ORIGINAL REPORT: EPIDEMIOLOGIC RESEARCH

Dental Caries Postradiotherapy in Head and Neck Cancer

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Abstract: ***Background:*** *Treatment for head and neck cancer (HNC) such as radiotherapy (RT) can lead to numerous acute and chronic head and neck sequelae, including dental caries. The goal of the present study was to measure 2-y changes in dental caries after radiotherapy in patients with HNC and test risk factors for caries increment.*

Methods: *Cancer and dental disease characteristics, demographics, and oral health practices were documented before and 6, 12, 18, and 24 mo after the start of RT for 572 adult patients with HNC. Patients were eligible if they were age 18 y or older, diagnosed with HNC, and planned to receive RT for treatment of HNC. Caries prevalence was measured as decayed, missing, and filled surfaces (DMFS). The association between change in DMFS and risk factors was evaluated using linear mixed models.*

Results: *On average, DMFS increased from baseline to each follow-up visit: 6 mo, +1.11; 12 mo, +2.47; 18 mo, +3.43; and 24 mo, +4.29 (*$P < 0.0001$*). The increase in DMFS during follow-up was significantly smaller for the following patient characteristics: compliant with daily fluoride use (*$P = 0.0004$*) and daily oral hygiene (brushing twice daily and flossing daily;* $P = 0.015$*), dental insurance (*$P = 0.004$*), and greater than high school education (*$P = 0.001$*). DMFS change was not significantly associated with average or maximum RT dose to the parotids (*$P > 0.6$*) or salivary flow (*$P > 0.1$*). In the subset of patients who had salivary hypofunction at baseline (*$n = 164$*), lower salivary flow at follow-up visits was associated with increased DMFS.*

Conclusion: *Increased caries is a complication soon after RT in HNC. Fluoride, oral hygiene, dental insurance, and education level had the strongest association with caries increment after radiotherapy to the head and neck region. Thus, intensive oral hygiene measures, including fluoride and greater accessibility of dental care, may contribute to reducing the caries burden after RT in HNC.*

Knowledge Transfer Statement: *The results of this study can be used by clinicians when deciding how to minimize oral complications related to cancer therapy for patients with head and neck cancer. Identification of modifiable factors (e.g., oral hygiene and prescription fluoride compliance) associated with increased caries risk can minimize radiation caries burden.*

Keywords: head and neck neoplasms, cohort study, risk factors, patient compliance, fluoride, dental caries

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A supplemental appendix to this article is available online.

Introduction

Approximately 63,000 new cases of head and neck cancer (HNC) are diagnosed in the United States with 13,360 annual deaths (Choi et al. 2016; American Cancer Society 2017). Most patients with HNC (50%–60%) have disease involving regional nodes at the time of diagnosis (Adrien et al. 2014). HNC management can include surgical resection, chemotherapy, and radiotherapy (RT), which can lead to numerous acute and chronic head and neck sequelae. Acute adverse events include mucositis, oral pain, taste abnormalities, xerostomia, and mucosal infections. Chronic, long-term oral complications include limited opening (trismus), salivary hypofunction and xerostomia, taste abnormalities, dental caries, tooth loss, and osteoradionecrosis (ORN) (Lalla et al. 2010).

Higher incidence of dental caries post-RT in patients with HNC increases the risk of dental extraction, which increases the risk of ORN (Reuther et al. 2003). Pre-RT dental assessment and treatment for patients with HNC is considered best practice, but practice varies widely due to lack of clear data on dental outcomes in this patient population (Kerr 2003). To address gaps in knowledge of dental/oral outcomes, a multicenter, prospective study of patients with HNC receiving curative-intent RT (OraRad) was funded by the US National Institute for Dental and Craniofacial Research (NIDCR) (Lalla et al. 2017). Outcomes included tooth loss, exposed bone/ORN, changes in dental caries, periodontal disease, and stimulated whole salivary flow during the 2-y study period; a study aim was assessing risk factors for these outcomes. The present article reports the change over time and risk factors for dental caries post-RT.

Methods

Patient Enrollment

The Clinical Registry of Dental Outcomes in Head and Neck Cancer Patients (OraRad) enrolled patients with HNC at 6 clinical centers: Brigham and Women's Hospital, University of Pennsylvania, Atrium Health Carolinas Medical Center, University of Connecticut, New York University, and University of North Carolina. A full description of the OraRad study is available (Lalla et al. 2017). Institutional review board approval was obtained for patients with HNC. Each participant had a baseline visit and follow-up visits at 6-mo intervals for 2 y after RT began. A total of 572 participants were enrolled between April 2014 and October 2018 and were eligible for follow-up post-RT.

Study Procedures

The baseline visit was scheduled before RT but after the pre-RT dental evaluation and after completing any recommended dental treatment (e.g., extractions). Demographics, insurance status/type, medical and dental history, oral cancer characteristics, cancer treatment details, self-reported oral hygiene practices, and prescription fluoride use were collected at baseline. The baseline dental examination was performed by calibrated examiners. These dental disease characteristics were collected at baseline: number of teeth present and decayed, missing, and filled surfaces (DMFS) and stimulated salivary flow rate, as previously described (Lalla et al. 2017).

At each follow-up visit, a comprehensive oral examination was performed collecting data on tooth loss, DMFS measures, and self-reported prescription fluoride use and oral hygiene practices. Salivary flow rate was collected at the 6- and 18-mo follow-up visits and included chewing on unflavored gum base for 5 min using a digital timer. Compliant oral hygiene practices were defined as brushing at least 2 times/d and cleaning between the teeth 1 time/d (e.g., flossing/proxy brushes); compliant prescription fluoride use was daily application (either brush-on or in a tray).

Statistical Analysis

To obtain a robust assessment of the change in caries after RT, 2 measures were evaluated: total number of DMFS and the proportion of evaluable surfaces that were decayed, missing, or filled (%DMFS). The %DMFS measure weights DMFS changes more heavily for individuals with fewer evaluable surfaces.

Linear mixed-effects models with patient-specific random intercepts were used to evaluate change in caries measurements over time. Associations between potential risk factors and change in caries (DMFS or %DMFS) were evaluated by testing interaction terms between study visit and the risk factor. Results for risk factors that were associated ($P < 0.05$) with at least 1 DMFS measure are further described in the text. The Appendix gives a full description of risk factors considered.

As a sensitivity analysis, outcomes were transformed based on the Box–Cox procedure. Analyses with transformed outcomes gave findings largely similar to those with untransformed outcomes (Appendix Table 1), so for ease of explanation, the text presents only results for untransformed outcomes. *P* values are not adjusted for multiple comparisons. For the continuous measures evaluated, DMFS and %DMFS, analyses are significant at the $\alpha = 0.05$ level if the corresponding 95% confidence interval excludes 0. All analyses were conducted using R version 3.6.0 (R Core Team 2019) using versions 1.1–23, 3.1–2, and 1.4.6 of the "lme4" (Bates et al. 2015), "lmerTest" (Kuznetsova et al. 2017), and "emmeans" (Lenth 2020) packages, respectively.

Results

Patient Characteristics

The OraRad cohort consisted of 572 patients with HNC (Table 1), with 77% male, mean (SD) age of 58.3 (11.1) y, and 83% Caucasians, 8% African Americans, and 5% Hispanics. Education beyond high school was reported by 72% of participants. Nearly all (96%) had some type of medical insurance, with 25% having Medicare and 10% Medicaid. A total of 366 (64%) had dental insurance.

Table 1.
Baseline Clinical and Demographic Characteristics of the Patients.

Characteristic	Study Population ($N = 572$)
Age at baseline visit, y	58.3 ± 11.1
Female sex	132 (23.1)
Race	
White only	474 (82.9)
Black only	45 (7.9)
Other	51 (8.9)
Unknown	2 (0.3)
Ethnicity	
Hispanic	29 (5.1)
Not Hispanic	543 (94.9)
Highest grade	
≤ High school	158 (27.6)
> High school	412 (72.0)
Type of medical insurance	
Private insurance	435 (76.0)
Medicare	144 (25.2)
Medicaid	60 (10.5)
No insurance	20 (3.5)
Dental insurance	366 (64.0)
Type of cancer	
SCC	469 (82.0)
SGC	66 (11.5)
Non-SCC, non-SGC	37 (6.5)
Primary site of RT	
Oropharynx	262 (45.8)
Oral cavity	82 (14.3)
Salivary gland	54 (9.4)
Larynx/hypopharynx	40 (7.0)
Other	134 (23.4)
Routine dental care in 12 mo prior	414 (72.4)

Table 1.
(continued)

Characteristic	Study Population ($N = 572$)
Fluoride compliant during follow-up	
Yes	154 (26.9)
No	364 (63.6)
Unknown	54 (9.4)
OH compliant at BL visit	
Yes	242 (42.3)
No	330 (57.7)
OH compliant during follow-up	
Yes	174 (30.4)
No	344 (60.1)
Unknown	54 (9.4)
Chemotherapy	314 (54.9)
RT dose (cGy) to parotids	
Average mean dose	2,739.1 ± 1,027.9
Maximum of maximum dose	6,387.3 ± 1,388.1
Prescription parasympathomimetic use	45 (7.9)
Salivary flow	
BL flow	
Low BL flow (<0.7 g/min)	164 (28.7)
Normal BL flow (≥0.7 g/min)	380 (66.4)
Unknown BL flow	28 (4.9)
% 18 mo vs. BL, median (range)	57.6 (0–2,750.0)

Values are presented as *n* (%) or mean ± SD unless otherwise indicated.
BL, baseline; OH, oral hygiene; RT, radiotherapy; SCC, squamous cell carcinoma; SGC, salivary gland cancer.

Squamous cell carcinoma (SCC) was the most common histology ($n = 469$, 82%); the oropharynx was the most frequent primary location ($n = 262$, 46%). The average mean and maximum (SD) doses to parotids were 2,739 (1,028) and 6,387 (1,388) cGy, respectively. The mean RT dose to the primary tumor site was 6,573 cGy (range: 636–7,802 cGy).

The Appendix gives a description of the number of individuals at each stage of the study (Appendix Fig.).

Oral Care/Dental Characteristics

At baseline (i.e., before RT began), participants had a mean (SD) of 22.9 (5.8) teeth, and 31.7% had at least 1 tooth with active caries. Most patients (72%) reported seeing a dentist for a routine checkup or cleaning in the 12 mo before their cancer diagnosis. Less than half (42%) were compliant with oral hygiene practices (brushing 2 times/d and cleaning between the teeth 1 time/d) at the baseline visit, and fewer reported practicing optimal oral hygiene at all attended follow-up visits ($n = 174$: 30%). Slightly fewer patients (26.9%) complied with daily prescription fluoride use during all attended follow-up visits (Table 1).

DMFS: Overall

Average DMFS and %DMFS were higher than baseline at all follow-up visits (Fig. 1, Table 2, *P* values for all

Table 2.
Change in DMFS (Number of Surfaces and Proportion of Surfaces) from Baseline to Each Visit and Difference in Change Based on Demographics, Surrogate Measures of Economics, Oral Hygiene Compliance, and Salivary Flow Measures.

		Difference in Change								
		Age	Education	Dental Insurance	Routine Care Years Prior to Study	Fluoride Compliant during FU	Oral Hygiene Compliance at BL	Oral Hygiene Compliance during FU	6-mo Salivary Flow for Individuals with Low BL Flow[a]	Change in Salivary Flow from BL to V18 for Individuals with Low BL Flow[b]
	Change in DMFS Measure	10-y Difference	> HS vs. ≤ HS	Has vs. Does Not Have	Yes vs. No	No vs. Yes	No vs. Yes	No vs. Yes	1-mL/min Difference	Increase of 10% of Baseline Salivary Flow
DMFS										
***P* value**	≤0.0001	0.1221	0.0010	0.0045	≤0.0001	≤0.0001	0.0043	0.0154	0.0181	0.1477
V06 vs. BL	1.11 (0.43, 1.78); 0.0014	0.05 (–0.56, 0.67); 0.8682	–0.67 (–2.19, 0.84); 0.385	–0.11 (–1.52, 1.3); 0.8771	0.08 (–1.45, 1.61); 0.9212	0.04 (–1.45, 1.52); 0.9601	–0.01 (–1.37, 1.35); 0.9882	–0.25 (–1.68, 1.18); 0.7322	0.32 (–5.9, 6.54); 0.9188	0 (–0.21, 0.22); 0.9711
V12 vs. BL	2.47 (1.77, 3.16); ≤0.0001	0.21 (–0.42, 0.85); 0.5055	–2.03 (–3.6, –0.46); 0.0112	–1.48 (–2.93, –0.03); 0.0449	–1.22 (–2.81, 0.38); 0.1351	1.66 (0.13, 3.19); 0.0333	1.51 (0.1, 2.91); 0.0355	1.28 (–0.22, 2.77); 0.0938	–1.62 (–7.88, 4.64); 0.6127	–0.09 (–0.3, 0.12); 0.4181
V18 vs. BL	3.43 (2.71, 4.15); ≤0.0001	0.61 (–0.06, 1.28); 0.0728	–1.96 (–3.61, –0.31); 0.0200	–2.02 (–3.52, –0.52); 0.0084	–2.46 (–4.13, –0.8); 0.0037	2.25 (0.66, 3.84); 0.0057	1.02 (–0.42, 2.47); 0.1659	1.65 (0.12, 3.18); 0.0348	–6.88 (–13.32, –0.44); 0.0368	–0.13 (–0.34, 0.08); 0.2108
V24 vs. BL	4.29 (3.58, 4.99); ≤0.0001	0.74 (0.09, 1.4); 0.0268	–3.2 (–4.79, –1.62); ≤0.0001	–2.28 (–3.74, –0.81); 0.0024	–3.65 (–5.29, –2); ≤0.0001	2.92 (1.38, 4.46); 0.0002	2.39 (0.97, 3.8); 0.001	1.91 (0.41, 3.41); 0.0124	–8.79 (–15.26, –2.32); 0.008	–0.24 (–0.45, –0.03); 0.0283
%DMFS										
***P* value**	≤0.0001	0.0073	≤0.0001	0.0027	≤0.0001	≤0.0001	0.0007	0.0022	0.1347	0.0465
V06 vs. BL	0.9 (0.4, 1.4); 0.0008	0 (–0.4, 0.5); 0.8814	–0.6 (–1.8, 0.6); 0.3177	–0.1 (–1.2, 1); 0.8104	0 (–1.2, 1.2); 0.9588	0.1 (–1.1, 1.2); 0.8797	0 (–1, 1.1); 0.9874	–0.2 (–1.3, 0.9); 0.7757	0 (–4.4, 4.5); 0.9892	0 (–0.2, 0.2); 0.9929
V12 vs. BL	2.1 (1.6, 2.7); ≤0.0001	0.3 (–0.2, 0.8); 0.1798	–1.7 (–2.9, –0.5); 0.0069	–1.5 (–2.6, –0.3); 0.011	–1.1 (–2.4, 0.1); 0.0714	1.3 (0.2, 2.5); 0.0255	1.3 (0.2, 2.4); 0.0202	1.1 (0, 2.3); 0.0602	–1.7 (–6.2, 2.8); 0.4599	–0.1 (–0.2, 0.1); 0.2918
V18 vs. BL	3 (2.4, 3.5); ≤0.0001	0.7 (0.1, 1.2); 0.0124	–2.1 (–3.4, –0.8); 0.0013	–1.6 (–2.8, –0.4); 0.0067	–1.8 (–3, –0.5); 0.0077	2 (0.8, 3.2); 0.0015	1.1 (0, 2.2); 0.0533	1.5 (0.3, 2.7); 0.013	–3.7 (–8.3, 0.9); 0.1201	–0.1 (–0.3, 0); 0.1119
V24 vs. BL	3.7 (3.2, 4.3); ≤0.0001	0.8 (0.3, 1.3); 0.0022	–2.9 (–4.2, –1.7); ≤0.0001	–1.7 (–2.9, –0.6); 0.0027	–2.7 (–3.9, –1.4); ≤0.0001	2.3 (1.1, 3.5); ≤0.0001	2.1 (1, 3.2); 0.0002	1.8 (0.6, 3); 0.0024	–5.2 (–9.8, –0.5); 0.0298	–0.2 (–0.3, –0.1); 0.009

Estimate (95% confidence interval); *P* values are presented.
BL, baseline; DMFS, decayed, missing, and filled surface; FU, follow-up; HS, high school.
[a]Low BL flow was defined as <0.7 mL/min.
[b]One individual with extreme changes in salivary flow (>2,000% change) removed from analysis. Results with individual included are provided in Appendix Table 1.

comparisons <0.002). Estimated mean (SE) DMFS scores were 47.6 (1.3) at baseline and increased to 48.7 (1.3) at 6 mo, 50.1 (1.3) at 12 mo, 51.1 (1.3) at 18 mo, and 51.9 (1.3) at 24 mo post-RT.

Change in DMFS: Associations

Demographics (sex, race, ethnicity, age)

Sex was not associated with change in DMFS or %DMFS ($P > 0.7$, Appendix Table 1). Race had only a modest, nonsignificant association with change in DMFS and %DMFS over time ($P = 0.091$ and 0.055, respectively).

Age was not linearly associated with change in DMFS ($P = 0.12$) but was associated with a linear change in %DMFS ($P = 0.0073$, Table 2, Fig. 2). Each additional decade in age was associated with a 0.7% (95% CI, 0.1%–1.2%) greater absolute increase in %DMFS from baseline to the 18-mo visit and a 0.8% (95% CI, 0.3%–1.3%) greater increase from baseline to the 24-mo visit. Restricting the population to those between 40 and 80 y old (which includes over 90% of the population), age was not associated with either DMFS or %DMFS ($P > 0.9$).

Socioeconomic status measures

Education. Education was strongly associated with change in caries ($P \leq 0.001$, Table 2). Individuals with at most

Figure 1. Model estimated mean and 95% confidence interval for decayed, missing, and filled surface (DMFS) and %DMFS across study visits. Count of individuals with DMFS measures by visit: $N = 571$ at the baseline visit (visit month = 0), $N = 454$ at visit month 6, $N = 418$ at visit month 12, $N = 384$ at visit month 18, and $N = 408$ at visit month 24. %DMFS is presented on the proportion scale with 0.50 corresponding to 50% of evaluable surfaces decayed, missing, or filled.

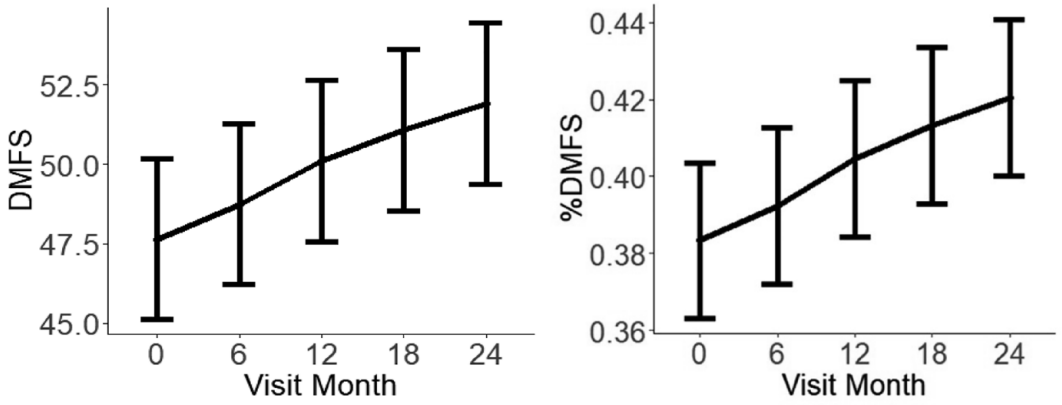
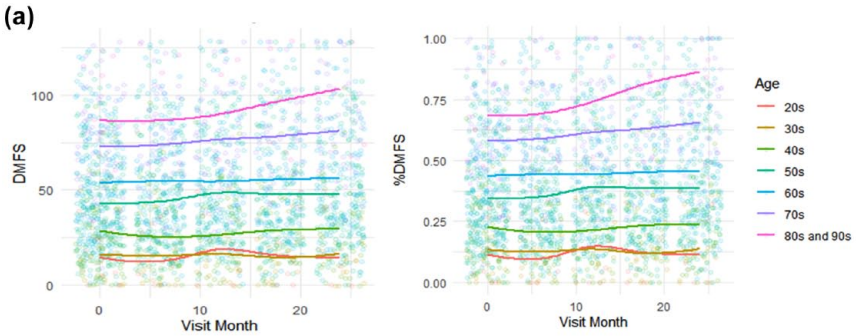
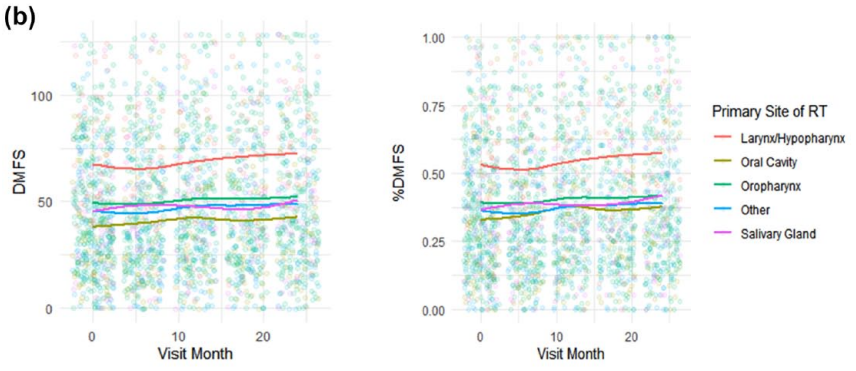


Figure 2. Loess curve for decayed, missing, and filled surface (DMFS) and %DMFS at each visit. Curves are stratified by (**a**) age categorized by decade and (**b**) primary site of radiotherapy (RT). Visit month has been jittered for visualization purposes. %DMFS is presented on the proportion scale with 0.50 corresponding to 50% of evaluable surfaces decayed, missing, or filled.



Count of Participants by Visit Month

Age	Visit Month				
	0	6	12	18	24
20s	8	7	5	5	4
30s	24	19	21	18	17
40s	61	48	42	40	43
50s	218	177	159	148	158
60s	182	148	136	127	132
70s	68	48	49	42	49
80s and 90s	10	7	6	4	5



Count of Participants by Visit Month

Primary Site of RT	Visit Month				
	0	6	12	18	24
Larynx/ Hypopharynx	40	28	30	27	29
Oral Cavity	82	63	51	50	46
Oropharynx	261	210	195	183	200
Other	134	107	100	85	90
Salivary Gland	54	46	42	39	43

a high school education experienced significantly greater increase in DMFS from baseline to the 12-mo visit (2.03; 95% CI, 0.46–3.6 more surfaces), 18-mo visit (1.96; 95% CI, 0.31–3.61), and 24-mo visit (3.2; 95% CI, 1.62–4.79) compared to individuals with more education.

Dental insurance. Dental insurance was strongly associated with change in caries across study visits ($P < 0.005$). Individuals without dental insurance experienced a significantly greater increase in DMFS from baseline to the 12-mo visit (1.48; 95% CI, 0.03–2.93 more surfaces), 18-mo visit (2.02; 95% CI, 0.52–3.52), and 24-mo visit (2.28; 95% CI,

0.81–3.74) compared to individuals with dental insurance.

Compliance

Oral hygiene compliance. Compliance with routine oral hygiene practices was defined as toothbrushing at least 2 times/d and cleaning between the teeth (e.g., flossing) at least daily. Individuals who were compliant at baseline or during follow-up had smaller increase in caries compared to individuals who were not compliant during those periods (Table 2, $P < 0.02$). Individuals who were not compliant at baseline experienced a greater increase in DMFS from baseline to the 12-mo visit (1.51; 95% CI, 0.1–2.91 more surfaces) and 24-mo visit (2.39; 95% CI, 0.97–3.8) compared to those who were compliant. Those who were not compliant during at least 1 follow-up visit experienced a greater increase in DMFS from baseline to the 18-mo visit (1.65; 95% CI, 0.12–3.18 more surfaces) and 24-mo visit (1.91; 95% CI, 0.41–3.41) compared to those who were compliant at each attended visit.

Fluoride use compliance. Compliance with prescription fluoride use was defined as at least once-daily application. Individuals who reported using fluoride at each attended follow-up visit experienced smaller increases in DMFS compared to those who were not compliant with fluoride recommendations ($P \leq 0.001$, Table 2). Noncompliant individuals experienced a greater increase in DMFS from baseline to the 12-mo visit (1.66; 95% CI, 0.13–3.19 more surfaces), 18-mo visit (2.25; 95% CI, 0.66–3.84 more surfaces), and 24-mo visit (2.92; 95% CI, 1.38–4.46) compared to individuals compliant with fluoride recommendations.

Routine dental care. Routine dental care in the 12 mo before RT was strongly associated with change in caries ($P \leq 0.0001$, Table 2). Those who did not have dental care experienced significantly greater increase in DMFS from baseline to the 18-mo visit (2.46; 95% CI, 0.8–4.13 more surfaces) and 24-mo visit (3.65; 95% CI, 2.00–5.29) compared to individuals who had routine dental care in the year prior.

Chemotherapy

Chemotherapy was not associated with change in DMFS or %DMFS ($P > 0.6$, Appendix Table 1).

Radiotherapy

RT dose to the parotids. Neither maximum nor average RT dose to the parotids was associated with change in caries ($P > 0.50$, Appendix Table 1).

Primary RT site. Primary RT site was not strongly associated with change in DMFS ($P = 0.10$) but was associated with change in %DMFS ($P = 0.027$, Table 3, Fig. 2). Larynx/hypopharynx primary site was associated with a greater increase in %DMFS from baseline to the 18-mo visit (2.6%; 95% CI, 0.3%–4.9% more surfaces) and 24-mo visit (3.1%; 95% CI, 0.9%–5.3%) compared to the oropharynx. Individuals with a primary site of larynx/hypopharynx also had a greater increase in %DMFS and from baseline to the 24-mo visit (3.0%; 95% CI, 0.3%–5.6%) compared to individuals with a salivary gland primary site. Having a primary site of oral cavity was associated with a greater increase in %DMFS from baseline to the 12-mo (2.5%; 95% CI, 0.7%–4.2%), 18-mo (2.4%; 95% CI, 0.7%–4.2%), and 24-mo (3.7%; 95% CI, 1.9%–5.4%) visits compared to individuals with a primary site of oropharynx, and a greater increase in %DMFS from baseline to the 12-mo (2.6%; 95% CI, 0.3%–4.9%) and 24-mo (3.6%; 95% CI, 1.2%–5.9%) visits compared to individuals with a primary site of salivary gland.

Salivary flow

In the full OraRad population, change in DMFS or %DMFS was not associated with any salivary flow measure considered: prescription parasympathomimetic use ($P > 0.2$), change in salivary flow at 6 mo ($P > 0.2$), absolute salivary flow at 6 mo ($P > 0.6$), change in salivary flow at 18 mo ($P > 0.6$), absolute salivary flow at 18 mo ($P > 0.7$), or low baseline salivary flow defined as <0.7 g/min ($P > 0.3$; Appendix Table 1). When restricted to the population of individuals with low baseline salivary flow ($N = 164$), salivary flow at 6 mo was associated with change in DMFS ($P = 0.02$), and change in salivary flow from baseline to 18 mo was marginally associated with change in %DMFS ($P = 0.05$). Specifically, a 1-mL/min lower flow rate at the 6-mo visit was associated with a 6.88 (95% CI, 0.44–13.32) greater increase in DMFS from baseline to the 18-mo visit and an 8.79 (95% CI, 2.32–15.26) greater increase in DMFS from baseline to the 24-mo visit. We found similar trends between change in salivary flow from baseline to the 18-mo visit and change in %DMFS, with the strongest association observed for change in %DMFS from baseline to the 24-mo visit.

Discussion

This prospective cohort study of 572 subjects was the first contemporary multicenter study in patients with HNC with a large enough sample to identify risk factors for adverse dental outcomes after modern RT. Approximately one-third of OraRad participants had at least 1 carious tooth at baseline and the DMFS score consistently increased post-RT. Systematic reviews have found dental caries develop in approximately 30% of patients with HNC post-RT (Hong et al. 2010; Moore et al. 2020). The mean DMFS for OraRad participants at baseline was 47.6 and steadily increased to 51.9 at the 24-mo visit. This baseline score is similar to a recently published HNC cohort from India, with average DMFS of 47.3 within the first year after RT but not pre-RT (Bhandari et al. 2021). Follow-up DMFS scores were higher in the Indian cohort with an average of 69.0 between 1 and 3 y and 77.6 at 3 to 5 y post-RT. A key difference between these 2 HNC cohorts was that the Indian cohort had no oral assessment or dental treatment pre-RT and did not follow any professionally guided regimen for maintaining oral health

Table 3.
Difference in Change in DMFS Measures by Primary Site of RT.

	Larynx/ Hypopharynx vs. Oral Cavity	Larynx/ Hypopharynx vs. Oropharynx	Larynx/ Hypopharynx vs. Other	Larynx/ Hypopharynx vs. Salivary Gland	Oral Cavity vs. Oropharynx	Oral Cavity vs. Other	Oral Cavity vs. Salivary Gland	Oropharynx vs. Other	Oropharynx vs. Salivary Gland	Other vs. Salivary Gland
DMFS										
6 mo vs. BL	0.27 (–2.97, 3.52); 0.8694	1.38 (–1.48, 4.24); 0.3425	0.62 (–2.4, 3.65); 0.6852	0.76 (–2.67, 4.19); 0.6626	1.11 (–0.97, 3.19); 0.2944	0.35 (–1.95, 2.65); 0.7636	0.49 (–2.32, 3.3); 0.7322	–0.76 (–2.47,0.95); 0.3836	–0.62 (–2.98, 1.74); 0.6052	0.14 (–2.41,2.69); 0.9153
12 mo vs. BL	0.55 (–2.74, 3.84); 0.7425	2.29 (–0.52, 5.11); 0.1106	0.71 (–2.28, 3.7); 0.6398	2.26 (–1.17, 5.7); 0.1960	1.74 (–0.48, 3.97); 0.1248	0.16 (–2.28, 2.6); 0.8958	1.71 (–1.25, 4.68); 0.2574	–1.58 (–3.33, 0.18); 0.0777	–0.03 (–2.46, 2.4); 0.9815	1.55 (–1.08, 4.18); 0.2480
18 mo vs. BL	1.38 (–2, 4.75); 0.4243	3.42 (0.5, 6.33); 0.0218	1.53 (–1.59, 4.65); 0.3359	4.54 (1, 8.09); 0.0120	2.04 (–0.21, 4.29); 0.0757	0.15 (–2.35,2.66); 0.9041	3.17 (0.15, 6.19); 0.0398	–1.89 (–3.72, –0.05); 0.0442	1.13 (–1.37, 3.62); 0.3751	3.01 (0.29, 5.74); 0.0302
24 mo vs. BL	1.13 (–2.23, 4.49); 0.5082	3.98 (1.14, 6.82); 0.0061	2.14 (–0.91, 5.18); 0.1689	5.08 (1.64, 8.53); 0.0039	2.85 (0.56, 5.14); 0.0149	1.00 (–1.53, 3.54); 0.4376	3.95 (0.95, 6.96); 0.0100	–1.84 (–3.64, –0.05); 0.0441	1.1 (–1.31, 3.52); 0.3695	2.95 (0.3, 5.59); 0.0291
%DMFS										
6 mo vs. BL	–0.1 (–2.6, 2.4); 0.9601	1.1 (–1.1, 3.3); 0.3255	0.5 (–1.8, 2.8); 0.6697	0.6 (–2, 3.3); 0.6409	1.2 (–0.4, 2.8); 0.1528	0.6 (–1.2, 2.3); 0.5277	0.7 (–1.5, 2.9); 0.5311	–0.6 (–1.9, 0.7); 0.3732	–0.5 (–2.3, 1.3); 0.607	0.1 (–1.8, 2.1); 0.9032
12 mo vs. BL	–0.8 (–3.3, 1.8); 0.5568	1.7 (–0.5, 3.9); 0.1241	0.5 (–1.8, 2.8); 0.6473	1.8 (–0.8, 4.5); 0.1745	2.5 (0.7, 4.2); 0.0049	1.3 (–0.6, 3.2); 0.1763	2.6 (0.3, 4.9); 0.0263	–1.2 (–2.5, 0.2); 0.0911	0.1 (–1.7, 2); 0.8928	1.3 (–0.7, 3.3); 0.2108
18 mo vs. BL	0.2 (–2.5, 2.8); 0.9063	2.6 (0.3, 4.9); 0.0236	1.2 (–1.2, 3.6); 0.3351	2.4 (–0.4, 5.1); 0.0914	2.4 (0.7, 4.2); 0.0058	1 (–0.9, 3); 0.2977	2.2 (–0.1, 4.5); 0.0643	–1.4 (–2.8, 0); 0.0500	–0.2 (–2.2, 1.7); 0.8035	1.2 (–0.9, 3.3); 0.2740
24 mo vs. BL	–0.6 (–3.2, 2); 0.6538	3.1 (0.9, 5.3); 0.0061	1.7 (–0.7, 4); 0.1609	3 (0.3, 5.6); 0.0289	3.7 (1.9, 5.4); ≤0.0001	2.3 (0.3, 4.2); 0.0227	3.6 (1.2, 5.9); 0.0027	–1.4 (–2.8, 0); 0.0488	–0.1 (–2, 1.8); 0.9097	1.3 (–0.8, 3.3); 0.2176

The omnibus *P* value for primary site of RT by study visit interaction was 0.1016 for DMFS and 0.0274 for %DMFS. Estimate (95% confidence interval); *P* values are presented.
BL, baseline; DMFS, decayed, missing, and filled surface.

and preventing caries (e.g., routine dental care or prescription fluoride use). The OraRad cohort did not receive any study-related interventions, as this was an observational, prospective study by design, but participants did receive center-specific standard recommendations for post-RT oral care.

The present study identified numerous factors associated with increased DMFS scores over time, including noncompliance with prescription fluoride use and daily oral hygiene, not having dental insurance, and less education. Interestingly, change in DMFS was not associated with RT dose to the parotids or salivary flow in the full cohort. Prior studies that assessed risk factors for caries post-RT in patients with HNC have been retrospective, single-site, and underpowered. A recent systematic review of dental caries post-RT in patients with HNC found a higher caries rate with increased mean/median radiation dose and concurrent chemotherapy but did not find an association with fluoride use, use of intensity-modulated radiation therapy, radiation dose, site of tumor, sex, age, or salivary flow (Moore et al. 2020). The findings of this systematic review are not consistent with OraRad's findings.

Socioeconomic factors were important risks for caries in the current cohort. Surrogate indicators of lower socioeconomic status associated with worsening DMFS scores included lower education level and lack of dental insurance. Research on the impact of socioeconomic status on dental outcomes in HNC is limited, although the link between lower socioeconomic status (SES) and increased caries risk has been well established with different child and adult populations (Deng et al. 2015; Schwendicke et al. 2015). Thus, it not unexpected that surrogates for low SES are risk factors associated with caries experienced post-RT in patients with HNC.

Poor compliance with oral hygiene, fluoride use, and dental care were all identified as risk factors for an increase in DMFS in the present HNC cohort. This finding has been reported in previous studies, in which poor oral hygiene compliance was associated with post-RT radiation caries (Walker et al. 2011). Siala et al. (2014) found that initial poor oral hygiene practices were a risk factor for dental complications (defined primarily as dental caries, dental pain, and ORN) after RT. Poor compliance with daily fluoride use has also been noted to increase caries risk in patients with HNC. Thariat et al. (2012) found only 19% of patients with HNC continued to use daily fluoride 1 y post-RT, with half of patients developing carious lesions. Another

study found compliance with fluoride (defined as daily use of fluoride 50% of the time) was lower in the group without regular post-RT dental care (27%) compared to the group with regular post-RT dental care (67%) (Epstein et al. 1995). Lastly, we found that patients who did not see a dentist for routine care in the 12 mo before their diagnosis of HNC were more likely to have worsening DMFS scores post-RT. Thus, increasing compliance with routine dental care, oral hygiene practices, and prescription fluoride all represent approaches to improve caries outcomes in patients with HNC.

Radiation-induced salivary hypofunction can negatively affect key biologic properties of saliva, including maintenance of tooth structure (i.e., inhibiting demineralization and caries) (Dawes et al. 2015). As salivary function decreases with increased radiation dose (Deasy et al. 2010), loss of saliva should increase risk of dental caries post-RT (Vissink et al. 2003; Kielbassa et al. 2006). Bhandari et al. (2021) found higher DMFS scores in patients with higher levels of subjective complaints of dry mouth, but this study did not measure the level of salivary flow. The current cohort's sample size and prospective nature provided an opportunity to determine if decreased salivary function related to a higher RT dose increased the caries risk post-RT. While analysis of the full cohort found no association between change in DMFS and mean and maximum RT dose to the parotids, levels of stimulated whole salivary flow at 6 and 18 mo post-RT, or change in salivary flow from baseline to 6 or 18 mo post-RT, there was an association between further salivary loss at follow-up visits and increased DMFS among patients who had lower salivary flow at baseline. It is possible that the relatively modest mean amount of increase in DMFS scores over a 2-y period was not enough to be able to confirm this association across all patients, including those whose salivary function was not negatively affected. In addition, the proactive management of dry mouth may also affect dental caries experience. Only 45 (7.9%) of participants in the present cohort used a prescription parasympathomimetic during the study, while information on over-the-counter dry mouth management strategies was not collected. There was not a difference in change in DMFS scores in participants who used versus did not use a parasympathomimetic. The present study did not assess unstimulated saliva flow or sialochemistry that may affect dental caries incidence.

Primary RT sites of larynx/hypopharynx or oral cavity were associated with worsening DMFS over time compared to both the oropharynx and salivary glands. OraRad patients with human papillomavirus (HPV)–positive oropharyngeal cancers (47% of the current cohort) differed in many ways from those with all other HNCs (Brennan et al. 2021). Patients with HPV-positive oropharyngeal cancer had higher socioeconomic status (more education, increased likelihood of private medical and dental insurance, decreased likelihood of Medicaid, or receipt of public assistance), were more likely to be white and married, used tobacco less but used alcohol more frequently, and had less dental disease burden with more teeth at baseline and less periodontal disease. Thus, the differences in DMFS associated with different primary cancer sites may be more attributable to differences in demographics and socioeconomic status characteristics (which were found to be strongly associated with change in DMFS) and less likely the direct impact of RT to the cancer site and more likely associated with differences in demographics, SES, and dental disease burden.

The OraRad study does have limitations. As participants were enrolled at academic medical centers with dental services, the findings may be less generalizable to nonacademic oncology services. Although the follow-up rate was higher than anticipated, we did not have follow-up data after baseline for 52 (9%) persons (most of whom died), and we did not have 2-y follow-up data for 84 (16%) participants who could have attended the 24-mo follow-up visit. Despite a sample size of 572, assessment of certain variables may have been underpowered. We are unable to estimate the true incidence of dental caries for OraRad participants. True dental caries incidence can only be measured with cross-sectional studies or with cohorts that only received dental care at enrollment sites. As many OraRad patients received dental care from private dentists in the community, it is not possible to document all carious teeth for the present study's 24-mo follow-up period as patients were only seen at 6-mo intervals and caries management with restoration (or extraction) continued as part of standard treatment. Thus, DMFS served as a surrogate measure for caries post-RT. We assessed the overall DMFS change in the present study versus individual tooth DMFS changes. Future analyses to assess risk factors (e.g., radiation dose) for individual teeth are vital to understand risk for dental disease at the individual tooth level. In the present article, parotid gland doses are used as a surrogate for RT dose to other anatomical areas, since standard of care for documentation of RT to anatomical sites only includes documentation of mean and maximum doses in the parotids. Future analyses of the OraRad data will assess RT dose to specific sites of the oral cavity and teeth, but these data are not part of the current OraRad database and will include reassessment of dosimetry files. Thus, risk factor analysis for individual teeth is beyond the scope of the current study and will be addressed in future analyses with the OraRad data set. Despite these limitations, OraRad represents the first prospective study with detailed information collected by calibrated examiners pre-RT and during follow-up visits to allow assessment of potential risk factors for dental/oral outcomes in HNC.

The incidence of dental caries increases following RT for HNC. Factors associated with an increased risk of caries included poor compliance with daily oral

hygiene and fluoride use, lack of dental insurance, and not routinely seeing a dentist before RT. These findings point to populations at potential increased risk, while other factors (e.g., oral hygiene and prescription fluoride compliance) represent modifiable factors that can minimize radiation caries burden.

Author Contributions

M.T. Brennan, R.V. Lalla, contributed to conception, design, data acquisition, analysis, and interpretation, drafted and critically revised the manuscript; N.S. Treister, T.P. Sollecito, B.L. Schmidt, L.L. Patton, A. Lin, L.S. Elting, contributed to conception, design, data acquisition, critically revised the manuscript; E.S. Helgeson, contributed to design, data analysis and interpretation, drafted and critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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References

Adrien J, Bertolus C, Gambotti L, Mallet A, Baujat B. 2014. Why are head and neck squamous cell carcinoma diagnosed so late? Influence of health care disparities and socio-economic factors. Oral Oncol. 50(2):90–97.

American Cancer Society. 2017. Cancer facts & figures 2017. Atlanta (GA): American Cancer Society.

Bates D, Mächler M, Bolker B, Walker S. 2015. Fitting linear mixed-effects models using lme4. J Stat Softw. 67(1):1–48.

Bhandari S, Soni BW, Ghoshal S. 2021. Impact of non-compliance with oral care on radiation caries in head and neck cancer survivors. Support Care Cancer. 29(8):4783–4790.

Brennan MT, Treister NS, Sollecito TP, Schmidt BL, Patton LL, Yang Y, Lin A, Elting LS, Hodges JS, Lalla RV. 2021. Epidemiologic factors in patients with advanced head and neck cancer treated with radiation therapy. Head Neck. 43(1):164–172.

Choi SH, Terrell JE, Fowler KE, McLean SA, Ghanem T, Wolf GT, Bradford CR, Taylor J, Duffy SA. 2016. Socioeconomic and other demographic disparities predicting survival among head and neck cancer patients. PLoS One. 11(3):e0149886.

Dawes C, Pedersen AM, Villa A, Ekstrom J, Proctor GB, Vissink A, Aframian D, McGowan R, Aliko A, Narayana N, et al. 2015. The functions of human saliva: a review sponsored by the World Workshop on Oral Medicine VI. Arch Oral Biol. 60(6):863–874.

Deasy JO, Moiseenko V, Marks L, Chao KS, Nam J, Eisbruch A. 2010. Radiotherapy dose-volume effects on salivary gland function. Int J Radiat Oncol Biol Phys. 76(3 Suppl):S58–S63.

Deng J, Jackson L, Epstein JB, Migliorati CA, Murphy BA. 2015. Dental demineralization and caries in patients with head and neck cancer. Oral Oncol. 51(9):824–831.

Epstein JB, van der Meij EH, Emerton SM, Le ND, Stevenson-Moore P. 1995. Compliance with fluoride gel use in irradiated patients. Spec Care Dentist. 15(6):218–222.

Hong CH, Napenas JJ, Hodgson BD, Stokman MA, Mathers-Stauffers V, Elting LS, Spijkervet FK, Brennan MT, Dental Disease Section OCSG, Multi-national Association of Supportive Care in Cancer (MASCC)/International Society of Oral Oncology (ISOO). 2010. A systematic review of dental disease in patients undergoing cancer therapy. Oral Care Study Group, Multi-National Association of Supportive Care in Cancer (MASCC)/International Society of Oral Oncology (ISOO). Support Care Cancer. 18(8):1007–1021.

Kerr AR. 2003. Decision-making for preradiation dental extractions is based primarily on experience and opinion. Evid Based Dent. 4(1):11.

Kielbassa AM, Hinkelbein W, Hellwig E, Meyer-Luckel H. 2006. Radiation-related damage to dentition. Lancet Oncol. 7(4):326–335.

Kuznetsova A, Brockhoff PB, Christensen RH. 2017. Lmertest package: tests in linear mixed effects models. J Stat Softw. 82(13):1–26.

Lalla RV, Brennan MT, Schubert MM. 2010. Oral complications of cancer therapy. In: Yagiela JA, Dowd F, Johnson B, Mariotti A, Neidle E, editors. Pharmacology and therapeutics for dentistry. 6th ed. St. Louis (MO): Mosby/Elsevier.

Lalla RV, Long-Simpson L, Hodges JS, Treister N, Sollecito T, Schmidt B, Patton LL, Brennan MT. 2017. Clinical registry of dental outcomes in head and neck cancer patients (OraRad): rationale, methods, and recruitment considerations. BMC Oral Health. 17(1):59.

Lenth RV. 2020. Emmeans: Estimated Marginal Means, aka Least-Squares Means. R package version 1.4.6. https://CRAN.R-project.org/package=emmeans

Moore C, McLister C, Cardwell C, O'Neill C, Donnelly M, McKenna G. 2020. Dental caries following radiotherapy for head and neck cancer: a systematic review. Oral Oncol. 100:104484.

R Core Team. 2019. A language and environment for statistical computing. Vienna (Austria): R Foundation for Statistical Computing; [accessed October 29, 2019]. http://www.R-project.org/.

Reuther T, Schuster T, Mende U, Kubler A. 2003. Osteoradionecrosis of the jaws as a side effect of radiotherapy of head and neck tumour patients—a report of a thirty year retrospective review. Int J Oral Maxillofac Surg. 32(3):289–295.

Schwendicke F, Dorfer CE, Schlattmann P, Foster Page L, Thomson WM, Paris S. 2015. Socioeconomic inequality and caries: a systematic review and meta-analysis. J Dent Res. 94(1):10–18.

Siala W, Mnejja W, Elloumi F, Ghorbel A, Mnif J, Frikha M, Daoud J. 2014. Late toxicities after conventional radiotherapy for nasopharyngeal carcinoma: incidence and risk factors. J Radiother. 2014:268340.

Thariat J, Ramus L, Darcourt V, Marcy PY, Guevara N, Odin G, Poissonnet G, Castillo L, Ali AM, Righini C. 2012. Compliance with fluoride custom trays in irradiated head and neck cancer patients. Support Care Cancer. 20(8):1811–1814.

Vissink A, Jansma J, Spijkervet FK, Burlage FR, Coppes RP. 2003. Oral sequelae of head and neck radiotherapy. Crit Rev Oral Biol Med. 14(3):199–212.

Walker MP, Wichman B, Cheng AL, Coster J, Williams KB. 2011. Impact of radiotherapy dose on dentition breakdown in head and neck cancer patients. Pract Radiat Oncol. 1(3):142–148.