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RESEARCH

Oral health-related quality of life after radiation therapy for head and neck cancer: the OraRad study

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Abstract

Purpose Head and neck cancer (HNC) treatment results in morbidity impacting quality of life (QOL) in survivorship. This analysis evaluated changes in oral health-related QOL (OH-QOL) up to 2 years after curative intent radiation therapy (RT) for HNC patients and factors associated with these changes.

Methods 572 HNC patients participated in a multicenter, prospective observational study (OraRad). Data collected included sociodemographic, tumor, and treatment variables. Ten single-item questions and 2 composite scales of swallowing problems and senses problems (taste and smell) from a standard QOL instrument were assessed before RT and at 6-month intervals after RT.

Results The most persistently impacted OH-QOL variables at 24 months included: dry mouth; sticky saliva, and senses problems. These measures were most elevated at the 6-month visit. Aspects of swallowing were most impacted by oropharyngeal tumor site, chemotherapy, and non-Hispanic ethnicity. Problems with senses and dry mouth were worse with older age. Dry mouth and sticky saliva increased more among men and those with oropharyngeal cancer, nodal involvement, and use of chemotherapy. Problems with mouth opening were increased by chemotherapy and were more common among non-White and Hispanic individuals. A 1000 cGy increase in RT dose was associated with a clinically meaningful change in difficulty swallowing solid food, dry mouth, sticky saliva, sense of taste, and senses problems.

Conclusions Demographic, tumor, and treatment variables impacted OH-QOL for HNC patients up to 2 years after RT. Dry mouth is the most intense and sustained toxicity of RT that negatively impacts OH-QOL of HNC survivors.

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Keywords Radiation therapy · Quality of life · Dry mouth · Senses problems · Head and neck cancer

Introduction

Head and neck cancer (HNC) and its treatment often leaves survivors with multiple morbidities that impact quality of life (QOL). QOL among survivors can vary based on involved cancer site, treatment rendered (surgery, radiation therapy [RT] and chemotherapy [CT]), lifestyle factors, and other sociodemographic characteristics [1]. Questionnaires specific to HNC QOL are important to capture the patient experience of how their life is changed by disease and/or treatment related toxicity. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-HNC specific module-35 items (H&N35) scale is generally considered the most used and validated instrument for these assessments [2–4]. It has been shown to be reliable and sensitive across different cancer patient and treatment groups in many countries [5].

RT is a primary definitive treatment modality for HNC. RT may be delivered alone, with or without surgery, and with or without CT [6]. Recognition of long-term sequela of inadvertent exposure of radiosensitive salivary gland tissue lying in proximity to tumors and nodal beds has led to efforts to alter radiation technique to help preserve salivary gland function [7]. With gradual advances in HNC RT techniques from two-dimensional RT (2DRT), to three-dimensional conformal RT (3D-CRT), and finally to intensity modulated RT (IMRT), HNC patients have had better outcomes in swallowing, senses (taste/smell), teeth complications,

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mouth opening, dry mouth and sticky saliva [7]. With technological advances in RT beyond traditional photon therapy, use of proton therapy [8] and functional magnetic resonance imaging (MRI)-guided biologically adapted proton therapy [9] are new options for treatment to avoid nearby critical structures, such as salivary glands.

This analysis reports changes in oral health QOL (OH-QOL) responses over the first 2 years after curative intent RT in the multicenter Clinical Registry of Dental Outcomes in Head and Neck Cancer Patients (OraRad) cohort.

Subjects and Methods

Subjects

The prospective, longitudinal, multicenter clinical registry of dental outcomes in HNC patients (OraRad study) has been previously described, [10]. Institutional Review Board approval was obtained at all sites. From April 2014 to October 2018, 572 participants were enrolled before initiating curative-intent (definitive or postoperative) head and neck RT and were followed at 6-month intervals until 24-months post-RT. Eligibility requirements included: age 18 or older; diagnosed with head and neck squamous cell carcinoma (SCC) or a salivary gland cancer (SGC), or with a non-SCC, non-SGC malignancy of the head and neck region; planned to receive at least 4500 cGy RT to the head and neck region; and had no prior RT to the head and neck region. The first (baseline) study assessments occurred after the pre-radiation dental evaluation and any required extractions and before the first radiation treatment session.

Demographic, tumor and treatment variables

The clinical protocol and variable definition and collection timepoints have been previously reported [10]. Tumor and treatment data were obtained by health record review. Primary tumor site was classified 5 domains: oropharynx (base of tongue, tonsil, oropharynx, and soft palate); oral cavity (oral tongue, oral cavity, gingival/alveolar ridge, mandible, buccal/labial mucosa, floor of mouth, maxilla, retromolar trigone, hard palate, and lip); larynx/hypopharynx (larynx, hypopharynx, and epiglottis); salivary gland (submandibular gland, parotid, and sublingual gland); and other (neck, nasopharynx, pharynx, maxillary sinus, nasal cavity and other sites).

OH-QOL variables

Patient-reported symptoms important to OH-QOL were assessed at each study visit: baseline prior to RT and at 6, 12, 18, and 24-months post-RT, using selected single item questions and composite scales from the EORTC QLQ -H&N35 scale [2, 3]. Ten individual question items were scored on a four-point scale (1 = not at all; 2 = a little; 3 = quite a bit; 4 = very much). These items included patient experience in the past week of problems swallowing liquids, pureed food, and solid foods and choking when swallowing, problems with sense of smell and taste, problems with teeth, opening mouth, dry mouth, and sticky saliva. Two composite scales were assessed: problems with swallowing (which summarizes the problems swallowing liquids, pureed food, and solid foods and choking when swallowing items), and senses problems (which summarizes the problems with sense of smell and taste items). Prior to analysis the ten 4-point scale items and two composite scales were transformed into 1-to-100 scales, with higher scores representing higher level of symptoms. These scales were treated as continuous in all analyses. A 10 unit or more change on a 1–100 scale of variations in mean scores over time for items and scales has been rated as clinically meaningful [2]. Problem severity is demonstrated by percentage of patients who reported mean scores over 50, which corresponds to responses "quite a bit" or "very much" on single items.

Statistical Methods

Linear mixed-effects models with subject specific random intercepts were used to evaluate change in QOL measures across study time points. Associations between covariates and change in QOL measures were evaluated by testing interaction terms between study visits (treated as categorical) and the covariate. Results for covariates that were statistically associated (p-value < 0.05) with a clinically meaningful (≥ 10 unit) change in at least one QOL measure are further described in the text. Trends were visualized using locally estimated scatterplot smoothing (loess) lines [11]. The supplementary appendix gives results for all risk factors considered. Analyses were conducted using R version 4.2.0 [12] using versions 1.1.29, 3.1.3, and 1.7.4.1 of the "lme4" [13], "lmerTest" [14], and "emmeans" [15] packages, respectively. All p-values are two-sided and have not been adjusted for multiple comparisons.

Results

The study enrolled 572 participants with a mean age of 58 (range 21–97) years (Table 1). Males and whites comprised the majority (76.9% and 82.9%, respectively). Most (72.0%) had education beyond high school, were former (51.4%) or current (4.9%) smokers, and (62.7%) currently drink alcohol. Approximately half of primary tumors were in the oropharynx and of those 87.4% were HPV-positive tumors. Regional lymph nodes were involved in 75% of patients. Most (93.2%)

Table 1 Baseline clinical and demographic characteristics of the OraRad cohort ($N=572$)

Characteristic	Study population *N* (%)
Sex	
Female	132 (23.1%)
Male	440 (76.9%)
Age in years	
< 50	93 (16.3%)
50–65	339 (59.3%)
> 65	140 (24.5%)
Race	
White only	474 (82.9%)
Black only	45 (7.9%)
Other/unknown	53 (9.3%)
Ethnicity	
Hispanic	29 (5.1%)
Non-Hispanic	543 (94.9%)
Educational level	
≤ High school	158 (27.6%)
> High school	412 (72.0%)
Declined to answer	2 (0.3%)
Tobacco user	
Never	248 (43.4%)
Former	294 (51.4%)
Current	28 (4.9%)
Declined/Don't know	2 (0.3%)
Alcohol consumption	
Nondrinker	188 (32.9%)
< 7 drinks/week	237 (41.4%)
≥ 7 drinks/week	122 (21.3%)
Declined/Don't know drinks/week	25 (4.4%)
Dental Insurance	
Does not have	206 (36.0%)
Has	366 (64.0%)
Medical Insurance	
Private only	352 (61.5%)
Public (Medicare/aid)	195 (34.1%)
None/unknown	25 (4.4%)
Primary Tumor site	
Oropharynx	270 (47.2%)
Oral Cavity	88 (15.4%)
Salivary gland	55 (9.6%)
Larynx/Hypopharynx	38 (6.6%)
Other	87 (15.2%)
Unknown	34 (5.9%)
HPV positive tumor*	
Yes	236 (41.3%)
No	17 (0.4%)
Not collected	319 (55.8%)
T category (AJCC 7th edition)	
I/II	344 (60.1%)
III/IV	178 (31.1%)
Unknown	50 (8.7%)
N category (AJCC 7th edition)	
0	136 (23.8%)
≥ 1	429 (75.0%)
Unknown	7 (1.2%)

Table 1 (continued)

Characteristic	Study population *N* (%)
Treatment**	
RT only	39 (6.8%)
RT + CT	219 (38.3%)
Sur + RT	169 (29.5%)
Sur + RT + CT	145 (25.3%)
Total RT dose to primary site (cGy)***	
< 6000	34 (6.0%)
6000–7000	296 (51.8%)
> 7000	241 (42.2%)
Type of RT***	
IMRT with image guidance	494 (86.4%)
Proton	31 (5.4%)
3-D conformal radiation	14 (2.4%)
IMRT with image guidance + 3-D conformal radiation	11 (1.9%)
IMRT with image guidance + Proton	10 (1.7%)
IMRT without image guidance	8 (1.4%)
IMRT with image guidance + 3-D conformal radiation + Proton	1 (0.2%)
OTHER (including 2-D radiation)	2 (0.3%)

Key: *HPV* Human Papilloma Virus, *RT* Radiation therapy, *CT* Chemotherapy, *Sur* Surgery, *cGY* centigray, *SCC* squamous cell carcinoma, *AJCC* American Joint Committee on Cancer TNM system, *T* primary tumor size, *N* nodal involvement, *SD* standard deviation, *w/* with, *w/o* without, *IMRT* intensity modulated radiation therapy, *3DCRT* 3-D conformal radiation therapy

* HPV status only assessed on oropharynx primary tumor site, thus 236/270 (87.4%) oropharynx primaries were HPV positive

** CT use as additional therapy in 364 individuals included 253 with concurrent chemoradiation, 107 with induction and concurrent chemoradiation, and 4 individuals with only induction chemotherapy. Surgery prior to RT

*** One subject withdrew after enrollment resulting in RT dose and technique $n = 571$

received either chemotherapy and/or surgery as additional therapies besides RT. Most RT was delivered by IMRT. The total RT dose to the primary tumor was a mean (sd) of 6572.8 (662.6) cGy, with 42.2% receiving over 7000 cGy and 6% under 6000 cGy.

OH-QOL trends over time

OH-QOL, as assessed by the 10 single QOL items and 2 combined scales, demonstrated variable levels of change over the 2-year period (Table 2). All items except problems with teeth significantly changed (p-values < 0.01), with senses problems (including problems with taste), sticky saliva, and dry mouth having clinically meaningful (≥ 10 unit) changes.

The senses problems scale significantly increased from average scores of 11.5 (95% CI 9.5 to 13.4) at baseline to a peak of 33.4 (95% CI: 31.3 to 35.4) at 6-months. Scores decreased to 27.3 (95% CI: 25.2 to 29.4) at 12-months but continued to remain elevated compared to baseline at the 18-month and 24-month visits. The problems with sense of taste subscale increased from an average score of 14.8 (95% CI: 12.3 to 17.3) at baseline to 48.6 (95% CI: 45.9 to 51.3) at 6-months. Scores slightly improved to 39.6 (95% CI: 36.8 to 42.4) at 12-months but were still significantly elevated compared to baseline at the 18- and 24-month visits.

Average self-reported dry mouth scores increased from 21.1 (95% CI: 18.5 to 23.7) at baseline to 65.4 (95% CI: 62.7 to 68.2) at 6-months, decreased slightly to 58.3 (95% CI: 55.5 to 61.1) at 12-months, but continued to remain significantly elevated compared to baseline at the 18- and 24-month visits. The sticky saliva scale followed similar trends as the dry mouth scale with an increase from baseline (16.3, 95% CI: 13.7 to 18.8) to 6-months (45, 95% CI: 42.3 to 47.7), slight improvement at 12-months (36.5, 95% CI: 33.6 to 39.3), and continued elevation at 18- and 24- months compared to baseline.

Relationship between patient characteristics and OH-QOL measures

Sex, Age, Race, Ethnicity

Men experienced significantly and clinically meaningful (≥ 10 point) greater increases in problems with sticky saliva

Table 2 Quality of Life Measures at each time-point and comparison of change from pre-RT. Visit specific model estimated mean (95% CI) for EORTC measures are presented. EORTC scale scores range from 0 to 100 with higher scores representing decreased quality of life

	Liquids	Pureed Food	Solid Food	Choked	Teeth	Opening mouth	Dry mouth	Sticky saliva	Smell	Taste	Swallowing	Senses problems
Mean (95% CI)												
BL (N = 572)	13.9 (12.1, 15.6)	9.9 (8.3, 11.5)	26.5 (23.9, 29)	9.1 (7.3, 10.9)	15.9 (13.8, 17.9)	22.1 (19.6, 24.6)	21.1 (18.5, 23.7)	16.3 (13.7, 18.8)	8.1 (6, 10.2)	14.8 (12.3, 17.3)	14.8 (13.2, 16.4)	11.5 (9.5, 13.4)
V06 (N = 473)	14.2 (12.3, 16.1)	10.7 (8.9, 12.4)	33.2 (30.5, 35.9)	14.9 (12.9, 16.8)	16.0 (13.8, 18.2)	26.8 (24.1, 29.4)	65.4 (62.7, 68.2)	45 (42.3, 47.7)	18 (15.8, 20.2)	48.6 (45.9, 51.3)	18.3 (16.6, 20.1)	33.4 (31.3, 35.4)
V12 (N = 427)	10.9 (8.9, 12.9)	8.8 (7.0, 10.7)	30.3 (27.5, 33.1)	15.4 (13.4, 17.4)	16.1 (13.8, 18.4)	23.5 (20.8, 26.3)	58.3 (55.5, 61.1)	36.5 (33.6, 39.3)	15 (12.7, 17.3)	39.6 (36.8, 42.4)	16.5 (14.8, 18.3)	27.3 (25.2, 29.4)
V18 (N = 394)	10.8 (8.8, 12.9)	7.5 (5.6, 9.4)	28.2 (25.4, 31.1)	15.8 (13.7, 17.8)	16.6 (14.2, 19)	21.6 (18.8, 24.4)	53.9 (51, 56.8)	34.4 (31.4, 37.3)	15.5 (13.1, 17.9)	31.9 (29.1, 34.8)	15.9 (14.1, 17.7)	23.7 (21.6, 25.9)
V24 (N = 420)	10.6 (8.6, 12.6)	7.1 (5.3, 9.0)	27 (24.2, 29.8)	16.7 (14.7, 18.7)	17.3 (14.9, 19.6)	22.5 (19.7, 25.2)	51.5 (48.7, 54.4)	33.5 (30.7, 36.4)	15.4 (13, 17.7)	32.3 (29.5, 35.1)	15.6 (13.8, 17.4)	23.8 (21.7, 26)
P-values												
Overall	0.0005	0.0022	≤0.0001	≤0.0001	0.8219	0.0007	≤0.0001	≤0.0001	≤0.0001	≤0.0001	0.0005	≤0.0001
V06 vs. BL	0.7836	0.4241	≤0.0001	≤0.0001	0.9061	0.0002	≤0.0001	≤0.0001	≤0.0001	≤0.0001	≤0.0001	≤0.0001
V12 vs. BL	0.0066	0.2819	0.0052	≤0.0001	0.8385	0.2708	≤0.0001	≤0.0001	≤0.0001	≤0.0001	0.0459	≤0.0001
V18 vs. BL	0.0067	0.0193	0.2056	≤0.0001	0.5463	0.6997	≤0.0001	≤0.0001	≤0.0001	≤0.0001	0.2407	≤0.0001
V24 vs. BL	0.0030	0.0058	0.7080	≤0.0001	0.2701	0.7686	≤0.0001	≤0.0001	≤0.0001	≤0.0001	0.3669	≤0.0001

Key: *RT* radiation therapy, *BL* baseline pre-RT, *V06* visit 6 months post-RT, *V12* visit 12 months post-RT, *V18* visit 18 months post-RT, *V24* visit 24 months post-RT

from baseline to 12-months and dry mouth from baseline to 6- and 12-months compared to women (Table 3).

Individuals older than 65 years experienced a greater increase in dry mouth from baseline to 18-months compared to individuals < 50 years. The oldest age group (over 65 years) also experienced a greater increase in senses problems from baseline to all subsequent visits compared to individuals aged < 50 years. Results followed similar trends but were more pronounced for the sense of taste subscale.

Compared to White individuals, Black individuals had a greater increase in difficulty opening mouth wide from baseline to 6-, 12- and 24-months. Similarly, individuals of other/unknown races had a greater increase in difficulty opening mouth wide scores from baseline to 6-, 18- and 24-months, compared to White individuals.

Non-Hispanic individuals experienced a greater increase in difficulty swallowing solid foods from baseline to 6-months compared to Hispanic individuals. However, Hispanic individuals experienced a greater increase in difficulty opening mouth wide from baseline to 12-, 18-, and 24-months.

Tumor site

Figure 1 presents QOL trends by tumor site. Tumor site was associated with changes in difficulty swallowing solid food ($p = 0.037$), choking while swallowing ($p = 0.038$), dry mouth ($p < 0.001$), and sticky saliva ($p = 0.026$; Supplementary Table S2).

Oropharynx tumors were associated with a significant and clinically meaningful increase in difficulty swallowing solid food from baseline to 12-, 18- and 24-months compared to oral cavity and from baseline to 18- and 24-months compared to larynx/hypopharynx. Individuals with tumors in "other" sites had an increase in difficulty swallowing solid food from baseline to 6-, 12-, and 24-months compared to oral cavity and from baseline to 24-months compared to larynx/hypopharynx.

Larynx/hypopharynx tumors were associated with a decrease in choking while swallowing from baseline to 12- and 18-months compared to oral cavity and oropharynx; from baseline to 12- and 18-months compared to "other" sites.

Oropharynx tumors were associated with increased dry mouth from baseline to 6-, 12-, and 24-months compared to larynx/hypopharynx; baseline to 6- and 12- months compared to oral cavity, baseline to 6- and 18 months compared to "other" sites; and baseline to all subsequent visits compared to salivary gland. A primary site of salivary gland was associated with less of an increase in dry mouth from baseline to 6-months compared to larynx/hypopharynx; baseline to all subsequent visits compared to oral cavity; and baseline to 6-, 12-, and 24-months compared to "other" sites. A primary site of larynx/hypopharynx was associated with less of an increase in dry mouth from baseline to 24-months compared to oral cavity and "other" sites.

Oropharynx tumors were associated with an increase in sticky saliva from baseline to 6-months compared to oral cavity and from baseline to 6-, 12-, and 18-months compared to salivary gland. A primary site of larynx/hypopharynx was associated with an increase in sticky saliva from baseline to 6-months compared to salivary gland tumors.

Tumor stage

Nodal involvement was associated with an increase in dry mouth from baseline to all subsequent visits (p-values < 0.001). In addition, individuals with nodal involvement had an increase in sticky saliva from baseline to 6- and 24-months compared to individuals without nodal involvement (Table 4).

Radiation dose

Total RT dose to the primary site was associated with an increase in the swallowing scale ($p = 0.001$), problems swallowing solid foods ($p < 0.001$), the senses problems scale ($p < 0.001$), problems with sense of smell ($p = 0.031$) and taste ($p < 0.001$), problems opening mouth ($p < 0.003$), dry mouth ($p < 0.001$), and sticky saliva ($p < 0.001$; Table 4). A 1000 cGy difference in dose (the interquartile range in this population) was associated with a clinically meaningful (≥ 10 point) increase in difficulty swallowing solid food, dry mouth, sticky saliva, sense of taste, and the senses problems scale from baseline to 6-months and dry mouth from baseline to 6- and 12-months.

Impact of Treatment Modalities Used

Treatment modality was associated with change in the swallowing scale ($p < 0.001$); problems swallowing liquids ($p < 0.001$), pureed foods ($p = 0.009$), and solid foods ($p < 0.001$); problems opening mouth wide ($p = 0.003$); dry mouth ($p < 0.001$); sticky saliva ($p < 0.001$); problems with teeth ($p = 0.007$), senses ($p = 0.034$), and taste ($p = 0.036$) (Supplementary Table S3; Fig. 2).

RT + CT was associated with a greater increase from baseline in problems swallowing solid food compared to surgery + RT (all visits), surgery + RT + CT (all visits), and RT alone (6-months); problems swallowing liquids compared to surgery + RT + CT (6-months) and RT alone (6-months); and problems swallowing pureed food compared to RT alone

Table 3 Difference in change in selected EORTC measures from baseline to each visit based on demographics. Only models with a significant ($p < 0.05$) relationship between demographic and change in EORTC item are presented. See Supplementary Table S1 for full results. Estimate (95%); p-values are presented

	Sex		Age									Race			Ethnicity		Education	
	Dry mouth	Sticky saliva	Dry mouth			Taste			Senses problems			Opening mouth			Solid Food	Opening mouth	Solid Food	Swallowing
	Male vs. female	Male vs. female	< 50 vs (50–65)	< 50 vs > 65	(50–65) vs. > 65	< 50 vs (50–65)	< 50 vs > 65	(50–65) vs. > 65	< 50 vs (50–65)	< 50 vs > 65	(50–65) vs. > 65	Black Only vs. Other	Black Only vs. White Only	Other vs. White Only	Not Hisp. vs. Hisp.	Not Hisp. vs. Hisp.	> HS vs. ≤ HS	> HS vs. ≤ HS
p-val	0.0014	0.0078	0.0376			0.0002			0.0020			0.0002			0.0083	0.0241	0.0469	0.0228
V06 vs. BL	13.1 (6.5, 19.7); ≤0.0001	8.7 (1.7, 15.8); 0.0153	-3.5 (-11.2, 4.2); 0.3756	3.4 (-5.5, 12.4); 0.4537	6.9 (0.1, 13.7); 0.0464	-10.3 (-18.0, -2.6); 0.0091	-15.7 (-24.7, -6.8); 0.0006	-5.5 (-12.3, 1.3); 0.1159	-5.4 (-10.9, 0.1); 0.0525	-10.8 (-17.2, -4.4); 0.001	-5.4 (-10.2, -0.5); 0.0309	5.2 (-6.8, 17.2); 0.3966	17.1 (7.6, 26.6); 0.0004	11.9 (3.6, 20.2); 0.0050	22.2 (9.4, 35); 0.0007	-3.5 (-15.7, 8.7); 0.5758	-1.7 (-7.5, 4.1); 0.5680	-2.2 (-5.8, 1.4); 0.2322
V12 vs. BL	11.1 (4.2, 18.0); 0.0017	10.8 (3.4, 18.2); 0.0043	-8.6 (-16.6, -0.6); 0.0362	-8.1 (-17.3, 1.0); 0.0818	0.4 (-6.4, 7.3); 0.8994	-7.7 (-15.8, 0.3); 0.0600	-19.1 (-28.3, -9.9); ≤0.0001	-11.4 (-18.3, -4.5); 0.0012	-4 (-9.7, 1.8); 0.1731	-10.8 (-17.4, -4.2); 0.0013	-6.8 (-11.8, -1.9); 0.0067	3.8 (-8.7, 16.2); 0.5553	13.3 (3.4, 23.1); 0.0082	9.5 (0.9, 18.2); 0.0311	5.1 (-8.0, 18.2); 0.4485	-13 (-25.5, -0.5); 0.0425	-9.0 (-15.1, -2.9); 0.0037	-5.7 (-9.4, -1.9); 0.0033
V18 vs. BL	8.4 (1.3, 15.6); 0.0213	5.9 (-1.8, 13.5); 0.1337	-9.6 (-17.8, -1.4); 0.0221	-11.3 (-20.7, -1.9); 0.0187	-1.7 (-8.8, 5.4); 0.6369	-5.4 (-13.6, 2.8); 0.1992	-18.1 (-27.6, -8.7); 0.0002	-12.8 (-19.9, -5.7); 0.0004	-1.5 (-7.4, 4.4); 0.6113	-11.4 (-18.1, -4.7); 0.0009	-9.9 (-14.9, -4.8); ≤0.0001	-1.9 (-15.3, 11.6); 0.7861	9.5 (-1.4, 20.4); 0.0860	11.4 (2.6, 20.2); 0.0112	13.4 (-0.2, 27.0); 0.0548	-17.5 (-30.5, -4.4); 0.0088	-2.2 (-8.5, 4.2); 0.5020	-0.1 (-4.0, 3.8); 0.9543
V24 vs. BL	7.4 (0.3, 14.5); 0.0422	-0.5 (-8.1, 7.1); 0.8914	-7.4 (-15.5, 0.7); 0.0750	-8.0 (-17.3, 1.3); 0.0937	-0.6 (-7.5, 6.4); 0.8748	-7.4 (-15.5, 0.7); 0.0750	-17.6 (-26.9, -8.3); 0.0002	-10.2 (-17.1, -3.2); 0.0041	-4.8 (-10.6, 1.0); 0.1080	-10.1 (-16.7, -3.4); 0.0031	-5.3 (-10.2, -0.3); 0.0369	10.5 (-2.9, 23.8); 0.1242	22.2 (11.3, 33.1); ≤0.0001	11.8 (3.1, 20.4); 0.0078	3.4 (-9.7, 16.5); 0.6102	-16.2 (-28.7, -3.7); 0.0115	-4.7 (-10.8, 1.4); 0.1317	-3.5 (-7.3, 0.3); 0.0724

Key: *HS* high school, *Hisp*. Hispanic, *BL* baseline pre-RT, *V06* visit 6 months post-RT, *V12* visit 12 months post-RT, *V18* visit 18 months post-RT, *V24* visit 24 months post-RT

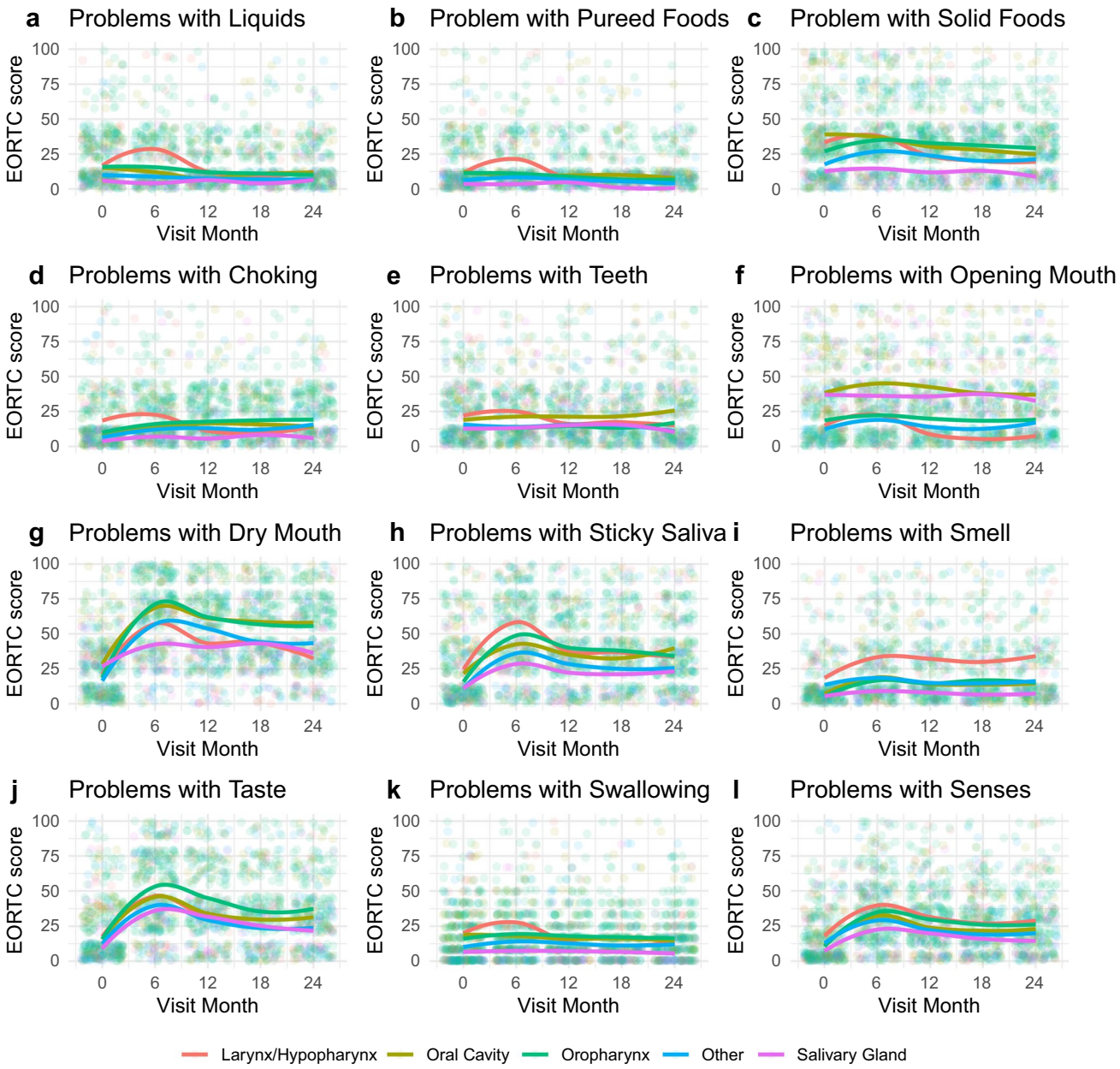

Fig. 1 Relationship between tumor site and OH-QOL measures. Loess curve for EORTC scale by primary site of RT. Visit month has been jittered for visualization purposes. Statistical comparisons between sites are provided in Supplementary Tables S1-S2

(6-months). RT alone was associated with a greater increase in problems swallowing solids from baseline to 24-months compared to surgery + RT + CT, and surgery + RT.

RT + CT was associated with a greater increase from baseline in difficulty opening mouth compared to surgery + RT (12- and 24-months) and RT alone (12-months). Surgery + RT + CT was associated with a greater increase from baseline in difficulty opening mouth compared to surgery + RT (12- and 24-months) and RT only (12-months).

RT + CT was associated with a greater increase from baseline in dry mouth compared to surgery + RT (all visits), surgery + RT + CT (6- and 12-months), and RT alone (6-months). Surgery + RT + CT was associated with a greater increase in dry mouth from baseline to 6-, 12-, and 18-months compared to surgery + RT. RT alone was associated with a greater increase in dry mouth from baseline to all visits compared to surgery + RT. RT + CT had an increase in sticky saliva from baseline to 6-months compared to all other modalities.

RT only was associated with a greater increase in problems with teeth from baseline to 12-months compared to

Table 4 Difference in change in selected EORTC measures from baseline to each visit based on AJCC (7th edition) classification and total RT dose to primary site. Only models with a significant ($p < 0.05$) relationship between classification and change in EORTC item are presented. See supplementary Table S1 for full results. Estimate for specified category or dose (95% CI); p-values are presented

	T category *T III/IV vs. I/II*				N category *≥1 vs. 0*		Total RT dose to primary site *per 100 cGy greater dose*							
	Liquids	Pureed Food	Solid Food	Swallowing	Dry mouth	Sticky saliva	Solid Food	Opening mouth	Dry mouth	Sticky Saliva	Smell	Taste	Swallowing	Senses problems
P-val	0.0178	0.0047	0.0258	0.0022	≤0.0001	0.0159	≤0.0001	0.0029	≤0.0001	0.0004	0.0309	≤0.0001	0.0011	≤0.0001
V06 vs. BL	3.7 (-0.9, 8.3); 0.1147	5.3 (1.2, 9.5); 0.0125	5.0 (-0.8, 10.7); 0.0908	4.6 (1.1, 8.2); 0.0114	17.6 (11.2, 24.1); ≤0.0001	10.6 (3.6, 17.5); 0.0031	1.0 (0.6, 1.5); ≤0.0001	0.6 (0.1, 1); 0.0087	1.4 (0.9, 1.9); ≤0.0001	1.2 (0.6, 1.7); ≤0.0001	0.6 (0.2, 1); 0.0022	1.3 (0.8, 1.8); ≤0.0001	0.6 (0.3, 0.9); ≤0.0001	1.0 (0.6, 1.3); ≤0.0001
V12 vs. BL	-4.1 (-8.9, 0.7); 0.0961	-1.6 (-5.9, 2.8); 0.4827	-5.6 (-11.6, 0.4); 0.0666	-2.8 (-6.5, 1); 0.1516	14.3 (7.5, 21); ≤0.0001	7.7 (0.4, 15); 0.0379	0.8 (0.4, 1.2); 0.0004	0.6 (0.2, 1.0); 0.0056	1 (0.6, 1.5); ≤0.0001	0.5 (0, 1); 0.0476	0.3 (0, 0.7); 0.0721	0.8 (0.3, 1.2); 0.0009	0.3 (0.1, 0.6); 0.02	0.6 (0.2, 0.9); 0.0009
V18 vs. BL	-2.9 (-7.8, 2.1); 0.2552	-1.9 (-6.5, 2.6); 0.3972	-0.5 (-6.7, 5.7); 0.8775	-1.7 (-5.6, 2.1); 0.3817	11.8 (4.9, 18.7); 0.0008	9.0 (1.6, 16.4); 0.0168	0.6 (0.2, 1); 0.0071	0.4 (0, 0.8); 0.0383	0.7 (0.3, 1.2); 0.0013	0.6 (0.1, 1.1); 0.0152	0.4 (0, 0.8); 0.0307	0.6 (0.2, 1.1); 0.0082	0.2 (-0.1, 0.4); 0.1807	0.5 (0.2, 0.8); 0.0021
V24 vs. BL	-2.7 (-7.5, 2.1); 0.2725	-2.3 (-6.7, 2); 0.2988	-0.6 (-6.6, 5.4); 0.846	-0.9 (-4.7, 2.8); 0.6209	14.8 (8.1, 21.5); ≤0.0001	10.4 (3.2, 17.7); 0.0048	0.8 (0.4, 1.2); ≤0.0001	0.8 (0.3, 1.2); 0.0003	0.7 (0.2, 1.1); 0.0027	0.4 (0, 0.9); 0.0751	0.3 (-0.1, 0.6); 0.1574	0.6 (0.2, 1.1); 0.0055	0.3 (0.1, 0.6); 0.0174	0.5 (0.1, 0.8); 0.0062

Key: *AJCC* American Joint Committee on Cancer TNM system, *T* primary tumor size, *N* nodal involvement, *RT* radiation therapy, *BL* baseline pre-RT, *V06* visit 6 months post-RT, *V12* visit 12 months post-RT, *V18* visit 18 months post-RT, *V24* visit 24 months post-RT

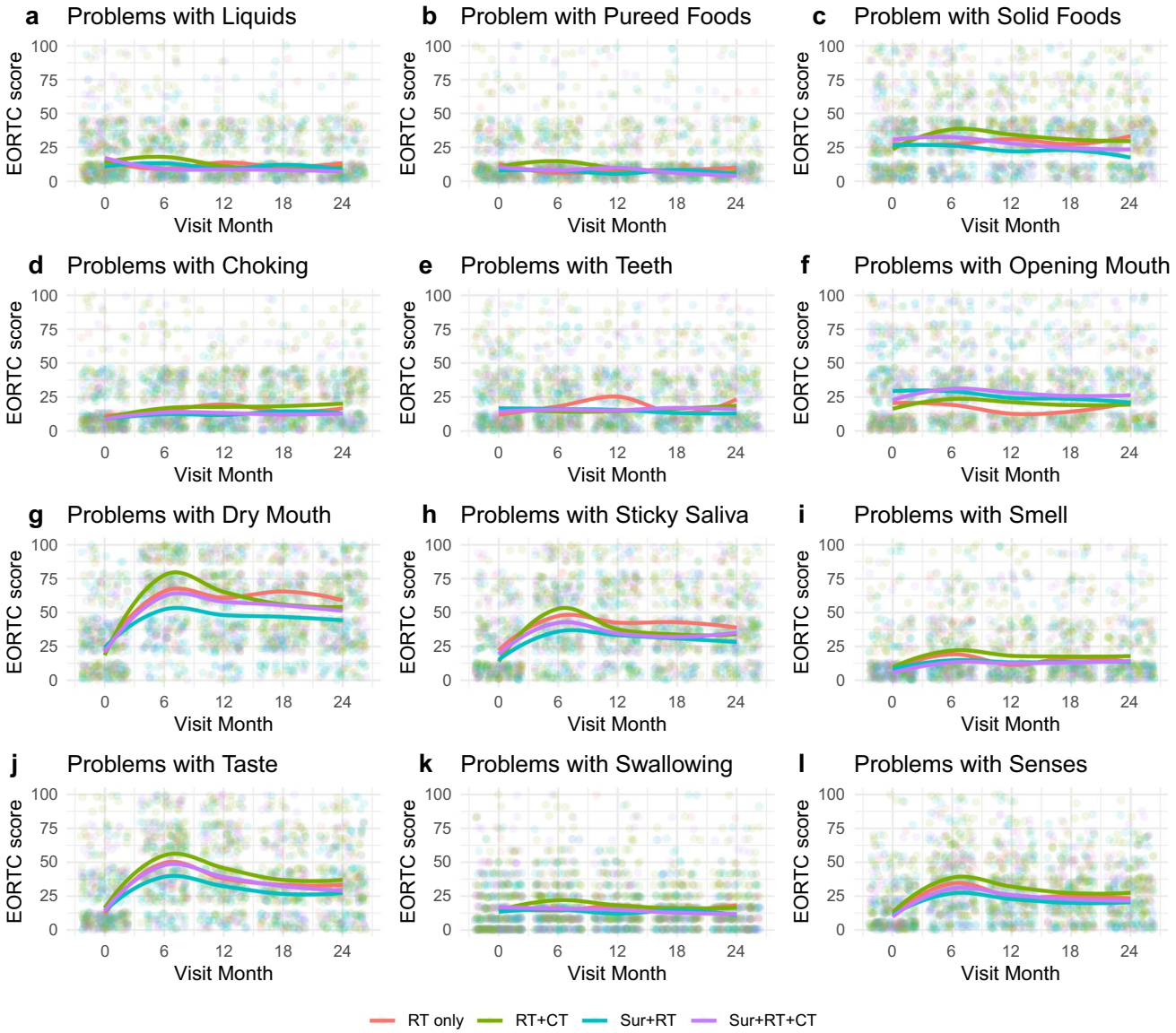

Fig. 2 Relationship between cancer treatment modalities and OH-QOL measures. Loess curve for EORTC scale by treatment modality. Visit month has been jittered for visualization purposes. Statistical comparisons are provided in Supplementary Tables S1 and S3

all other modalities and baseline to 24-months compared to surgery + RT + CT and surgery + RT.

RT + CT was associated with an increase from baseline in problems with senses (6-months) and problems with taste (6- and 12-months) compared to surgery + RT. RT alone was associated with an increase in problems with taste from baseline to 12-months compared to surgery + RT.

Discussion

Curative intent treatment involving multimodality therapy for HNC contributes to treatment-related toxicities that impact survivor QOL. Improved understanding of OH-QOL, as reported by survivors, can better prepare the cancer care team to develop and select individual treatment plans that not only improve local control and achieve cancer remission, but lessen the long-term burden of treatment toxicities. Mitigation of treatment toxicities can improve the chance of leaving survivors with higher quality years remaining. This is increasingly important because HNC epidemiology is changing to reflect more HPV-positive tumors, that generally result in longer survivorship, [16] extending the interest and focus on enjoying life. Despite technological advances in photon-based RT, including IMRT, the impact of RT dose on salivary glands creates burden for HNC survivors. Our study agrees with a systematic review and meta-analysis [17] that treatment

of oropharyngeal tumors results in marked sequelae of dry mouth and sticky saliva.

Numerous retrospective and prospective studies have documented short and long-term functional deficits using patient-reported outcomes from various HNC radiation techniques in single center studies, identifying salivary and swallowing challenges [18–20]. Few studies have documented OH-QOL changes among HNC patients after treatment including RT out to 2 years or beyond focusing on impact of IMRT [21, 22]. We previously reported that in the OraRad cohort, salivary flow reduced to 37% of pre-RT level at 6-months, with partial recovery to 59% of pre-RT dose at 18-months and subjective changes in swallowing, mouth opening, dry mouth, and sticky saliva were significantly associated with salivary flow changes [23]. This is consistent with the Likhterov et al. [20] finding of among patients receiving RT, salivary weight declines and improves over 36 months, creating correlated changes in EROTC scores for dry mouth (strongest association), sticky saliva and senses in a prospective study of HNC patients at Mt Sinai Beth Israel Hospital in New York. Although designed to test the validity, reliability and sensitivity of the EORTC questionnaires only up to 1-year post-RT, Bjordal et al. [2] found in their 500 Norwegian, Swedish and Dutch patient cohort (86% received RT; 43% surgery and 14% CT) that dry mouth was the only item in the original study with a mean score post-treatment over 50, indicating severity of symptom report, consistent with our finding.

Adding CT to RT for HNC treatment increases survival [24] and creates higher local toxicity risk [25] thus making CT + RT impact on muscles of mastication and salivary dysfunction more detrimental than RT alone, as suggested in this study. The OraRad study enrolled patients at academic medical centers during a time of multiple trials of de-escalation therapy for HPV-positive oropharyngeal tumors and did not exclude these trial patients from enrollment. De-escalation approaches to HNC treatment are intended to reduce acute and chronic toxicity of therapy without compromising survival by omitting, modifying, or reducing CT or RT dose and volume [26]. While only 6% of our patients received less than 6000 cGy, it is unlikely the OraRad cohort is able to demonstrate any impact of these de-escalation protocols on lowering oral toxicities and thus reducing OH-QOL variables of interest.

The 270 oropharyngeal tumors in our OraRad cohort were mostly (87%) HPV-positive, limiting ability to directly assess HPV-positivity's impact on OH-QOL changes for this tumor site. However, Korsten et al. [27] reported among 270 oropharyngeal cancer patients, the 29% with HPV-positive tumors had a global QOL pattern that scored better pre-treatment, worse during treatment and recovered faster and more fully at 2 years follow-up, than those with HPV-negative tumors, adjusting for sociodemographic, clinical and lifestyle factors, suggesting possible higher adaptability in this often younger population.

HNC treatment may result in long-term challenges with swallowing function. In a study of 228 survivors from 1 month to 40 years post-RT, in a multidisciplinary HNC survivorship clinic at the University of Pittsburgh, 91.2% reported at least one treatment-related impact and 56% reported at least three treatment-related effects impacting their daily life in the last week, with the most important specific outcome occurrence rates being: 51.3% swallowing, 37.3% saliva and 30.3% pain [28]. Choking when swallowing negatively impacted patients' QOL throughout the 24 months they were followed in the OraRad study. Our finding that swallowing function was most impacted by tumor location in the oropharynx is consistent with Bjordal et al. [2] who report that those with pharyngeal cancer had the highest levels of problems with swallowing. Patients with larger primary tumors also reported greater challenges with swallowing, particularly in the first year post-RT. Radiation approaches have also been attempted to spare dysphagia/aspiration at risk anatomic structures, such as pharyngeal constrictor muscles, involved in post-RT dysphagia and aspiration [29, 30].

Different patient susceptibilities may require different and more patient-specific approaches during pretreatment planning. Considering the assertion of Bjordal et al. [2], that a 10 unit or more change in mean scores over time for items and scales is clinically meaningful to patients, in our study cohort problems with dry mouth, sticky saliva, taste, and senses problems were the assessed OH-QOL aspects of importance as patient reported outcomes at 24-months. RT dose unsurprisingly was most meaningful in a progressive manner at diminishing OH-QOL. Senses of taste and smell were most impacted in older patients. A report of oral and pharyngeal cancer survivor prevalence on January 1, 2022 in the United States (U.S.), estimates 64% being over age 65 years and 63% being alive more than 5 years since their cancer diagnosis [31]. Even in healthy aging, there is a strong inverse influence of age on taste perceptions and preferences [32]. Older patients also experienced greater increases in dry mouth which is consistent with diminished secretory reserve capacity in the aging [33].

The primary outcome of the OraRad study was tooth failure, defined as a tooth being deemed hopeless and/or extracted, by the 24-month post-RT visit. Subjects often had pre-RT oral health assessments and treatment to prevent post-RT dental problems before study enrollment and obtaining baseline assessments. The 2-year estimated fraction of tooth failure was 17.8% and was significantly associated with greater reduction in salivary flow [34]. The OH-QOL question of "during the past week have you had problems with your teeth?" did not show statistically significant changes over the 24-month study period; however,

the scores did demonstrate a trend of worsening at each subsequent visit. It is possible that the clinical changes to the dentition and their subsequent impact on OH-QOL is a gradual process over time that will be more impactful for QOL in later years of cancer survivorship. An additional study visit at approximately 7 years after RT is planned for survivors in this OraRad cohort to help answer this question.

There were some limitations to our study including generalizability since OraRad was restricted to HNC patients receiving RT in U.S. academic medical centers, where multidisciplinary cancer management teams including dentists are available for dental care coordination. Time points of assessment of OH-QOL parameters at 6-month intervals may miss more nuanced time-related changes in patient perception. With lack of assessments beyond 24-months after RT we are not able to determine longer term changes in OH-QOL outcomes. QOL measures are subject to recall bias by participants and may be influenced by the Hawthorne effect of participation in a clinical study of oral side effects of RT. Our selected OH-QOL measures could have failed to detect true changes in the patient perception of these outcomes.

Demographic, cancer and treatment variables impacted OH-QOL for HNC patients through the first 24 months after undergoing RT. Despite improving RT techniques designed to limit toxicities, dry mouth, swallowing, and taste impacts of RT remain for at least 2 years, as reminders of the prior cancer treatment, that are made worse by additional use of CT. This work demonstrated toxicity profiles that might be anticipated by various baseline and treatment parameters that should be considered in designing HNC treatment plans and providing patient education about clinical course and duration of OH-QOL-impacting toxicities.

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Author contributions All authors contributed to the study conception and design. Data collection was performed by Michael Brennan, Rajesh Lalla, Thomas Sollecito, Nathaniel Treister, Brian Schmidt, Alexander Lin, Bhishamjit Chera and Lauren Patton. Data analysis was performed by Erika Helgeson. The first draft of the manuscript was written by Lauren Patton and Erika Helgeson and all authors commented on versions of the manuscript. Figures and tables were prepared by Erika Helgeson. All authors read and approved the final manuscript.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate This study was performed in line with the principles of the Declaration of Helsinki. This is an observational study. Approval was granted by the Ethics Committees of each participating enrolling University prior to enrolling patients at each respective University site. UNC Biomedical IRB# 15–2192 approved 12/7/2015. Informed consent was obtained from all individual participants included in the study.

Permissions Dr. Rajesh Lalla obtained permission from EORTC for academic use of EORTC-QLQ (H&N35) questions and scales on 11/21/2012.

Consent for publication No individual person's data is identifiable; consent to participate in this observational study included consent for publication of individual person's data as collective datasets.

Competing interests The authors have no relevant financial or non-financial interests to disclose.

References

1. Han X, Robinson LA, Jensen RE, Smith TG, Yabroff KR (2021) Factors associated with health-related quality of life among cancer survivors in the United States. JNCI Cancer Spectr 5:pkaa123. https://doi.org/10.1093/jncics/pkaa123
2. Bjordal K, Hammerlid E, Ahlner-Elmqvist M, de Graeff A, Boysen M, Evensen JF et al (1999) 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 17:1008–1019. https://doi.org/10.1200/JCO.1999.17.3.1008
3. EORTC Quality of Life Study Group. EORTC Quality of Life Questionnaire: Head & Neck Module (QLQ-H&N35): EORTC Quality of Life Study Group; 1994 [updated 1994; cited 2011 11/9/2011]. 1.0:[Available from: http://groups.eortc.be/qol/sites/default/files/img/specimen_for_printing_hn35.pdf.
4. Kolator M, Kolator P, Zatoński T (2018) Assessment of quality of life in patients with laryngeal cancer: A review of articles. Adv Clin Exp Med 27:711–715. https://doi.org/10.17219/acem/69693
5. Bjordal K, de Graeff A, Fayers PM, Hammerlid E, van Pottelsberghe C, Curran D et al (2000) 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 36:1796–1807. https://doi.org/10.1016/s0959-8049(00)00186-6
6. Anderson G, Ebadi M, Vo K, Novak J, Govindarajan A, Amini A (2021) An updated review of head and neck cancer treatment with radiation therapy. Cancers 13:4912. https://doi.org/10.3390/cancers13194912
7. Wan Leung S, Lee TF, Chien CY, Chao PJ, Tsai WL, Fang FM (2011) Health-related quality of life in 640 head and neck cancer survivors after radiotherapy using EORTC QLQ-C30 and QLQ-H&N35 questionnaires. BMC Cancer 12(11):128. https://doi.org/10.1186/1471-2407-11-128
8. Li X, Lee A, Cohen MA, Sherman EJ, Lee NY (2020) Past, present and future of proton therapy for head and neck cancer. Oral Oncol 110:104879. https://doi.org/10.1016/j.oraloncology.2020.104879
9. Pham TT, Whelan B, Oborn BM, Delaney GP, Vinod S, Brighi C et al (2022) Magnetic resonance imaging (MRI)

guided proton therapy: A review of the clinical challenges, potential benefits and pathway to implementation. Radiother Oncol Mar 4:S0167–8140(22)00116–5. https://doi.org/10.1016/j.radonc.2022.02.031.
10. Lalla RV, Long-Simpson L, Hodges JS, Treister N, Sollecito T, Schmidt B et al (2017) Clinical registry of dental outcomes in head and neck cancer patients (OraRad): rationale, methods, and recruitment considerations. BMC Oral Health 17:59. https://doi.org/10.1186/s12903-017-0344-y
11. Cleveland WS, Devlin SJ (1988) Locally Weighted Regression: An Approach to Regression Analysis by Local Fitting. J Am Stat Assoc 83(403):596–610. https://doi.org/10.1080/01621459.1988.10478639
12. R Core Team (2019) R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Available at: https://www.R-project.org/.
13. Bates D, Mächler M, Bolker B, Walker S (2015) Fitting linear mixed-effects models using lme4. J Stat Softw 67:1–48
14. Kuznetsova A, Brockhoff PB, Christensen RH (2017) Lmertest package: Tests in linear mixed effects models. J Stat Softw 82:1–26
15. Lenth R (2020) Emmeans: Estimated marginal means, aka least-squares means. R package version 1.4.6. ed
16. D'Souza G, Anatharaman D, Gheit T, Abedi-Ardekani G, Beachler DC, Conway DI et al (2016) Effect of HPV on head and neck cancer patient survival, by region and tumor site: A comparison of 1362 cases across three continents. Oral Oncol 62:20–27. https://doi.org/10.1016/j.oraloncology.2016.09.005
17. HøxbroeMichaelsen S, Grønhøj C, HøxbroeMichaelsen J, Friborg J, von Buchwald C (2017) Quality of life in survivors of oropharyngeal cancer: A systematic review and meta-analysis of 1366 patients. Eur J Cancer 78:91–102. https://doi.org/10.1016/j.ejca.2017.03.006
18. Cartmill B, Cornwell P, Ward E, Davidson W, Porceddu S (2012) Long-term functional outcomes and patient perspective following altered fractionation radiotherapy with concomitant boost for oropharyngeal cancer. Dysphagia 27:481–490. https://doi.org/10.1007/s00455-012-9394-0
19. Barnhart MK, Robinson RA, Simms VA, Ward EC, Cartmill B, Chandler SJ et al (2018) Treatment toxicities and their impact on oral intake following non-surgical management for head and neck cancer: a 3-year longitudinal study. Support Care Cancer 26:2341–2351. https://doi.org/10.1007/s00520-018-4076-6
20. Likhterov I, Ru M, Ganz C, Urken ML, Chai R, Okay D et al (2018) Objective and subjective hyposalivation after treatment for head and neck cancer: Long-term outcomes. Laryngoscope 128:2732–2739. https://doi.org/10.1002/lary.27224
21. Chen AM, Daly ME, Farwell DG, Vazquez E, Courquin J, Lau DH et al (2014) Quality of life among long-term survivors of head and neck cancer treated by intensity-modulated radiotherapy. JAMA Otolaryngol Head Neck Surg 140:129–133. https://doi.org/10.1001/jamaoto.2013.5988
22. Huang TL, Chien CY, Tsai WL, Liao KC, Chou SY, Lin HC et al (2016) Long-term late toxicities and quality of life for survivors of nasopharyngeal carcinoma treated with intensity-modulated radiotherapy versus non-intensity-modulated radiotherapy. Head Neck 38(Suppl 1):E1026-1032. https://doi.org/10.1002/hed.24150
23. Lin A, Helgeson ES, Treister NS, Schmidt BL, Patton LL, Elting LS et al (2022) The impact of head and neck radiotherapy on salivary flow and quality of life: Results of the ORARAD study. Oral Oncol 127:105783. https://doi.org/10.1016/j.oraloncology.2022.105783
24 Parmar A, Macluskey M, Mc Goldrick N, Conway DI, Glenny AM, Clarkson JE et al (2021) Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy. Cochrane Database Syst Rev 12:CD006386. https://doi.org/10.1002/14651858.CD006386.pub4
25. Calais G, Alfonsi M, Bardet E, Sire C, Germain T, Bergerot P et al (1999) Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. J Natl Cancer Inst 91:2081–2086. https://doi.org/10.1093/jnci/91.24.2081
26. Tawk B, Debus J, Abdollahi A (2022) Evolution of a Paradigm Switch in Diagnosis and Treatment of HPV-Driven Head and Neck Cancer-Striking the Balance Between Toxicity and Cure. Front Pharmacol 12:753387. https://doi.org/10.3389/fphar.2021.753387
27. Korsten LHA, Jansen F, Lissenberg-Witte BI, Vergeer M, Brakenhoff RH, Leemans CR et al (2021) The course of health-related quality of life from diagnosis to two years follow-up in patients with oropharyngeal cancer: does HPV status matter? Support Care Cancer 29:4473–4483. https://doi.org/10.1007/s00520-020-05932-w
28. Nilsen ML, Mady LJ, Hodges J, Wasserman-Wincko T, Johnson JT (2019) Burden of treatment: reported outcomes in a head and neck cancer survivorship clinic. Laryngoscope 129:E437-e444. https://doi.org/10.1002/lary.27801
29. Eisbruch A, Schwartz M, Rasch C, Vineberg K, Damen E, Van As CJ et al (2004) Dysphagia and aspiration after chemoradiotherapy for head-and-neck cancer: which anatomic structures are affected and can they be spared by IMRT? Int J Radiat Oncol Biol Phys 60:1425–1439. https://doi.org/10.1016/j.ijrobp.2004.05.050
30. Petkar I, Rooney K, Roe JW, Patterson JM, Bernstein D, Tyler JM et al (2016) DARS: a phase III randomised multicentre study of dysphagia- optimised intensity- modulated radiotherapy (Do-IMRT) versus standard intensity- modulated radiotherapy (S-IMRT) in head and neck cancer. BMC Cancer 16:770. https://doi.org/10.1186/s12885-016-2813-0
31. Miller KD, Nogueira L, Devasia T, Mariotto AB, Yabroff KR, Jemal A et al (2022) Cancer treatment and survivorship statistics, 2022. CA Cancer J Clin 0:1–28. https://doi.org/10.3322/caac.21731
32. Ghezzi EM, Ship JA (2003) Aging and secretory reserve capacity of major salivary glands. J Dent Res 82:844–848. https://doi.org/10.1177/154405910308201016
33. Barragán R, Coltell O, Portolés O, Asensio EM, Sorlí JV, Ortega-Azorín C et al (2018) Bitter, Sweet, Salty, Sour and Umami Taste Perception Decreases with Age: Sex-Specific Analysis, Modulation by Genetic Variants and Taste-Preference Associations in 18 to 80 Year-Old Subjects. Nutrients 10:1539. https://doi.org/10.3390/nu10101539
34. Brennan MT, Treister NS, Sollecito TP, Schmidt BL, Patton LL, Lin A et al (2022) Tooth Failure Post-Radiotherapy in Head and Neck Cancer: Primary Report of the Clinical Registry of Dental Outcomes in Head and Neck Cancer Patients (OraRad) Study. Int J Radiat Oncol Biol Phys 113(2):320–330. https://doi.org/10.1016/j.ijrobp.2021.11.021

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