

ORIGINAL ARTICLE

Oral complications at 6 months after radiation therapy for head and neck cancer

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Objective: To examine oral complications 6 months after modern radiation therapy (RT) for head and neck cancer (HNC).**Methods:** Prospective multicenter cohort study of patients with HNC receiving intensity-modulated radiation therapy or more advanced RT. Stimulated whole salivary flow, maximal mouth opening, oral mucositis, oral pain, oral health-related quality of life (OH-QOL), and oral hygiene practices were measured in 372 subjects pre-RT and 216 subjects at 6 months from the start of RT.**Results:** Mean stimulated whole salivary flow declined from 1.09 to 0.47 ml/min at 6 months ($p < .0001$). Mean maximal mouth opening reduced from 45.58 to 42.53 mm at 6 months ($p < .0001$). 8.1% of subjects had some oral mucositis at 6 months, including 3.8% with oral ulceration. Mean overall pain score was unchanged. OH-QOL was reduced at 6 months, with changes related to dry mouth, sticky saliva, swallowing solid foods, and sense of taste ($p \leq .0001$). At 6 months, there was greater frequency of using dental floss and greater proportion using supplemental fluoride ($p < .0001$).**Conclusions:** Despite advances in RT techniques, patients with HNC experience oral complications 6 months after RT, with resulting negative impacts on oral function and quality of life.**KEYWORDS**

head and neck cancer, mouth opening, oral complications, quality of life, radiation therapy, salivary flow

1 | INTRODUCTION

Radiation therapy (RT) is a common treatment modality for patients with head and neck cancer (HNC). RT for HNC typically involves total

doses of 6,000–7,000 cGy, delivered in daily fractions over 6–7 weeks (Pfister et al., 2015), and is known to cause a number of oral complications. These include oral mucositis, oral pain, hyposalivation, increased risk of dental caries, reduced mouth opening, and osteoradionecrosis

(Buglione, Cavagnini, Di Rosario, Maddalo, et al., 2016; Buglione, Cavagnini, Di Rosario, Sottocornola, et al., 2016). Much of the data on oral complications of RT for HNC come from smaller single-center studies using older RT techniques. Intensity-modulated radiation therapy (IMRT) is now considered standard of care for HNC (Pfister et al., 2015). Using IMRT, it is possible to decrease the radiation dose to adjacent structures (such as the salivary glands), potentially reducing incidence and/or severity of oral complications (Duarte et al., 2014). The current manuscript reports on oral complications at 6 months after RT in a large multicenter cohort of patients with HNC.

2 | METHODS

2.1 | Study design

OraRad is an ongoing prospective multicenter longitudinal cohort study of patients with HNC who receive high-dose RT with curative intent. Enrollment began in 2014 with a total planned enrollment of 756 subjects at six primary clinical sites (and their affiliated sites) in the United States. A baseline visit is conducted before the beginning of RT to the head and neck (H&N) region using IMRT or newer techniques. Follow-up visits are conducted at 6, 12, 18, and 24 months after the start of RT. The primary outcome measure is the 2-year rate of tooth loss in patients who have received at least one session of external beam RT for HNC. Secondary outcome measures include incidence of exposed intraoral bone; incidence of postextraction complications; change in decayed, missing, and filled surfaces (DMFS); change in periodontal measures; change in stimulated whole salivary flow rates; change in mouth opening; topical fluoride utilization; oral mucositis incidence; changes in RT-specific quality-of-life measures; and change in oral pain scores. Additional details on the study, including a listing of clinical sites, are on www.clinicaltrials.gov (NCT02057510). The study was performed in accordance with the Declaration of Helsinki. All subjects provided written informed consent. The study received ethical approval from the following institutional review boards (IRBs): Carolinas HealthCare System IRB, University of Connecticut Health IRB, University of Pennsylvania IRB, Dana-Farber Cancer Institute IRB, New York University IRB, University of North Carolina IRB, and University of Minnesota IRB.

2.2 | Subject selection criteria

2.2.1 | Inclusion criteria

To be eligible to participate in this study, a patient must meet all of the following criteria: (i) diagnosed with H&N squamous cell carcinoma (SCC) or a salivary gland cancer (SGC), and intends to receive external beam RT with curative intent (tumor eradication), with or without concomitant chemotherapy, or diagnosed with a non-SCC, non-SGC malignancy of the H&N region, and expected to receive at least 4,500 cGy RT to at least one of 26 specified sites in the H&N region, with or without concomitant chemotherapy; (ii) aged 18 years and older; and (iii) at least one natural tooth remaining or expected to remain in the mouth after completion of pre-RT dental extractions, if

any. After completion of the baseline study visit, it must be verified that the subject has received at least one RT session, to confirm eligibility for continued follow-up.

2.2.2 | Exclusion criteria

A potential subject meeting any of the following criteria is excluded from participation in this study: (i) receiving palliative RT; (ii) history of prior curative RT to the H&N region to eradicate a malignancy; and (iii) incarcerated at the time of screening.

2.3 | Assessments

2.3.1 | Salivary flow

Stimulated whole salivary flow is measured by trained study coordinators. The subject is first asked to rinse out the mouth for 30 s using tap water. During the collection period, the subject is seated upright with head tilted slightly forward. The subject is told to swallow all the saliva in the mouth before the collection period. Then, the subject is given two pellets of gum base (total weight 0.45–0.60 g) and asked to chew them once per second for 2 min, using a timer. All saliva produced is spit into a plastic tube. This initial saliva collection is to standardize salivary flow and is not used to calculate flow rate. The subject is then given a new tube and asked to chew the pellets once per second for 5 min. All saliva produced is spit into the second tube, and the pellets are also spit into the tube at the end of 5 min. The tube is weighed, and the difference between the pellet-containing tube before and after the addition of saliva is recorded. The stimulated salivary flow rate per minute is calculated based on the total weight of saliva produced and the period of collection.

2.3.2 | Maximal mouth opening

Maximal mouth opening is measured by trained clinical examiners (dental hygienists or dentists) using a disposable Therabite® Range of Motion Scale (Altos Medical, West Allis, WI, USA) with gradations in millimeters. The subject is asked to open the mouth as wide as possible, while avoiding excessive pain. The measurement is performed in the following order of preference:

1. Tooth to tooth: used for a subject with remaining maxillary and mandibular anterior teeth or who is partially edentulous, but wears a partial denture to replace missing anterior teeth. Interincisal distance is measured as the distance between the maxillary and mandibular incisors. Measurement is from the mesial–distal midpoint of the facial–incisal edge of each tooth.
2. Tooth to alveolar ridge: used for a subject who is missing anterior teeth in one arch, but does not have a partial denture. The measurement is the distance between the mesial–distal midpoint of the facial–incisal edge of the right central incisor (or closest anterior tooth) of the dentate ridge to the edentulous alveolar ridge in the area of the right central incisor.

3. Alveolar ridge to alveolar ridge: used for a subject who is completely edentulous in the anterior areas. The distance between the alveolar ridges in the area of the right central incisors is measured.

2.3.3 | Oral mucositis

Oral mucositis is scored by clinical examiners, trained on appropriate scoring using the WHO Oral Mucositis Scale (World Health Organization, 1979). Oral mucositis is scored based on a clinical examination of the oral cavity and questioning of the subject about pain and diet. The following grades are used: grade 0: no oral mucositis; grade 1: erythema and soreness (no ulcer); grade 2: ulcer(s) present, subject able to eat solids; grade 3: ulcer(s) present, subject requires a liquid diet (due to mucositis); and grade 4: ulcer(s) present, alimentation not possible (due to mucositis).

2.3.4 | Oral pain

The Oral Pain form used in this study is a selection of eight relevant items from the UCSF Oral Cancer Pain Scale and is self-completed by the subject (Connelly & Schmidt, 2004). Six of the items assessed describe the intensity, sharpness, and aching quality of pain, each assessed separately when not talking, eating, or drinking and again when doing so. Each item is scored on a 100-mm visual analog scale with "No Pain" at the extreme left and "The most (intense/sharp/aching) pain sensation imaginable" at the extreme right. The subject is asked to put a mark through the 100-mm line to indicate the level of pain experienced during the past week. The other items assessed are sensitivity of the (bothersome) area in the mouth to touch by teeth, food, or fluids ("No sensitivity" on extreme left to "Most sensitive pain imaginable" on extreme right) and restriction of talking, eating, or drinking due to mouth pain ("No restriction" on extreme left to "Most severe restriction imaginable" on extreme right). Each item's score is determined by measuring the distance (in mms) between the left end of the 100-mm line and the mark made by the subject, using a standardized study-provided ruler.

2.3.5 | Oral health-related quality of life

The subject is asked questions related to oral health-related quality of life using selected relevant items from the EORTC QLQ-H&N35 scale (EORTC, 2009). Questions are asked about occurrence of the following 10 issues within the past week: problems swallowing liquids, pureed foods, and solid foods; choking when swallowing; problems with teeth; problems opening the mouth wide; dry mouth; sticky saliva; problems with taste; and problems with smell. The four options for each item are as follows: Not at all; A little; Quite a bit; and Very much.

2.3.6 | Oral hygiene practices

The subject is asked questions about the following oral hygiene practices: frequency of brushing teeth, frequency of using floss or other

interdental aids, and use of supplemental fluoride including modality (rinse or gel with brush or tray) and frequency. Questions related to frequency provided five options: More than once a day, Once a day, 4–6 times a week, 1–3 times a week, and less than once a week.

2.4 | Statistical analyses

Changes in outcome measures from baseline to 6 months were estimated and tested using generalized estimating equations (GEEs), with clusters being persons and using empirical standard errors. When sexes are compared, the predictors in the analysis were sex, visit, and their interaction; the latter tests whether the sexes differ in the change from baseline to 6 months; when another grouping was compared, the predictors were analogous, with sex replaced by the other grouping. Analyses used the identity link except for oral mucositis, which was analyzed as a binary outcome (present vs absent) using the logit link, and the oral hygiene outcomes, which used the logit or cumulative logit link if the outcome had two or more categories, respectively. Salivary flow was analyzed using both the original measurements and their logarithms, with the latter testing whether changes in males and females differed proportionately as well as absolutely. Pearson's correlations of oral health-related quality of life (OH-QOL) with other measures use *p* values from the corresponding linear regression. All analyses used SAS (University Edition 3.5, SAS Institute Inc., Cary, NC, USA); GEEs were done using the GENMOD procedure.

3 | RESULTS

3.1 | Sample characteristics

At the time of these analyses, a total of 1,080 patients had been screened for the study. Of these, 372 were eligible, agreed to participate, and had completed the baseline visit. Another 41 patients were eligible, but the baseline visit was not yet completed. A total of 667 patients were not eligible or interested to move forward in the study. The reasons were as follows: not interested/too busy—394 (59%); no teeth to remain—103 (15%); moving/not in area—40 (6%); too ill—30 (4%); and other—100 (15%).

As of the date of these analyses, there were 20 deaths among enrolled subjects (all unrelated to study participation) and one subject withdrew from the study. Data from a total of 372 subjects at baseline and 216 subjects at 6 months were used for these analyses. The lower number of subjects at the 6-month visit as compared to baseline is mainly because this is an ongoing study. All data available for each outcome measure were used. Table 1 reports the demographics, tumor characteristics, and treatment details.

3.2 | Salivary flow

Stimulated whole salivary flow data were available for 354 subjects at baseline (before the start of RT) and for 216 subjects at 6 months. The mean stimulated whole salivary flow for all subjects together declined significantly from 1.09 ml/min (SD 0.67) at baseline to

TABLE 1 Subject characteristics

Characteristic	Baseline (n (%))	Sample size at baseline	6 months (n (%))	Sample size at 6 Months
Sex		372		216
Male	284 (76.3%)		168 (77.8%)	
Female	88 (23.7%)		48 (22.2%)	
Age (years)	59.8 (10.9) ^a	372	58.8 (11.1) ^a	216
Race		372		216
White	309 (83.1%)		173 (80.1%)	
Black	33 (8.9%)		18 (8.3%)	
Multiracial	5 (1.3%)		4 (1.9%)	
Asian	16 (4.3%)		14 (6.5%)	
Native Hawaiian	1 (0.3%)		1 (0.5%)	
Native American	1 (0.3%)		1 (0.5%)	
Don't know/declined	7 (1.9%)		5 (2.3%)	
Ethnicity		372		216
Hispanic	18 (4.8%)		6 (2.8%)	
Non-Hispanic	354 (95.2%)		210 (97.2%)	
Type of cancer		369		215
Squamous cell carcinoma	302 (81.8%)		180 (83.7%)	
Salivary gland cancer	43 (11.7%)		23 (10.7%)	
Other	24 (6.50%)		12 (5.58%)	
Primary site of RT		360		213
Base of tongue	71 (19.7%)		40 (18.6%)	
Buccal/Labial Mucosa	7 (1.9%)		3 (1.4%)	
Epiglottis	1 (0.3%)		0 (0%)	
Floor of mouth	3 (0.8%)		0 (0%)	
Gingiva/alveolar ridge	1 (0.3%)		1 (0.5%)	
Hard plate	4 (1.1%)		3 (1.4%)	
Hypopharynx	9 (2.5%)		5 (2.3%)	
Larynx	18 (5.0%)		11 (5.1%)	
Lip	3 (0.8%)		1 (0.5%)	
Mandible	2 (0.6%)		2 (0.9%)	
Maxilla	2 (0.6%)		2 (0.9%)	
Maxillary sinus	2 (0.6%)		1 (0.5%)	
Nasal cavity	1 (0.3%)		0 (0%)	
Nasopharynx	23 (6.4%)		17 (7.9%)	
Neck	44 (12.2%)		27 (12.6%)	
Oral cavity	7 (1.9%)		3 (1.4%)	
Oral tongue	20 (5.6%)		9 (4.2%)	
Oropharynx	25 (6.9%)		17 (7.9%)	
Paranasal sinus/orbit	0 (0%)		0 (0%)	
Parotid	30 (8.3%)		17 (7.9%)	
Pharynx	4 (1.1%)		3 (1.4%)	
Retromolar trigone	1 (0.3%)		1 (0.5%)	
Soft palate	0 (0%)		0 (0%)	
Sublingual gland	0 (0%)		0 (0%)	
Submandibular gland	5 (1.4%)		3 (1.4%)	

(Continues)

TABLE 1 (Continued)

Characteristic	Baseline (n (%))	Sample size at baseline	6 months (n (%))	Sample size at 6 Months
Tonsil	63 (17.5%)		41 (19.1%)	
Other	14 (3.9%)		6 (2.8%)	
Type of RT		360		213
IMRT with image guidance	299 (83.1%)		168 (78.9%)	
IMRT without image guidance	32 (8.9%)		25 (11.7%)	
3D conformal radiation	19 (5.3%)		7 (3.3%)	
Proton	27 (7.5%)		19 (8.9%)	
Other	1 (0.3%)		1 (0.5%)	
Total RT dose to primary site (cGy)	6,577 (703) ^a	360	6,639 (575) ^a	213
RT to primary site		360		213
Unilateral	237 (65.8%)		142 (66.7%)	
Bilateral	123 (34.2%)		71 (33.3%)	
Surgery prior to RT		360		213
No	158 (43.9%)		90 (42.3%)	
Yes	202 (56.1%)		123 (57.7%)	
Chemotherapy received		360		213
No	120 (33.3%)		76 (35.7%)	
Yes	240 (66.7%)		137 (64.3%)	
Before the start of RT	92 (25.6%)		53 (24.9%)	
During RT	237 (65.8%)		136 (63.8%)	
Both	89 (24.7%)		52 (24.4%)	

^aThese table entries are average (SD).

0.47 ml/min (SD 0.47) at 6 months ($p < .0001$). Mean salivary flow rates were significantly higher for males than for females at both baseline (males 1.17 ml/min [SD 0.69]; females 0.82 ml/min [SD 0.50]; $p < .0001$) and 6 months (males 0.50 ml/min [SD 0.50]; females 0.36 ml/min [SD 0.30]; $p = .0185$). Salivary flow in males declined by a greater absolute amount, consistent with their higher starting salivary flow (sex-by-visit interaction, $p = .004$). However, the proportionate reductions in salivary flow were similar in males and females ($p = .42$). Mean stimulated whole salivary flow at 6 months after the start of RT for the different RT modalities was as follows: 3D conformal RT: 0.38 ml/min; IMRT without image guidance: 0.56 ml/min; IMRT with image guidance: 0.54 ml/min; and proton therapy: 0.80 ml/min. These differences were not statistically significant. The primary site of RT was not significantly associated with the stimulated whole salivary flow rate at 6 months ($p = .25$). No significant association was found between unilateral vs bilateral RT and stimulated whole salivary flow rate at 6 months ($p = .8657$).

3.3 | Maximal mouth opening

Data on maximal mouth opening were available for 371 subjects at baseline and 208 subjects at 6 months. For all subjects together, mean maximal mouth opening was significantly reduced from 45.58 mm

(SD 10.40) at baseline to 42.55 mm (SD 9.52) at 6 months ($p < .0001$). Mean maximal mouth opening was significantly higher for males than for females at both baseline (males 47.07 mm [SD 9.98]; females 40.74 mm [SD 10.30]; $p < .0001$) and 6 months (males 43.82 mm [SD 9.47]; females 37.75 mm [SD 8.16]; $p < .0001$). Males and females did not differ significantly in their respective reductions in maximal mouth opening ($p = .92$).

3.4 | Oral mucositis

Data on oral mucositis were available for 371 subjects at baseline and 211 subjects at 6 months. Only five subjects (1.3%) had oral mucositis prior to RT, and oral mucositis was resolved in most subjects by the 6-month visit. However, 17 of 211 subjects (8.1%) had some oral mucositis at 6 months. Of these 17 subjects, nine subjects had WHO grade 1 oral mucositis, six subjects had grade 2 oral mucositis, and two subjects had grade 3 oral mucositis. Subjects who had induction chemotherapy (prior to RT) were significantly more likely to have oral mucositis at the subsequent baseline study visit ($p = .005$). Induction chemotherapy was not associated with the presence of oral mucositis at 6 months after the start of RT ($p = .20$). Oral mucositis was present at 6 months in 9.0% of subjects receiving concurrent chemotherapy as compared to 5.9% of subjects not receiving concurrent chemotherapy ($p = .17$). Oral mucositis was recorded at the 6-month visit

TABLE 2 Oral pain scores

Pain attribute	Mean score ^a at baseline (SD) (n = 371)	Mean score ^a at 6 months (SD) (n = 211)	Time main effect p value	Sex main effect p value	Interaction p value
Overall oral pain score	9.24 (16.44)	9.24 (17.07)	.5377	.386	.4806
Pain intensity at rest	7.44 (16.83)	6.16 (16.72)	.4042		
Pain intensity when talking, eating, or drinking	12.86 (23.06)	11.44 (22.14)	.4078		
Pain sharpness at rest	5.50 (15.09)	5.57 (16.12)	.9191		
Pain sharpness when talking, eating, or drinking	9.36 (19.98)	10.00 (21.76)	.7999		
Pain aching at rest	7.51 (17.17)	6.31 (18.39)	.4304		
Pain aching when talking, eating, or drinking	10.55 (20.62)	9.19 (19.94)	.3851		
Sensitivity to touch by teeth, food, or fluids	9.92 (19.80)	14.42 (24.07)	.0128		
Restriction of talking, eating, or drinking due to mouth pain	10.75 (22.12)	10.83 (21.83)	.9199		

^aHigher score = greater pain intensity/sharpness/aching/sensitivity/restriction.

in 8% of patients receiving IMRT with image guidance, 13% of those receiving IMRT without image guidance, and 0% of patients receiving proton therapy or 3D conformal radiation ($p = .72$).

3.5 | Oral pain

Oral pain scores were available for 371 subjects at baseline and 211 subjects at 6 months (Table 2). Females showed a non-significant trend toward higher mean oral pain score than males at both baseline (females 12.56 [SD 2.00]; males 8.20 [SD 0.92]) and 6 months (females 11.00 [SD 2.67]; males 8.67 [SD 1.25]). The mean overall pain score for all subjects was unchanged comparing baseline to 6 months. Most components of the overall pain score were also unchanged, except for “sensitivity to touch by teeth, food, or fluids,” which increased from 9.92 (SD 19.80) to 14.42 (SD 24.07; $p = .013$). No relationship was found between surgical treatment of H&N cancer and oral pain score at baseline or 6 months ($p = .45$). The use of concomitant chemotherapy during RT also was not significantly associated with pain scores at 6 months ($p = .59$).

3.6 | Oral health-related quality of life

Data on OH-QOL (1–4 scale) were available for 371 subjects at baseline and 211 subjects at 6 months (Table 3). The mean overall OH-QOL score (averaging all 10 included items together) significantly worsened from 1.48 (SD 0.42) at baseline to 1.86 (SD 0.47) at 6 months ($p < .0001$). Contributing to this decline were subject-reported negative changes related to swallowing solid food, choking

when swallowing, opening the mouth wide, dry mouth, sticky saliva, smell, and taste ($p < .0001$ for each). Gender was not significantly associated with overall OH-QOL score or with the change in this score. Unilateral vs bilateral RT was not significantly associated with the OH-QOL score at 6 months ($p = .06$).

We also examined correlations of OH-QOL with oral pain, maximal mouth opening, and salivary flow. Of these, OH-QOL was significantly correlated with oral pain at both baseline ($r = .47$; $p < .0001$) and 6 months ($r = .54$; $p < .0001$). Furthermore, changes in oral pain between baseline and 6 months were significantly correlated with changes in OH-QOL ($r = .51$; $p < .0001$). Reduced mouth opening was significantly correlated with worse OH-QOL at baseline ($r = -.15$; $p = .004$) but not at 6 months ($r = -.01$; $p = .88$).

3.7 | Oral hygiene practices

Data on oral hygiene practices were available for 371 subjects at baseline and 211 subjects at 6 months (Table 4). The frequency of brushing teeth did not change significantly between baseline and 6 months, with more than 75% of subjects reporting that they brushed more than once/day at both time points. The frequency of using dental floss or other interdental devices increased at 6 months ($p < .0001$). The proportion of subjects using supplemental fluoride (defined as fluoride use other than over-the-counter toothpaste) increased significantly from 41% at baseline to 68.2% at 6 months ($p < .0001$). Among subjects using supplemental fluoride, a shift was seen away from non-prescription rinses toward greater use of prescription gels with a toothbrush at 6 months ($p = .0015$).

TABLE 3 Oral health-related quality of life (OH-QOL) scores

Item	Mean score ^a at baseline (SD) (n = 371)	Mean score ^a at 6 months (SD) (n = 211)	Time main effect p value	Sex main effect p value
Overall OH-QOL score	1.48 (0.42)	1.86 (0.47)	<.0001	.0662
Problem with...				
Swallowing liquids	1.42 (0.68)	1.40 (0.68)	.7942	
Swallowing pureed foods	1.31 (0.65)	1.33 (0.68)	.7651	
Swallowing solid food	1.78 (0.93)	2.00 (0.91)	.0001	
Choking when swallowing	1.25 (0.60)	1.42 (0.68)	<.0001	
Teeth	1.47 (0.76)	1.47 (0.89)	.9928	
Opening mouth wide	1.65 (0.90)	1.83 (0.95)	.0017	
Dry mouth	1.67 (0.83)	2.90 (0.96)	<.0001	
Sticky Saliva	1.51 (0.78)	2.33 (1.00)	<.0001	
Sense of smell	1.23 (0.62)	1.45 (0.76)	<.0001	
Sense of taste	1.46 (0.76)	2.42 (0.96)	<.0001	

^aScore of 1 = not at all; score of 4 = very much.

4 | DISCUSSION

OraRad is a large ongoing multicenter prospective cohort study, examining oral complications after RT for HNC, using modern-day RT techniques. The current analyses examine oral complications expected to occur during H&N RT or in the 6-month period following it. These include hyposalivation, reduced mouth opening, oral mucositis, oral pain, and impacts on quality of life. We also report on oral hygiene practices, which can influence longer-term oral complications such as dental caries and osteoradionecrosis.

Saliva is critically important to oral health. Reduced salivary flow is known to increase risk for dental caries, oral candidiasis, and mucosal trauma (Meurman & Gronroos, 2010). Modern RT techniques, including IMRT, allow greater protection of salivary glands from RT. This can be expected to result in a less significant compromise in salivary function (Marta et al., 2014). Nonetheless, we still found more than a 50% reduction in mean stimulated whole salivary flow rate, from 1.09 ml/min pre-RT to 0.47 ml/min 6 months after the start of RT. However, this 6-month flow rate is higher than that reported 6 months after RT using older treatment modalities (Jensen et al., 2010; Lal et al., 2010). Thus, use of the modern techniques does appear to provide a benefit. Furthermore, additional recovery of salivary flow beyond 6 months after RT has been reported (Braam et al., 2005). Future analyses of our study data, at follow-up times up to 18 months, will provide important insights about additional potential recovery of salivary flow rates with current treatment modalities.

Radiation therapy can cause inflammation and fibrosis of the muscles of mastication, which can lead to reduced mouth opening (called trismus when severely restricted) (Rapidis et al., 2015; Bensadoun et al., 2010). This can lead to significant compromise of diet/nutrition, speech, and oral hygiene (Satheeshkumar, Mohan, & Jacob, 2014). This study found a 3 mm reduction in mean maximal mouth opening for all subjects

together, from 45.58 mm pre-RT to 42.53 mm at 6 months after the start of RT. However, the mean mouth opening at 6 months is still higher than the commonly used definition of trismus (35 mm or less). Females may be particularly susceptible to developing clinical trismus as they start RT with a notably smaller maximal mouth opening on average. Female subjects in this study had a mean maximal mouth opening of 40.74 mm at baseline, which declined to 37.75 mm at 6 months.

Oral mucositis refers to erythema and ulceration of the oral mucosa, as a side effect of systemic chemotherapy and/or RT to the H&N region. Lesions of oral mucositis are intensely painful, with negative impacts on diet/nutrition, speech, and oral hygiene, and increased risk for infection (Lalla, Saunders, & Peterson, 2014). More than 80% of patients receiving RT for H&N cancer develop ulcerative oral mucositis by the fourth week of the 6- to 7-week regimen (Vera-Llonch, Oster, Hagiwara, & Sonis, 2006). Concurrent chemotherapy further increases the severity of oral mucositis (Vera-Llonch et al., 2006). In most H&N RT patients, the ulcerative lesions heal within a month or so after the end of RT. However, clinical experience has shown that for some patients, these lesions can persist for longer. Chronic oral mucositis after H&N RT has recently been described in four cases (Elad & Zadik, 2016). This study found that 17 subjects (8.3%) still had some degree of clinically diagnosed oral mucositis 6 months after the start of RT. Of these, nine subjects had grade 1 oral mucositis (erythema and soreness). However, eight subjects still had ulcerative oral mucositis, with two of them unable to tolerate a solid diet due to mucositis. A limitation of this study is that we did not record the incidence or severity of oral mucositis during RT or at post-RT time points earlier than 6 months. Also, in some cases the persistent lesions we identified may have another cause. Nevertheless, these findings suggest the need for clinicians to follow oral mucositis until complete resolution and to address secondary complications (such as infection and poor nutrition) that can delay healing.

TABLE 4 Oral hygiene practices

Oral hygiene practices	Number of subjects (%) at baseline (n = 371)	Number of subjects (%) at 6 months (n = 211)	p value
Frequency of brushing teeth			
More than once/day	287 (77.4%)	172 (81.5%)	.1683
Once/day	70 (18.9%)	31 (14.7%)	
4–6X/week	5 (1.4%)	1 (0.5%)	
1–3X/week	8 (2.2%)	6 (2.8%)	
Less than 1×/week	1 (0.3%)	1 (0.5%)	
Use of dental floss or other device to clean between teeth—frequency			
More than once/day	71 (19.1%)	57 (27.0%)	<.0001
Once/day	116 (31.3%)	72 (34.1%)	
4–6X/week	24 (6.5%)	23 (10.9%)	
1–3X/week	67 (18.1%)	24 (11.4%)	
Less than 1×/week	93 (25.1%)	35 (16.6%)	
Supplemental fluoride use			
Yes	152 (41.0%)	144 (68.2%)	<.0001
No	219 (59.0%)	67 (31.8%)	
Supplemental fluoride—type ^a			
Prescription gel with brush	96 (63.2%)	114 (79.2%)	.0015
Prescription gel with tray	18 (11.8%)	13 (9.0%)	
Non-prescription rinse	36 (23.7%)	17 (11.8%)	
Supplemental fluoride—frequency			
More than once/day	47 (30.9%)	34 (23.6%)	.0680
Once/day	80 (53.6%)	74 (51.4%)	
4–6×/week	7 (4.6%)	15 (10.4%)	
1–3×/week	9 (5.9%)	16 (11.1%)	
Less than 1×/week	9 (5.9%)	5 (3.5%)	

^aFor type of supplemental fluoride use at baseline, data on two subjects were not available.

Oral pain is a common complaint in this population, especially during and soon after RT. During this period, oral mucositis is the largest contributor to oral pain, with patients typically needing systemic opioids for pain management (Saunders et al., 2013). Another contributor to oral pain in this population, particularly before RT, is pain secondary to surgery, for patients whose tumors involve the oral cavity (Bianchini et al., 2016). This study assessed oral pain pre-RT and at 6 months after RT, and thus did not seek to capture the intense oral pain associated with ulcerative oral mucositis. The overall average oral pain score was 9.24 on a 0–100 scale at both baseline and 6 months. This supports our clinical experience that most patients are free of the intense pain associated with oral mucositis by 6 months after RT. However, we did find that subject-reported sensitivity of the oral mucosa (to touch by teeth, food, or fluids) increased at 6 months compared to baseline. This suggests that the oral mucosa may continue to be more sensitive to touch even after clinically visible ulcerations have healed.

Radiation therapy for HNC is known to substantially reduce quality of life, particularly as it relates to oral health and function (Egestad &

Emaus, 2014; Verdonck-de Leeuw et al., 2014). We found that this negative impact persists even 6 months after the start of RT. Particularly substantial problems reported by subjects at 6 months related to dry mouth, sticky saliva, swallowing solid foods, and the sense of taste. These findings are consistent with the large reduction in salivary flow at 6 months as compared to baseline. We also found a significant correlation between changes in oral pain and OH-QOL, suggesting that oral pain/sensitivity continues to negatively affect OH-QOL 6 months after the start of RT. It should be noted that this study measured QOL related to oral health specifically and not overall health-related QOL. Other groups have reported lower overall health-related QOL in patients with HNC receiving RT (Klein, Livergant, & Ringash, 2014).

Oral hygiene practices are very important after H&N RT, due to the increased risks for dental caries and osteoradionecrosis in this population (Hong et al., 2010; Raguse et al., 2016). Study subjects received education and strong reinforcement on the need for aggressive preventive measures, which is part of standard clinical practice at the study sites. As a result, we found an increased frequency of using dental floss or other interdental aids at 6 months as compared

to baseline. There was also a large increase in the proportion of subjects using supplemental fluoride (with a shift toward use of prescription gels), from 41% at baseline to 68.2% at 6 months after the start of RT. While quite positive, these data indicate room for improvement even at our academic centers. It is also recognized that these are subject-reported data that were not independently verified. In future analyses of data from later time points (up to 2 years after RT), we will examine the continuing use of such preventive measures and their effects on longer-term complications such as dental caries and osteoradionecrosis.

This is an observational cohort study, and this study design has some limitations. There was no separate control group. Subjects served as their own controls, with measurements compared before and after RT. Based on the knowledge of the effects of RT, it is reasonable to infer that the changes in outcomes seen were related to RT. For example, the biological effects of RT on salivary glands are well documented (Konings, Coppes, & Vissink, 2005). It should also be noted that there may be some selection bias due to the inclusion criteria for this study. To be eligible for this study, patients needed to have at least one tooth present after completion of pre-RT dental extractions. Thus, the least motivated patients with the worst oral hygiene may be excluded from the study due to becoming edentulous.

In conclusion, these analyses demonstrate that despite the use of modern RT techniques, patients with HNC continue to experience oral complications at 6 months after the start of RT, with resulting negative impacts on oral function and quality of life.

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AUTHOR CONTRIBUTIONS

All authors except Kusha Mohammadi contributed to the design and conduct of the research and the preparation of the manuscript. Kusha Mohammadi and James Hodges contributed to data analyses and the preparation of the manuscript.

CONFLICT OF INTERESTS

None to declare.

REFERENCES

Bensadoun, R. J., Riesenbeck, D., Lockhart, P. B., Elting, L. S., Spijkervet, F. K., & Brennan, M. T.; Oral Care Study Group, MASCC/ISOO. (2010). A

- systematic review of trismus induced by cancer therapies in head and neck cancer patients. *Supportive Care in Cancer*, 18(8), 1033–1038.
- Bianchini, C., Malago, M., Crema, L., Aimoni, C., Matarazzo, T., Bortolazzi, S., ... Pastore, A. (2016). Post-operative pain management in head and neck cancer patients: Predictive factors and efficacy of therapy. *Acta Otorhinolaryngologica Italica*, 36(2), 91–96.
- Braam, P. M., Roesink, J. M., Moerland, M. A., Raaijmakers, C. P., Schipper, M., & Terhaard, C. H. (2005). Long-term parotid gland function after radiotherapy. *International Journal of Radiation Oncology, Biology, Physics*, 62(3), 659–664.
- Buglione, M., Cavagnini, R., Di Rosario, F., Maddalo, M., Vassalli, L., Grisanti, S., ... Magrini, S. M. (2016). Oral toxicity management in head and neck cancer patients treated with chemotherapy and radiation: Xerostomia and trismus (Part 2). Literature review and consensus statement. *Critical Reviews in Oncology/Hematology*, 102, 47–54.
- Buglione, M., Cavagnini, R., Di Rosario, F., Sottocornola, L., Maddalo, M., Vassalli, L., ... Magrini, S. M. (2016). Oral toxicity management in head and neck cancer patients treated with chemotherapy and radiation: Dental pathologies and osteoradionecrosis (Part 1) literature review and consensus statement. *Critical Reviews in Oncology/Hematology*, 97, 131–142.
- Connelly, S. T., & Schmidt, B. L. (2004). Evaluation of pain in patients with oral squamous cell carcinoma. *The Journal of Pain*, 5(9), 505–510.
- Duarte, V. M., Liu, Y. F., Rafizadeh, S., Tajima, T., Nabili, V., & Wang, M. B. (2014). Comparison of dental health of patients with head and neck cancer receiving IMRT vs conventional radiation. *Otolaryngology-Head and Neck Surgery*, 150(1), 81–86.
- Egestad, H., & Emaus, N. (2014). Changes in health related quality of life in women and men undergoing radiation treatment for head and neck cancer and the impact of smoking status in the radiation treatment period. *European Journal of Oncology Nursing*, 18(4), 339–346.
- Elad, S., & Zadik, Y. (2016). Chronic oral mucositis after radiotherapy to the head and neck: A new insight. *Supportive Care in Cancer*, 24(11), 4825–4830.
- European Organization for Research and Treatment of Cancer (EORTC). (2009). EORTC QLQ-H&N35. [Internet document] [cited 2011 9 November]. Retrieved from http://groups.eortc.be/qol/sites/default/files/img/specimen_for_printing_hn35.pdf.
- Hong, C. H., Napenas, J. J., Hodgson, B. D., Stokman, M. A., Mathers-Stauffer, V., Elting, L. S., ... Brennan, M. T. (2010). A systematic review of dental disease in patients undergoing cancer therapy. *Supportive Care in Cancer*, 18(8), 1007–1021.
- Jensen, S. B., Pedersen, A. M., Vissink, A., Andersen, E., Brown, C. G., Davies, A. N., ... Brennan, M. T. (2010). A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: Prevalence, severity and impact on quality of life. *Supportive Care in Cancer*, 18(8), 1039–1060.
- Klein, J., Livergant, J., & Ringash, J. (2014). Health related quality of life in head and neck cancer treated with radiation therapy with or without chemotherapy: A systematic review. *Oral Oncology*, 50(4), 254–262.
- Konings, A. W., Coppes, R. P., & Vissink, A. (2005). On the mechanism of salivary gland radiosensitivity. *International Journal of Radiation Oncology, Biology, Physics*, 62(4), 1187–1194.
- Lal, P., Bajpai, R., Khurana, R., Das, K. J., Kumar, P., Tiwari, A., ... Kumar, S. (2010). Changes in salivary flow rates in head and neck cancer after chemoradiotherapy. *Journal of Cancer Research and Therapeutics*, 6(4), 458–462.
- Lalla, R. V., Saunders, D. P., & Peterson, D. E. (2014). Chemotherapy or radiation-induced oral mucositis. *Dental Clinics of North America*, 58(2), 341–349.
- Marta, G. N., Silva, V., de Andrade Carvalho, H., de Arruda, F. F., Hanna, S. A., Gadia, R., ... Riera, R. (2014). Intensity-modulated radiation therapy for head and neck cancer: Systematic review and meta-analysis. *Radiotherapy and Oncology*, 110(1), 9–15.

- Meurman, J. H., & Gronroos, L. (2010). Oral and dental health care of oral cancer patients: Hyposalivation, caries and infections. *Oral Oncology*, 46(6), 464–467.
- Pfister, D. G., Spencer, S., Brizel, D. M., Burtneess, B., Busse, P. M., Caudell, J. J., ... Hughes, M. (2015). Head and neck cancers, Version 1.2015. *Journal of the National Comprehensive Cancer Network*, 13(7), 847–855; quiz 856.
- Raguse, J. D., Hossamo, J., Tinhofer, I., Hoffmeister, B., Budach, V., Jamil, B., ... Stromberger, C. (2016). Patient and treatment-related risk factors for osteoradionecrosis of the jaw in patients with head and neck cancer. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, 121(3), 215–221.e211.
- Rapidis, A. D., Dijkstra, P. U., Roodenburg, J. L., Rodrigo, J. P., Rinaldo, A., Strojan, P., ... Ferlito, A. (2015). Trismus in patients with head and neck cancer: Etiopathogenesis, diagnosis and management. *Clinical Otolaryngology*, 40(6), 516–526.
- Satheeshkumar, P. S., Mohan, M. P., & Jacob, J. (2014). Restricted mouth opening and trismus in oral oncology. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, 117(6), 709–715.
- Saunders, D. P., Epstein, J. B., Elad, S., Allemano, J., Bossi, P., van de Wetering, M. D., ... Lalla, R. V. (2013). Systematic review of antimicrobials, mucosal coating agents, anesthetics, and analgesics for the management of oral mucositis in cancer patients. *Supportive Care in Cancer*, 21(11), 3191–3207.
- Vera-Llonch, M., Oster, G., Hagiwara, M., & Sonis, S. (2006). Oral mucositis in patients undergoing radiation treatment for head and neck carcinoma. *Cancer*, 106(2), 329–336.
- Verdonck-de Leeuw, I. M., Buffart, L. M., Heymans, M. W., Rietveld, D. H., Doornaert, P., de Bree, R., ... Langendijk, J. A. (2014). The course of health-related quality of life in head and neck cancer patients treated with chemoradiation: A prospective cohort study. *Radiotherapy and Oncology*, 110(3), 422–428.
- World Health Organization (1979). *Handbook for reporting results of cancer treatment*. Geneva: World Health Organization.

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