumor and was measured in grays. The RT fractionation schedules included the following categories: standard fractionation (70.0 Gy given in 33-35 fractions), accelerated fractionation (72.0 Gy given in 40 fractions or the use of a concomitant boost or Danish Head and Neck Cancer Group RT regimens), and no RT. Finally, xerostomia during RT could be associated with long-term xerostomia and, therefore, was included as a covariate in our multivariable models.

Statistical Analysis

A descriptive analysis was conducted, and to test for differences between groups, the Kruskal-Wallis test was used for continuous variables, and the Fisher exact test was used for categorical variables. Missing data on the covariates HPV, education, and ethnicity were coded as a missing category in the multiple regression analysis, and this allowed us to retain all the data. Univariate and multivariable logistic regression analyses investigated relationships between sociodemographic and clinical variables and patient-reported xerostomia. Clinically important covariates defined a priori included age at diagnosis, survival time, T category, subsite, treatment modality, and smoking. Multicollinearity was assessed with the variance inflation factor being greater than 10. Testwise statistical significance was conferred at a 2-sided P value $\leq .05$. To account for multiple comparisons, investigators use Bonferroni correction; however, this approach has been shown to be too conservative. Therefore, to assess the noteworthiness of the observed association, we calculated the Bayesian false-discovery probability (BFDP). In the multiple-hypothesis-testing context, BFDP allows the false-discovery rate to be controlled. We calculated the BFDP value by using a prior probability of .05 for an association. We used the standard recommended threshold value of ≤ 0.8 for the BFDP for declaring an observed association to be noteworthy.[36,37] Analyses were conducted with Stata software (version 14.0: StataCorp). The study was approved by the MD Anderson Cancer Center institutional review board with use of a consent statement on the survey cover letter for informed consent of survey responders.

RESULTS

Sample Characteristics

Sample characteristics are summarized in Table 1. Our study sample included a total of 906 OPC survivors with a median age at diagnosis of 56 years (range, 32-84 years) and a median survival duration at the time of survey of 6.0 years (range, 1-16 years). Among the participants, 766 (84.6%) were male, 837 (92.4%) were non-Hispanic White, 620 (68.4%) received chemotherapy, 25 were treated with definitive surgery (2.8%), and 898 were treated with RT (99.1%). Self-reported xerostomia scores were available for 877 OPC survivors; 343 of these survivors (39.1%) reported moderate to severe xerostomia. Higher percentages of survivors who were treated with 3D-CRT (29 of 49; 59.2%) reported moderate to severe xerostomia versus none to mild xerostomia. Interestingly, a greater proportion of patients who received concurrent weekly carboplatin chemotherapy (44 of 84; 52.4%) reported moderate to severe xerostomia, whereas a greater proportion of patients who received weekly cetuximab

TABLE 1. Characteristics and Distributions of Patients With OPC by Clinicodemographic Factors (n = 906)

Variable	All Patients With OPC (n = 906)	Xerostomia			*P*
		Information Missing (n = 29)	None to Mild (n = 534)	Moderate to Severe (n = 343)	
Age at diagnosis, median (range, IQR), (mean ± SD), y	56 (32-84, 51-63), (56.9 ± 8.8)	—	56 (32-84, 51-62), (56.7 ± 9.0)	56 (33-82, 51-63), (57.1 ± 8.7)	.641
Survival time, median (range, IQR), (mean ± SD), y	6 (1-16, 4-10), (7.0 ± 3.9)	—	7 (2-16, 4-10), (7.1 ± 3.8)	6 (1-16, 4-10), (6.9 ± 4.0)	.398
Radiation dose, median (range, IQR), (mean ± SD), Gy[a]	70 (40-72.6, 66-70), (68.1 ± 2.6)	—	69.2 (57-72, 66-70), (68.0 ± 2.5)	70.0 (40-72.6, 66-70), (68.3 ± 2.8)	.103
Sex, No. (%)					.007
Female	140 (15.5)	8	66 (50.0)	66 (50.0)	
Male	766 (84.6)	21	468 (62.8)	277 (37.2)	
Education, No. (%)					.004
>High school	650 (71.7)	18	406 (64.2)	226 (35.8)	
≤High school	171 (18.9)	8	83 (50.9)	80 (49.1)	
Missing	85 (9.4)	3	45 (54.9)	37 (45.1)	
Race/ethnicity, No. (%)					.817
Non-Hispanic White	837 (92.4)	25	494 (60.8)	318 (39.2)	
Non-Hispanic Black	17 (1.9)	1	10 (62.5)	6 (37.5)	
Hispanic	35 (3.8)	2	22 (66.7)	11 (33.3)	
Other	8 (0.9)	1	3 (42.9)	4 (57.1)	
Missing	9 (1.0)	0	5 (55.6)	4 (44.4)	
Primary site, No. (%)					.779
Tonsil	418 (46.1)	11	253 (62.2)	154 (37.8)	
Base of tongue + GPS	456 (50.3)	17	262 (59.7)	177 (40.3)	
Other	32 (3.5)	1	19 (61.3)	12 (38.7)	
T classification, No. (%)[b]					.171
1	335 (37.0)	16	202 (63.3)	117 (36.7)	
2	349 (38.5)	6	211 (61.5)	132 (38.5)	
3	134 (14.8)	3	79 (60.3)	52 (39.7)	
4	88 (9.7)	4	42 (50.0)	42 (50.0)	
N classification, No. (%)					.190
0	83 (9.2)	3	51 (63.8)	29 (36.3)	
1 + 2a	239 (26.4)	8	146 (63.2)	85 (36.8)	
2b + 3	434 (47.9)	10	262 (61.8)	162 (38.2)	
2c	150 (16.6)	8	75 (52.8)	67 (47.2)	
HPV status, No. (%)					.540
Negative	58 (6.4)	2	32 (57.1)	24 (42.8)	
Positive	440 (48.6)	14	254 (59.6)	172 (40.4)	
Unknown	408 (45.0)	13	248 (67.8)	147 (37.2)	
Cigarette smoking, No. (%)					.029
Never	420 (46.3)	12	252 (61.8)	156 (38.2)	
Former smoker at time of diagnosis	343 (37.9)	9	212 (63.5)	122 (36.5)	
Quit smoking subsequent to diagnosis	95 (10.5)	6	51 (57.3)	38 (42.7)	
Current smoker	36 (4.0)	2	12 (35.3)	22 (64.7)	
Don't know	12 (1.3)	0	7 (58.3)	5 (41.7)	
Solid food before treatment, No. (%)[c]					.759
Yes	894 (98.7)	28	528 (61.0)	338 (39.0)	
No	12 (1.3)	1	6 (54.6)	5 (45.4)	
Treatment group, No. (%)					.155
Single modality	280 (30.9)	9	175 (64.6)	96 (35.4)	
Multimodality	626 (69.1)	20	359 (59.2)	247 (40.8)	
Treatment group, No. (%)					.069
RT alone	272 (30.0)	9	167 (63.5)	96 (36.5)	
Surgery alone	8 (0.9)	0	8 (100.0)	0 (0.0)	
RT plus systemic	610 (67.3)	19	350 (59.2)	241 (40.8)	
Surgery plus adjuvant	16 (1.8)	1	9 (60.0)	6 (40.0)	
Chemotherapy, No. (%)					.118
No	286 (31.6)	10	179 (64.9)	97 (35.1)	
Yes	620 (68.4)	19	355 (59.1)	246 (40.9)	
Surgery, No. (%)					.110
No	881 (97.2)	28	516 (60.5)	337 (39.5)	
Yes—robotic	18 (2.0)	0	15 (83.3)	3 (16.7)	
Yes—open	7 (0.8)	1	3 (50.0)	3 (50.0)	
Neck dissection, No. (%)					.203
No	679 (74.9)	22	392 (59.7)	265 (40.3)	

TABLE 1. *Continued*

Variable	All Patients With OPC (n = 906)	Xerostomia			*P*
		Information Missing (n = 29)	None to Mild (n = 534)	Moderate to Severe (n = 343)	
Yes	227 (25.1)	7	142 (64.5)	78 (35.5)	
RT, No. (%)					.026
No	8 (0.9)	0	8 (100.0)	0 (0.0)	
Yes	898 (99.1)	29	526 (60.5)	343 (39.5)	
RT schedule, No. (%)[d]					.045
Standard fractionation	798 (88.1)	25	471 (60.9)	302 (39.1)	
Accelerated	100 (11.0)	4	55 (57.3)	41 (42.7)	
Missing/no RT	8 (0.9)	0	8 (100.0)	0 (0)	
RT type, No. (%)[e]					<.001
3D conformal	51 (5.6)	2	20 (40.8)	29 (59.2)	
Bilateral IMRT (SF + WF + VMAT) + proton	747 (82.5)	21	438 (60.3)	288 (39.7)	
Ipsilateral IMRT	100 (11.0)	6	68 (72.3)	26 (26.7)	
Missing/no RT	8 (0.9)	0	8 (100.0)	0 (0.0)	
Induction chemotherapy, No. (%)					.047
No	609 (67.2)	21	372 (63.3)	216 (36.7)	
Yes	297 (32.8)	8	162 (56.1)	127 (43.9)	
Concurrent chemotherapy, No. (%)					.298
No	418 (46.1)	15	253 (62.8)	150 (37.2)	
Yes	488 (53.9)	14	281 (59.3)	193 (40.7)	
Induction and concurrent chemotherapy, No. (%)					.075
No	739 (81.6)	25	445 (62.3)	269 (37.7)	
Yes	167 (18.4)	4	89 (54.6)	74 (45.4)	
Concurrent high-dose cisplatin, No. (%)					.375
No	809 (89.3)	27	472 (60.4)	310 (39.6)	
Yes	97 (10.7)	2	62 (65.3)	33 (34.7)	
Concurrent low-dose cisplatin weekly, No. (%)					.195
No	779 (86.0)	25	466 (61.8)	288 (38.2)	
Yes	127 (14.0)	4	68 (55.3)	55 (44.7)	
Concurrent carboplatin weekly, No. (%)					.010
No	820 (90.5)	27	494 (62.3)	299 (37.7)	
Yes	86 (9.5)	2	40 (47.6)	44 (52.4)	
Concurrent cetuximab weekly, No. (%)					.095
No	754 (83.2)	23	436 (59.6)	295 (40.4)	
Yes	152 (16.8)	6	98 (67.1)	48 (32.9)	
Xerostomia during RT, No. (%)					.285
No	257 (28.4)	8	149 (59.8)	100 (40.2)	
Yes	637 (70.3)	21	375 (60.9)	241 (39.1)	
Missing/no RT	12 (1.3)	0	10 (83.3)	2 (16.7)	

Abbreviations: 3D, 3-dimensional; GPS, glossopharyngeal sulcus; HPV, human papillomavirus; IMRT, intensity-modulated radiotherapy; IQR, interquartile range; MDASI-HN, MD Anderson Symptom Inventory Head and Neck Cancer Module; OPC, oropharyngeal cancer; RT, radiotherapy; SF, split field; VMAT, volumetric-modulated arc therapy; WF, whole field.

One patient was excluded because the MDASI-HN was not filled out. Twenty-nine patients did not answer the xerostomia question on the MDASI-HN. Self-reported xerostomia scores were available for 877 participants.

[a]The RT dose was the total radiation dose measured in grays.

[b]Primary tumor T categories included T1 (including Tx), T2, T3, and T4 (including both T4a and T4b).

[c]A solid food diet before treatment was controlled for as a surrogate control for pretreatment oral dysfunction/symptoms.

[d]The RT fractionation schedules included standard fractionation (70.0 Gy given in 33-35 fractions), accelerated fractionation (72.0 Gy given in 40 fractions or the use of a concomitant boost or Danish Head and Neck Cancer Group RT regimens), and no RT.

[e]The RT types included 3D conformal RT; bilateral IMRT with SF or WF, VMAT, and proton therapy; and ipsilateral IMRT regimens.

concurrently with RT (98 of 146; 67.1%) reported none to mild xerostomia. Furthermore, a total of 36 of 906 patients with OPC (4.0%) were current cigarette smokers at the time of survey, and 22 of 34 patients (64.7%) reported moderate to severe xerostomia on the survey.

Univariate and multivariable analysis results are summarized in Table 2. Variables adjusted for in the multivariable analysis included the following: age at diagnosis, RT dose, survival time, sex, race, education, subsite, T stage, N stage, HPV, cigarette smoking, solid food diet at the baseline, treatment modality, chemotherapy, surgery, neck dissection, RT schedule, RT type, and xerostomia during RT. Multicollinearity was evaluated and was found not to be a concern. Multivariable

TABLE 2. Multivariable Logistic Regression Analysis Assessing the Relationship Between Clinicodemographic Variables and Patient-Reported Moderate to Severe Xerostomia

Variable	Univariate OR	95% CI	Univariate *P*	Multivariable OR	95% CI	Multivariable *P*	BFDP
Age at diagnosis, y	1.00	0.99-1.02	.563	1.00	0.99-1.02	.605	0.999
Survival time, y	0.99	0.95-1.02	.517	0.98	0.92-1.05	.584	0.997
Radiation dose, Gy	1.04	0.98-1.10	.169	0.99	0.92-1.06	.711	0.998
Sex			.006				
Male	Reference			Reference			
Female	1.69	1.16-2.45	.006	1.82	1.22-2.71	.003	0.568
Education			.004				
>High school	Reference			Reference			
≤High school	1.73	1.22-2.45	.002	1.73	1.19-2.52	.004	0.636
Race/ethnicity							
Non-Hispanic White	Reference			Reference			
Non-Hispanic Black	0.93	0.34-2.59	.893	0.74	0.24-2.24	.594	0.968
Hispanic	0.78	0.37-1.62	.502	0.72	0.34-1.56	.410	0.971
Other	2.07	0.46-9.32	.343	1.98	0.41-9.54	.394	0.958
Subsite			.760				
Tonsil	Reference			Reference			
Base of tongue + GPS	1.11	0.84-1.46	.460	1.02	0.74-1.4	.901	0.990
Other	1.04	0.49-2.20	.923	0.87	0.39-1.92	.724	0.976
T classification			.175				
1	Reference			Reference			
2	1.08	0.79-1.48	.632	1.01	0.69-1.46	.973	0.988
3	1.14	0.75-1.73	.548	0.87	0.51-1.47	.594	0.982
4	1.73	1.06-2.80	.027	1.32	0.72-2.43	.374	0.974
N classification			.191				
0	Reference			Reference			
1 + 2a	1.02	0.60-1.74	.930	1.10	0.61-1.98	.752	0.981
2b + 3	1.09	0.66-1.79	.741	1.07	0.60-1.88	.825	0.982
2c	1.57	0.90-2.76	.115	1.33	0.71-2.5	.380	0.974
HPV status			.546				
Negative	Reference			Reference			
Positive	0.90	0.51-1.59	.722	1.17	0.62-2.18	.630	0.979
Unknown	0.79	0.45-1.39	.416	0.96	0.51-1.83	.905	0.981
Cigarette smoking							
Never	Reference			Reference			
Former smoker at time of diagnosis	0.93	0.69-1.25	.632	0.91	0.66-1.25	.565	0.988
Quit smoking subsequent to diagnosis	1.20	0.76-1.92	.435	1.05	0.63-1.73	.856	0.984
Current smoker	2.96	1.43-6.15	.004	2.56	1.19-5.47	.016	0.800
Don't know	1.15	0.36-3.70	.810	1.19	0.36-3.98	.772	0.969
Solid food before treatment			.667				
No	0.77	0.23-2.54	.665	Reference			
Yes	Reference			0.95	0.25-3.54	.940	0.968
Treatment group			.133				
Single modality	Reference			Reference			
Multimodality	1.25	0.93-1.69	.135	0.80	0.12-5.58	.824	0.961
Chemotherapy			.102				
No	Reference			Reference			
Yes	1.28	0.95-1.72	.103	1.22	0.18-8.23	.838	0.961
Surgery			.098				
No	Reference			Reference			
Yes—robotic	0.31	0.09-1.07	.063	0.49	0.10-2.31	.368	0.957
Yes—open	1.53	0.31-7.63	.603	3.01	0.42-21.42	.272	0.951
Neck dissection			.393				
No	Reference			Reference			
Yes	0.81	0.59-1.12	.200	0.86	0.6-1.22	.395	0.985
RT schedule			.493				
Standard fractionation	Reference			Reference			
Accelerated	1.16	0.76-1.79	.492	0.99	0.55-1.79	.983	0.982
RT type			.001				
3D-CRT	Reference			Reference			
Bilateral IMRT (SF + WF + VMAT) + proton	0.45	0.25-0.82	.008	0.35	0.16-0.73	.006	0.641
Ipsilateral IMRT	0.26	0.13-0.55	<.001	0.19	0.07-0.47	<.001	0.223
Xerostomia during RT				0.226			
No	Reference			Reference			
Yes	0.96	0.71-1.29	.777	0.99	0.72-1.36	.937	0.990

Abbreviations: 3D-CRT, 3-dimensional conformal radiotherapy; BFDP, Bayesian false-discovery probability; GPS, glossopharyngeal sulcus; HPV, human papillomavirus; IMRT, intensity-modulated radiotherapy; OR, odds ratio; RT, radiotherapy; SF, split field; VMAT, volumetric-modulated arc therapy; WF, whole field. Statistical significance was set at $P \leq .05$. BFDP ≤ 0.8 indicated noteworthy associations.

TABLE 3. Multivariable Regression Analysis Assessing the Relationship Between Concurrent Carboplatin Weekly and Concurrent Cetuximab Weekly and Patient-Reported Moderate to Severe Xerostomia

Variable	Univariate OR	95% CI	Univariate *P*	Multivariable OR	95% CI	Multivariable *P*	BFDP
Concurrent carboplatin weekly							
No	Reference						
Yes	1.82	1.16-2.85	.010	1.66	1.00-2.75	.052	0.916
Concurrent cetuximab weekly							
No	Reference						
Yes	0.72	0.50-1.05	.092	0.61	0.40-0.94	.027	0.876

Abbreviations: BFDP, Bayesian false-discovery probability; OR, odds ratio; RT, radiotherapy.
All models controlled for the following: age at diagnosis, RT dose, survival time, sex, race, education, subsite, T stage, N stage, human papillomavirus, cigarette smoking at diagnosis and survey, solid food diet at the baseline, treatment modality, chemotherapy, surgery, neck dissection, RT schedule, RT type, and xerostomia during RT. Statistical significance was set at $P \leq .05$. BFDP ≤ 0.8 indicated noteworthy associations.

logistic regression identified female sex (odds ratio [OR], 1.82; 95% CI, 1.22-2.71; $P = .003$; BFDP = 0.568), a high school or lower education level (OR, 1.73; 95% CI, 1.19-2.52; $P = .004$; BFDP = 0.636), and current cigarette smoking at the time of survey (OR, 2.56; 95% CI, 1.19-5.47; $P = .016$; BFDP = 0.800) as risk factors that increased the odds of developing moderate to severe xerostomia. Furthermore, bilateral IMRT combined with proton therapy (OR, 0.35; 95% CI, 0.16-0.73; $P = .006$; BFDP = 0.641) and ipsilateral IMRT (OR, 0.19; 95% CI, 0.07-0.47; $P < .001$; BFDP = 0.223) were protective factors that decreased the odds of developing moderate to severe xerostomia. Furthermore, single-item xerostomia scores were also moderately correlated with single-item swallowing scores on the MDASI-HN (Spearman $\rho = 0.557$; $P < .001$). No statistically significant interactions were identified. Xerostomia during RT was also not significantly associated with moderate to severe xerostomia in the univariate analysis (OR, 0.96; 95% CI, 0.71-1.29; $P = .777$) or the multivariable analysis (OR, 0.99; 95% CI, 0.72-1.36; $P = .937$; BFDP = 0.990).

Multivariable logistic regression identified concurrent weekly cetuximab chemotherapy (OR, 0.61; 95% CI, 0.40-0.94; $P = .027$; BFDP = 0.876) as a protective factor that decreased the odds of developing moderate to severe xerostomia; however, this association was not statistically significant after adjustments for multiple comparisons (Table 3). Multivariable adjusted associations between other concurrent chemotherapy drugs, induction chemotherapy regimens, and moderate to severe xerostomia were also assessed but not statistically significant.

DISCUSSION

This large xerostomia study provided a quantitative assessment of risk factors associated with moderate to severe patient-reported xerostomia among long-term OPC survivors. Among OPC survivors, approximately 40% reported moderate to severe xerostomia, and current smoking at the time of survey, being female, and having a high school or lower education were key risk factors of moderate to severe xerostomia. Furthermore, modern RT regimens, including bilateral IMRT combined with proton therapy and ipsilateral IMRT, had a protective effect on moderate to severe xerostomia. Most adjusted effect estimates of association for xerostomia varied across subgroups (ie, T stage, smoking status, and RT regimens), as would be expected by clinical performance. Survivors with T4 tumors had higher odds of reporting moderate to severe xerostomia than those with T1 tumors, and this was expected because advanced bulky tumors are likely to be treated with larger RT fields, which may include healthy salivary tissues, cause greater damage to salivary glands, and result in more severe xerostomia. Additionally, newer RT regimens that maximize sparing of salivary glands and organs at risk, including IMRT and proton therapy, contributed to less severe xerostomia.

Concurrent weekly cetuximab chemotherapy was associated with xerostomia at the testwise significance level (ie, $P \leq .05$) in our study population, although this association was not significant after adjustments for multiple comparisons. Clinicians may believe that cetuximab can cause mucositis, which may contribute to xerostomia; however, it is possible that the acute mucositis observed with cetuximab during RT may not translate to long-term chronic xerostomia. The De-ESCALaTE (Determination of Cetuximab Versus Cisplatin Early and Late Toxicity Events in HPV+ OPSCC) HPV trial demonstrated that patients treated with cetuximab CRT had acute and late severe grade 3 to 5 toxicities and swallowing function but were not significantly different from those treated with cisplatin CRT.[38] A previous study demonstrated that the addition of cetuximab to cisplatin and RT among patients with HNC resulted in a lower frequency of xerostomia both during CRT and at the end of CRT in comparison with those treated with RT plus cisplatin,

although these findings were not statistically significant.[39] Nonetheless, one may hypothesize that these are mechanistically plausible because of the possible induction of an elevated immune response by cetuximab and less RT treatment–related injury, including xerostomia.[40] Nevertheless, the role of cetuximab in xerostomia should be further investigated.

Our study also identified continued smoking after the diagnosis and treatment of OPC as a significant risk factor for moderate to severe xerostomia among OPC survivors even after adjustments for clinicodemographic factors. Our results are consistent with a previous study of patients with HNC demonstrating that smokers reported worse QOL outcomes and worse HNC symptoms, including dry mouth, in comparison with never smokers.[41] Furthermore, multiple authors have shown that smoking contributes to worse QOL scores among patients with HNC both during and after treatment.[42-44] Lastly, biological pathways that explain how smoking can contribute to xerostomia and an increased symptom burden are not known; however, smoking broadly can cause damage to the irradiated oral mucosa and head and neck region, which may result in xerostomia and other adverse treatment-related outcomes.

Female sex was found to be a significant risk factor for xerostomia in our study population. To our knowledge, this is a novel finding. Studies of patients with HNC at different points during treatment, including at the baseline, during RT, and 6 months and 1 year after RT, have demonstrated that females report more overall symptoms, including pain, fatigue, and depressive symptoms; worse mental, social, physical, and functional impairment; and worse QOL in comparison with males.[42,45-47] Females' reporting worse xerostomia symptoms in our study is plausible because of possible gender-related differences such as biological differences in symptom sensation and the descriptive aptitude of symptoms.[48,49] Additionally, women may be more vigilant to changes in symptoms and overall health, engage in preventive health strategies, be socially more open to reporting symptoms, and respond to chronic symptoms such as xerostomia with more psychological distress and, therefore, report more frequent and intense overall symptoms, including xerostomia and diminished QOL.[49] These factors may individually or collectively play a role in sex-related differences in the perception, reporting, and management/access of patient-reported xerostomia and QOL among patients with cancer.[48,49]

To our knowledge, this is the first study to report an association between education and xerostomia among patients with HNC; however, because of the observational nature of the study, the results should be interpreted with care. A population-based, longitudinal cohort study of patients with HNC demonstrated that a lower education level was significantly associated with worse physical, emotional, and functional well-being and increased HNC symptoms on posttreatment follow-up.[50] It has been suggested that a lower education level may be associated with worse health care access, poor social support networks, and low health literacy of strategies to alleviate symptoms; all of these may contribute to the perception of more intense symptoms and diminished health-related QOL after treatment.[50,51]

It is not surprising that OPC survivors who received more conformal bilateral IMRT and proton therapy and ipsilateral IMRT were less likely than survivors who received older 3D-CRT regimens to report moderate to severe xerostomia. IMRT minimizes radiation exposure to neighboring healthy tissues and critical structures, especially organs at risk such as the salivary glands, oral mucosa, spinal cord, brainstem, and optic pathways.[52] Proton therapy is superior to IMRT because of dosimetric advantages such as enhanced RT-dose deposition beams, which may contribute even more conformal irradiation and maximize sparing of critical anatomic structures.[22,53] Lastly, because ipsilateral IMRT maximizes contralateral salivary gland sparing in comparison with intermediate salivary gland sparing via conventional IMRT, ipsilateral IMRT was the RT regimen with the greatest protective effect in the current study.[21]

This research can inform the development of multidisciplinary xerostomia surveillance, treatment, and supportive management interventions, which are critical to address the xerostomia symptom burden across the continuum of long-term OPC cancer survivorship and care, especially in more socially disadvantaged populations. Longitudinal surveillance strategies can consider the use of patient-reported outcomes for the screening and identification of individuals at risk of xerostomia for the implementation of early supportive interventions.[54] Supportive rehabilitation interventions for xerostomia can include mealtime alternating food/liquid strategies, meal preparation strategies, health education and counselling efforts to encourage healthy coping to adjust patients' expectations for changes in their oral function and oral microbiome, and nutritional supportive therapy to minimize malnutrition and weight loss.[55,56]

There are limitations to our study that must be acknowledged. The study design may have contributed to a survival bias; however, the age at diagnosis and the

survival times were adjusted in our analyses. The study may also have been affected by a possible nonresponse bias, although the limited characteristics evaluated between nonrespondents and respondents were similar. Our observational study results also may have been influenced by an imbalance of some of the categorical variables. Xerostomia was measured as a patient-reported outcome from a single question of the MDASI-HN that asked about dry mouth symptoms. Importantly, Kamal et al[57] showed that this single dry mouth question in the MDASI-HN has a high correlation ($\rho = 0.80$; $P < .001$) with a composite score based on another xerostomia instrument that uses 8 items.[58] Furthermore, information on baseline xerostomia or salivary gland dysfunction information was lacking. However, multivariable models controlled for patients' pretreatment ability to eat a solid-food diet as a surrogate to control for baseline dysphagia and oral dysfunction. Because chemotherapy regimens, drugs, dosages, and completion rates may vary, assessments of chemotherapy may have some limitations that we addressed by adjusting our models for any chemotherapy treatment given to patients. There may be some lack of generalizability of these study findings because the study was conducted at a single tertiary cancer care institution, but the sample characteristics are representative of the current trends of patients with OPC in the United States.

In conclusion, in this large xerostomia study, approximately 40% of OPC survivors reported moderate to severe xerostomia. Our study found modern radiation treatments to be protective factors for moderate to severe xerostomia. Furthermore, continued smoking, female sex, and lower education were identified as additional contributing factors for moderate to severe xerostomia. Concurrent cetuximab CRT and its correlation with xerostomia need to be further investigated in future longitudinal studies. Among patients with OPC, xerostomia has a devastating impact on physical, psychological, and social QOL, especially because late RT-associated xerostomia is irreversible and permanent. Therefore, it is imperative to investigate and develop targeted, multidisciplinary, patient-centered OPC care interventions to monitor and manage RT-associated xerostomia and its oral sequelae across the cancer continuum and preserve QOL among patients with OPC. Continued smoking among patients with OPC is a highly prominent modifiable risk factor that potentially can be addressed by sustained targeted smoking cessation efforts through the OPC survivorship continuum. Lastly, the number of OPC survivors continues to grow, with patients likely to survive decades after treatment. Addressing xerostomia in this patient population is a priority.

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

Puja Aggarwal: Substantial contributions to the study conception or design; data management, supervision of analysis, and interpretation; drafting of the manuscript and manuscript revisions; and contributions to the final version of the manuscript. **Katherine A. Hutcheson:** Responsibility for data collection, project integrity, data collection infrastructure, programmatic oversight, and direct oversight of classified personnel; substantial contributions to the study conception or design or the acquisition or interpretation of data; critical revision of the manuscript for important intellectual content; and contributions to the final version of the manuscript. **Adam S. Garden:** Clinical data interpretation and analytic support, substantial contributions to the manuscript and critical revision for important intellectual content, and contributions to the final version of the manuscript. **Frank E. Mott:** Clinical data interpretation and analytic support, substantial contributions to the manuscript and critical revision for important intellectual content, and contributions to the final version of the manuscript. **Charles Lu:** Clinical data interpretation and analytic support, substantial contributions to the manuscript and critical revision for important intellectual content, and contributions to the final version of the manuscript. **Ryan P. Goepfert:** Clinical data interpretation and analytic support, substantial contributions to the manuscript and critical revision for important intellectual content, and contributions to the final version of the manuscript. **Clifton D. Fuller:** Clinical data interpretation and analytic support, substantial contributions to the manuscript and critical revision for important intellectual content, and contributions to the final version of the manuscript. **Stephen Y. Lai:** Clinical data interpretation and analytic support, substantial contributions to the manuscript and critical revision for important intellectual content, and contributions to the final version of the manuscript. **G. Brandon Gunn:** Clinical data interpretation and analytic support, substantial contributions to the manuscript and critical revision for

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