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Determinants of patient-reported xerostomia among long-term oropharyngeal cancer survivors

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Abstract

Background: This study was conducted to identify clinicodemographic risk factors for xerostomia among long-term oropharyngeal carcinoma (OPC) survivors.

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Conflicts of Interest: The funding source had no role in the design and conduct of the study; data collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Methods: This cross-sectional study included 906 disease-free, adult OPC survivors with median survival duration at time of survey of 6 years (range;1–16 years) of which 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 using MD Anderson Symptom Inventory Head and Neck Cancer Module. Clinico-demographic risk factors for moderate to severe xerostomia were identified using multivariable logistic regression.

Results: Moderate to severe xerostomia was reported by 343 (39.1%) of respondents. Female sex (OR:1.82, 95%CI:1.22–2.71, *P*=0.003, BFDP= 0.568), high school or lower education (OR:1.73, 95%CI:1.19–2.52, *P*=0.004, BFDP= 0.636) and current cigarette smoking at time of survey (OR: 2.56; 95% CI: 1.19–5.47; *P*= 0.016, 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 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 RT-associated xerostomia and preserve QoL among OPC patients.

Precis:

Xerostomia is a common cancer treatment-associated oral morbidity which can contribute to increased patient suffering and poorer overall quality of life among head and neck cancer patients. In the current study modern radiotherapy was a protective factor and continued cigarette smoking at 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.

Keywords

xerostomia; dry mouth; oropharyngeal cancer; survivorship; treatment-related effect

Introduction

Xerostomia, also known as dry mouth, is a common acute and late treatment-associated symptom of radiation therapy (RT) and chemoradiotherapy (CRT). Xerostomia may develop due to salivary gland injury and reduced or absent salivary flow among head and neck cancer (HNC) patients.[1,2] Xerostomia may lead to oral problems including pain, dysphagia, speech difficulty, reduced or altered sense of taste, increased risk of dental caries, infections, and osteoradionecrosis.[3] Xerostomia has been reported among the top 5 most severely reported symptoms in long-term oropharyngeal cancer (OPC) patients.[4] Braam et al. demonstrated that 91.8% of HNC patients (≥ 6 months post-RT) reported xerostomia and 64% of long-term (≥ 3 years post-RT) HNC cancer survivors reported moderate to severe xerostomia.[5] 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 HNC patients.[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 change in saliva volume, consistency, and pH, thereby resulting 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 severe decline in saliva production,[6] though many patients can develop xerostomia with even lower doses.[11] As most HNC patients receive a cumulative RT dose of 50–70 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 IMRT attempt to minimize salivary gland dose to reduce the severity of xerostomia, but it remains a common post-RT.[12] RT dose, fraction, fractionation schedule, irradiated tissue volume, and type of RT treatment can contribute to salivary tissue injury and xerostomia.[13] Further, some chemotherapy drugs can also cause acute xerostomia during treatment by altering salivary composition and flow, and may persist post-treatment.[2]

In the United States there has been a 5% annual increase in incidence of human papillomavirus (HPV)-associated OPC in recent years.[14] This increase has contributed to a demographic of OPC patients who are younger, often middle-aged, at diagnosis; have excellent prospects of 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 OPC patients in the future, however, it will take decades to realize such benefits. Of note, HPV vaccination rates are currently suboptimal in the United States.[18] Further, projections suggest that by 2030 OPC will account for half of HNCs.[14] Therefore, there is a growing pool of younger HNC patients 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 treatment-related risk factors of xerostomia easily accessible from electronic health records and quantified their associations among OPC survivors. Therefore, the objective of this study was to identify risk factors of xerostomia among long-term OPC survivors. Identification of risk factors of xerostomia would allow identification of high-risk populations who are most vulnerable and future implementation of targeted risk-reduction strategies to alleviate xerostomia and improve QoL among OPC survivors.

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 symptoms, validated, patient-reported outcome (PRO) instrument that evaluates symptom severity and interference in HNC patients.[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 severity of symptoms and interference on a scale of 0 to 10, with higher scores indicating more severe symptoms, limitations, and lower QoL.[28–30,32] The MDASI-HN's 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 based on the following question asking their experience with *"having dry mouth at its worst"* with severity item scores range from 0 to represent *"not present"* to 10 to represent *"as bad as you can imagine."*[31] For clinical application and to identify predictors of moderate to severe versus none to mild xerostomia the primary outcome variable was dichotomized based on presence of moderate to severe symptoms, with scores from 0 to 4 indicating no to mild xerostomia symptoms and scores from 5 to 10 indicating moderate to severe xerostomia symptoms.[30,33–35]

Clinical and sociodemographic variables

Clinical and treatment variables including T and N categories (American Joint Committee on Cancer version VII); primary tumor sub-site; treatment modality; RT dose, mode/type, and fractionation schedule; receipt of chemotherapy or surgery; and solid food diet at baseline (surrogate control for pre-treatment oral dysfunction/symptoms), age at diagnosis, and HPV-positive or p16-positive status were abstracted from electronic medical records.

Primary head and neck tumor subsites included tonsil, base of tongue and glossopharyngeal sulcus, and others (including soft palate, pharyngeal wall, and 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, 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 discontinued treatment, other drugs, changed treatment). Each of these drugs were coded into binary categories as receiving or not receiving the specific drug.

Information on Induction chemotherapy regimens including PCC (Paclitaxel, Carboplatin, and Cetuximab), TPF (Docetaxel, Cisplatin, and 5-Flurouracil), CTPF (Cetuximab, Docetaxel, Cisplatin, and 5-Flurouracil), and other chemotherapy drugs were also coded as a yes/no variable.

Survival time was defined as the number of years a patient survived after diagnosis and was calculated as the difference between age at time of survey and age at diagnosis of OPC. 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 diagnosis were considered former smokers at the time of diagnosis[10, 11], finally, current smokers at the time of diagnosis were further categorized into those who quit subsequently and those who continued to smoke.[35]

Types of radiation regimens/modalities evaluated in our study included modern RT: bilateral intensity modulated RT (IMRT) with split-field (IMRT-SF), whole-field (IMRT-WF), volumetric-modulated arc therapy (VMAT), proton therapy, and ipsilateral IMRT regimens and older RT technique: 3-dimensional conformal RT (3D-CRT) RT dose was total radiation dose to primary tumor and measured in Gray (Gy). RT fractionation schedule included the following categories; standard fractionation (70.0 Gy given in 33–35 fractions), accelerated fractionation (72.0 Gy given in 40 fractions or use of 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 therefore was included as a covariate in our multivariable models.

Statistical Analysis

Descriptive analysis was conducted, and to test for differences between groups, the Kruskal Wallis test was used for continuous variables and Fisher exact test was used for categorical variables. Missing Data on covariates HPV, education, and ethnicity was coded as a “missing” category in the multiple regression analysis allowing us to retain all the data. Univariate and multivariable logistic regression analysis 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 using the variance inflation factor being greater than 10. Test-wise statistical significance was conferred at 2-sided $P \leq .05$. To account for multiple comparisons, investigators use Bonferroni correction, however, this approach has been shown to be too conservative. Therefore, to assess noteworthiness of the observed association, we calculated Bayesian false-discovery probability (BFDP). In the multiple hypothesis-testing context, BFDP allows the false-discovery rate to be controlled. We calculated BFDP value using a prior probability of 0.05 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] Analysis was conducted using Stata software, version 14.0 (StataCorp).

Results

Sample Characteristics

Sample characteristics are summarized in Table 1. Our study sample included a total of 906 OPC survivors with median age at diagnosis of 56 (range, 32–84) years and a median survival duration at 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. Of these, 343 (39.1%) reported moderate to severe xerostomia. Higher percentages of survivors who were treated with 3D-CRT 29/49 (59.2%) reported moderate to severe versus none to mild xerostomia scores. Interestingly, greater proportion of patients who received concurrent weekly carboplatin chemotherapy (44/84; 52.4%) reported moderate to severe xerostomia, whereas greater proportion (98/146; 67.1%) of patients who received cetuximab weekly dose given concurrently with RT reported none to mild xerostomia. Further, a total of 36/906 (4.0%) of OPC patients were current cigarette smokers at time of survey of which 22/34 (64.7%) reported moderate to severe xerostomia on the survey.

Univariate and multivariable analysis results are summarized in Table 2. Variables adjusted for in multivariable analysis included age at diagnosis, RT dose, survival time, sex, race, education, subsite, T-stage, N-stage, HPV, cigarette smoking, solid food diet at baseline, treatment modality, chemotherapy, surgery, neck dissection, RT Schedule, RT Type, and xerostomia during RT. Multicollinearity was evaluated and was found to be not a concern. Multivariable logistic regression identified female sex (OR: 1.82, 95%CI: 1.22–2.71, P=0.003, BFDP= 0.568) and high school or lower education level (OR: 1.73, 95%CI: 1.19–2.52, P=0.004, BFDP= 0.636), and current cigarette smoking at time of survey (OR: 2.56; 95% CI: 1.19–5.47; P= 0.016; BFDP=0.800) were identified as risk factors that increased odds of developing moderate to severe xerostomia. Furthermore, bilateral IMRT combined with proton therapy (OR: 0.35, 95%CI: 0.16–0.73, P=0.006, BFDP=0.641) and Ipsilateral IMRT (OR: 0.19, 95%CI: 0.07–0.47, P = <0.001, BFDP=0.223) were protective factors that decreased 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's $\rho = 0.557$, $P < 0.001$). No statistically significant interactions were identified. Xerostomia during RT was also not significantly associated with moderate to severe xerostomia in both univariate (OR: 0.96; 95% CI: 0.71–1.29; P=0.777) as well as multivariable analysis (OR: 0.99; 95% CI: 0.72–1.36; P=0.937, BFDP=0.990).

Multivariable logistic regression identified concurrent weekly cetuximab chemotherapy (OR: 0.61; 95%CI: 0.40–0.94, P =0.027, BFDP= 0.876) as a protective factor that decreased odds of developing moderate to severe xerostomia, however, this association was not statistically significant after adjusting 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, about 40% reported moderate to severe xerostomia, and current smoking at time of survey, being female and having high school or lower education were key risk factors of moderate to severe xerostomia. Further, 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 (i.e., T stage, smoking status, and RT regimens), as would be expected by clinical performance. Survivors with T4 tumors had higher odds of reporting moderate-severe xerostomia versus those with T1 tumors, which is expected because advanced bulky tumors are likely to be treated with larger RT fields that 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 test-wise significance level i.e. $P \leq .05$ in our study population, though this association was not significant after adjustment for multiple comparisons. Clinicians may believe that cetuximab can cause mucositis which may contribute to xerostomia, however possibly acute mucositis observed with cetuximab during RT may not translate to long-term chronic xerostomia. The De-ESCALaTE HPV trial demonstrated that patients treated with cetuximab CRT had acute and late severe grade 3–5 toxicities and swallowing function but were not significantly different from those treated with cisplatin CRT.[38] A previous study demonstrated that addition of cetuximab to cisplatin and RT among HNC patients resulted in lower frequency of xerostomia both during CRT and at end of CRT in comparison to those treated with RT + cisplatin, though these findings were not statistically significant.[39]Nonetheless, one may hypothesize these are mechanistically plausible given the possible induction of an elevated immune response by cetuximab and less RT treatment-related injury including xerostomia.[40]. Nevertheless, role of cetuximab in xerostomia should be further investigated.

Our study also identified continued smoking after OPC diagnosis and treatment as a significant risk factor for moderate to severe xerostomia among OPC survivors even after adjusting for clinicodemographic factors. Our results are consistent with a previous study among HNC patients which demonstrated that smokers reported worse QoL outcomes and worse HNC symptoms including dry mouth compared with never smokers.[41] Further, multiple authors have shown that smoking contributes to worse QoL scores among HNC patients both during and after treatment.[42–44] Lastly, biological pathways that explain how smoking can contribute to xerostomia and increased symptom burden are not known; however, broadly smoking 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 HNC patients at different points

during treatment, including at baseline, during RT, and 6 months and 1 year after RT, have demonstrated that females reported more overall symptoms, including pain, fatigue, and depressive symptoms; worse mental, social, physical, and functional impairment; and worse QoL compared with males.[42,45–47] Females reporting worse xerostomia symptoms in our study is plausible given possible gender-related differences such as biological differences in symptom sensation and 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 like xerostomia with more psychological distress and thereby 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 cancer patients.[48,49]

To our knowledge, this is the first study to report an association between education and xerostomia among HNC patients however due to observational nature of the study results should be interpreted with care. A population-based longitudinal cohort study among HNC patients demonstrated that lower education level was significantly associated with worse physical, emotional, and functional well-being and increased HNC symptoms on post-treatment follow-up.[50] It has been suggested that lower education level may be associated with worse healthcare access, poor social support networks, and low health literacy of strategies to alleviate symptoms, all of which 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 due to 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, as ipsilateral IMRT maximizes contralateral salivary gland sparing compared with intermediate salivary gland sparing via conventional IMRT, ipsilateral IMRT was the RT regimen with 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 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 PROs for screening and identification of individuals at risk of xerostomia for implementation of early supportive interventions.[54] Supportive rehabilitation interventions for xerostomia can include mealtime alternating food/liquids strategies, meal preparation strategies, health education and counselling efforts to encourage healthy coping to adjust patient expectations for changes in oral function, 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 survival bias, however, age at diagnosis and survival times were adjusted in our analyses. The study may also be impacted by possible non-response bias although the limited characteristics evaluated between non-respondents and respondents were similar. Our observational study results may have also been influenced by imbalance of some of the categorical variables. Xerostomia was measured as a PRO from a single question of the MDASI-HN that asked about dry mouth symptoms. Importantly, Kamal et al.2018[57] showed that this single dry mouth question in MDASI-HN has a high correlation ($\rho = 0.80$, $p < 0.001$) with a composite score based on another xerostomia instrument that uses 8-items.[58] Further, information on baseline xerostomia or salivary gland dysfunction information was lacking. However, multivariable models controlled for patients' pre-treatment ability to eat a solid-food diet as a surrogate to control for baseline dysphagia and oral dysfunction. As chemotherapy regimens, drugs, dosage, and completion rates may vary, assessment of chemotherapy may have some limitations which we addressed by adjusting our models for any chemotherapy treatment given to patient. There may be some lack of generalizability of these study findings because the study was conducted at a single tertiary cancer care institution, but sample characteristics are representative of the current trends of OPC patients in the United States.

Conclusion

In this large xerostomia study, about 40% of OPC survivors reported moderate to severe xerostomia. Our study found modern radiation treatments as protective factors for moderate to severe xerostomia. Furthermore, continued smoking, female sex and lower education were identified as additional contributing factors of moderate to severe xerostomia. Concurrent cetuximab chemoradiotherapy and its correlation with xerostomia needs to be further investigated in future longitudinal studies. Among OPC patients, xerostomia has a devastating impact on physical, psychological, and social QoL, especially since late RT-associated xerostomia is irreversible and permanent. Therefore, it is imperative to investigate and develop targeted multi-disciplinary patient-centered OPC care interventions to monitor and manage RT-associated xerostomia and its oral sequelae across the cancer continuum and preserve QoL among OPC patients. Continued smoking among OPC patients is a highly prominent modifiable risk factor which can potentially 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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Table 1:

Characteristics and distribution of OPC Patients (N = 906) by clinic-demographic factors

Variables	All OPC pt. (N=906)	Xerostomia Information Missing (N=29)	Xerostomia none to mild (N=534)	Xerostomia moderate to severe (N=343)	*P*
Age at diagnosis, y median (range, IQR), (mean ±SD)	56 (32–84, 51–63), (56.9 ±8.8)	0	56 (32–84, 51–62), (56.7 ±9.0)	56 (33–82, 51–63), (57.1 ±8.7)	0.641
Survival time, y median (range, IQR), (mean ±SD)	6 (1–16, 4–10), (7.0±3.9)	0	7 (2–16, 4–10), (7.1 ±3.8)	6 (1–16, 4–10), (6.9 ±4.0)	0.398
Radiation Dose, Gy median (range, IQR), (mean ±SD)	70 (40–72.6, 66–70), (68.1 ±2.6)	0	69.2 (57–72, 66–70), (68.0 ±2.5)	70.0 (40–72.6, 66–70), (68.3 ±2.8)	0.103
Sex					**0.007**
Female	140 (15.5)	8	66 (50.0)	66 (50.0)	
Male	766 (84.6)	21	468 (62.8)	277 (37.2)	
Education					**0.004**
>Highschool	650 (71.7)	18	406 (64.2)	226 (35.8)	
≤ Highschool	171 (18.9)	8	83 (50.9)	80 (49.1)	
Missing	85 (9.4)	3	45 (54.9)	37 (45.1)	
Race/Ethnicity					0.817
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)	
Hispanics	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					0.779
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					0.171
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					0.190

Variables	All OPC pt. (N=906)	Xerostomia Information Missing (N=29)	Xerostomia none to mild (N=534)	Xerostomia moderate to severe (N=343)	*P*
N0	83 (9.2)	3	51 (63.8)	29 (36.3)	
N1+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					0.540
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)	
Cigarettes Smoking					**0.029**
Never	420 (46.3)	12	252 (61.8)	156 (38.2)	
Former smokers 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 pre-Tx					0.759
Yes	894 (98.7)	28	528 ((61.0)	338 (39.1)	
No	12 (1.3)	1	6 (54.6)	5 (45.4)	
Treatment Group					0.155
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					0.069
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					0.118
No	286 (31.6)	10	179 (64.9)	97 (35.1)	
Yes	620 (68.4)	19	355 (59.1)	246 (40.9)	
Surgery					0.110
No	881 (97.2)	28	516 (60.5)	337 (39.5)	

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Variables	All OPC pt. (N=906)	Xerostomia Information Missing (N=29)	Xerostomia none to mild (N=534)	Xerostomia moderate to severe (N=343)	*P*
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					0.203
No	679 (74.9)	22	392 (59.7)	265 (40.3)	
Yes	227 (25.1)	7	142 (64.5)	78 (35.5)	
Radiotherapy					**0.026**
No	8 (0.9)	0	8 (100.0)	0 (0.0)	
Yes	898 (99.1)	29	526 (60.5)	343 (39.5)	
RT Schedule					**0.045**
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					**<0.001**
3d Conformal	51 (5.6)	2	20 (40.8)	29 (59.2)	
IMRT Bilateral (SF+WF+VMAT) + Proton	747 (82.5)	21	438 (60.3)	288 (39.7)	
IMRT Ipsilateral	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					**0.047**
No	609 (67.2)	21	372 (63.3)	216 (36.7)	
Yes	297 (32.8)	8	162 (56.1)	127 (43.9)	
Concurrent Chemotherapy					0.298
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					0.075
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					0.375
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 weekly cisplatin					0.195

Variables	All OPC pt. (N=906)	Xerostomia Information Missing (N=29)	Xerostomia none to mild (N=534)	Xerostomia moderate to severe (N=343)	*P*
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					**0.010**
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					0.095
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					0.285
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)	

Note: One patient was excluded due to missing filling out the MDASI-HN. Twenty-nine patients did not answer the Xerostomia question on the MDASI-HN. Self-reported xerostomia scores were available for 877 participants.

Solid food diet pre-treatment was controlled for as a surrogate control for pre-treatment oral dysfunction/symptoms.

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

RT dose was total radiation dose measured in Gray (Gy).

RT fractionation schedule included standard fractionation (70.0 Gy given in 33–35 fractions), accelerated fractionation (72.0 Gy given in 40 fractions or use of concomitant boost or Danish Head and Neck Cancer Group RT regimens), and no RT.

RT types included 3-dimensional conformal RT (3D-CRT); bilateral intensity modulated RT (IMRT) with split-field (IMRT-SF), whole-field (IMRT-WF), volumetric-modulated arc therapy (VMAT) and proton therapy; and ipsilateral IMRT regimens

Abbreviations: IQR, interquartile range, T, tumor; RT, radiotherapy; 3D-CRT; three-dimensional conformal radiotherapy, IMRT-SF, Intensity modulated radiotherapy split-field technique; IMRT-WF, Intensity modulated radiotherapy whole-field technique; VMAT, Volumetric-modulated arc therapy

Table2:

Multivariable Logistic Regression Analysis Assessing Relationship between clinic-demographic variables and patient-reported moderate to severe xerostomia

Variables	Univariate OR	(95% CI)	Univariate *P*	Multivariable OR	(95% CI)	Multivariable *P*	BFDP
Age at diagnosis, y	1.00	(0.99–1.02)	0.563	1.00	(0.99–1.02)	0.605	0.999
Survival time, y	0.99	(0.95–1.02)	0.517	0.98	(0.92–1.05)	0.584	0.997
Radiation Dose, Gy	1.04	(0.98–1.10)	0.169	0.99	(0.92–1.06)	0.711	0.998
Sex			**0.006**				
Male	Ref			Ref			
Female	1.69	(1.16–2.45)	**0.006**	1.82	(1.22–2.71)	**0.003**	**0.568**
Education new			**0.004**				
>Highschool	Ref			Ref			
≤Highschool	1.73	(1.22–2.45)	**0.002**	1.73	(1.19–2.52)	**0.004**	**0.636**
Race/Ethnicity							
Non-Hispanic white	Ref			Ref			
Non-Hispanic black	0.93	(0.34–2.59)	0.893	0.74	(0.24–2.24)	0.594	0.968
Hispanics	0.78	(0.37–1.62)	0.502	0.72	(0.34–1.56)	0.410	0.971
Other	2.07	(0.46–9.32)	0.343	1.98	(0.41–9.54)	0.394	0.958
Subsite			0.760				
Tonsil	Ref			Ref			
Base of tongue + GPS	1.11	(0.84–1.46)	0.460	1.02	(0.74–1.4)	0.901	0.990
Others	1.04	(0.49–2.20)	0.923	0.87	(0.39–1.92)	0.724	0.976
T classification			0.175				
1	Ref			Ref			
2	1.08	(0.79–1.48)	0.632	1.01	(0.69–1.46)	0.973	0.988
3	1.14	(0.75–1.73)	0.548	0.87	(0.51–1.47)	0.594	0.982
4	1.73	(1.06–2.80	**0.027**	1.32	(0.72–2.43)	0.374	0.974
N classification			0.191				
N0	Ref			Ref			
N1+2a	1.02	(0.60–1.74)	0.930	1.10	(0.61–1.98)	0.752	0.981
2b+3	1.09	(0.66–1.79)	0.741	1.07	(0.60–1.88)	0.825	0.982

Variables	Univariate OR	(95% CI)	Univariate *P*	Multivariable OR	(95% CI)	Multivariable *P*	BFDP
2c	1.57	(0.90–2.76)	0.115	1.33	(0.71–2.5)	0.380	0.974
HPV status			0.546				
Negative	Ref			Ref			
Positive	0.90	(0.51–1.59)	0.722	1.17	(0.62–2.18)	0.630	0.979
Unknown	0.79	(0.45–1.39)	0.416	0.96	(0.51–1.83)	0.905	0.981
Cigarettes Smoking							
Never	Ref			Ref			
Former smokers at time of diagnosis	0.93	(0.69–1.25)	0.632	0.91	(0.66–1.25)	0.565	0.988
Quit smoking subsequent to diagnosis	1.20	(0.76–1.92)	0.435	1.05	(0.63–1.73)	0.856	0.984
Current smoker	2.96	(1.43–6.15)	**0.004**	2.56	(1.19–5.47)	**0.016**	**0.800**
Don’t know	1.15	(0.36–3.70)	0.810	1.19	(0.36–3.98)	0.772	0.969
Solid Food pre-Tx			0.667				
No	0.77	(0.23–2.54)	0.665	Ref			
Yes	Ref			0.95	(0.25–3.54)	0.940	0.968
Treatment Group			0.133				
Single Modality	Ref			Ref			
Multimodality	1.25	(0.93–1.69)	0.135	0.80	(0.12–5.58)	0.824	0.961
Chemotherapy			0.102				
No	Ref			Ref			
Yes	1.28	(0.95–1.72)	0.103	1.22	(0.18–8.23)	0.838	0.961
Surgery			0.098				
No 0	Ref			Ref			
Yes – Robotic	0.31	(0.09–1.07)	0.063	0.49	(0.10–2.31)	0.368	0.957
Yes – Open	1.53	(0.31–7.63)	0.603	3.01	(0.42–21.42)	0.272	0.951
Neck Dissection			0.393				
No	Ref			Ref			
Yes	0.81	(0.59–1.12)	0.200	0.86	(0.6–1.22)	0.395	0.985
RT Schedule			0.493				
Standard Fractionation	Ref			Ref			
Accelerated	1.16	(0.76–1.79)	0.492	0.99	(0.55–1.79)	0.983	0.982
RT Type			**0.001**				

Variables	Univariate OR	(95% CI)	Univariate *P*	Multivariable OR	(95% CI)	Multivariable *P*	BFDP
3D-CRT	Ref			Ref			
IMRT-Bilateral (SF+WF+VMAT) + Proton	0.45	(0.25–0.82)	**0.008**	0.35	(0.16–0.73)	**0.006**	**0.641**
Ipsilateral IMRT	0.26	(0.13–0.55)	< **0.001**	0.19	(0.07–0.47)	<**0.001**	**0.223**
Xerostomia During RT				0.226			
No	Ref			Ref			
Yes	0.96	(0.71–1.29)	0.777	0.99	(0.72–1.36)	0.937	0.990

Abbreviations: T, tumor; RT, radiotherapy; 3D-CRT; three-dimensional conformal radiotherapy; IMRT-SF, Intensity modulated radiotherapy split-field technique; IMRT-WF, Intensity modulated radiotherapy whole-field technique; VMAT, Volumetric-modulated arc therapy; BFDP, Bayesian false-discovery probabilities.

Statistical significance $P \leq 0.05$.

BFDP ≤ 0.8 noteworthy associations.

Table3:

Multivariable Regression Analysis Assessing Relationship between Concurrent Carboplatin weekly and Concurrent Cetuximab weekly and patient-reported moderate to severe xerostomia

Variables	Univariate OR	(95% CI)	Univariate *P*	Multivariable OR	95% CI	Multivariable *P*	BFDP
Concurrent Carboplatin weekly							
No	Ref						
Yes	1.82	(1.16–2.85)	**0.010**	1.66	(1.00–2.75)	0.052	0.916
Concurrent Cetuximab weekly							
No	Ref						
Yes	0.72	(0.50–1.05)	0.092	0.61	(0.40–0.94)	**0.027**	0.876

Abbreviations: BFDP, Bayesian false-discovery probabilities

Note:

*All models controlled for age at diagnosis, RT dose, survival time, sex, race, education, subsite, T-stage, N-stage, HPV, cigarette smoking at diagnosis and survey, solid food diet at baseline, treatment modality, chemotherapy, surgery, neck dissection, RT Schedule, RT Type, and xerostomia during RT.

Statistical significance $P \leq 0.05$.

BFDP ≤ 0.8 noteworthy associations.