Chronic Oral Complications of Oral Cancer Therapy

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KEYWORDS

• Post-radiation • Tooth loss • Radiation caries • Osteoradionecrosis • Oral cancer
• Head and neck cancer

KEY POINTS

- Head and neck radiation for oral cavity and oropharyngeal cancers has long-term effects on oral health.
- Unique risk for osteoradionecrosis of the jaw, elevated by dental extractions <2 w pre-RT or any time post-RT, and by presence of hopeless teeth not extracted prior to radiation.
- Elevated dental caries rates are related to hyposalivation, gingival recession, and shift in oral microbiome following head and neck radiation.
- Quality-of-life in survivorship is negatively impacted by negative oral health outcomes.
- Dental providers can support good patient outcomes by prioritizing dental extractions >2 w pre-RT, dental restorations pre-RT, fluoride treatment, oral hygiene compliance at home, and dental care following radiation.

INTRODUCTION

Head and neck cancers (HNC) involve the oral cavity, oropharynx, and hypopharynx. As of 2021, 434,915 people in the United States were living with oral and oropharyngeal cancer and 11.5 of every 100,000 people (95% confidence interval [CI], 11.4 – 11.7) were diagnosed in 2021.[1] There is notable mortality associated with oral and oropharynx cancer: 2.7 of every 100,000 deaths were attributable to oral and oropharynx cancers in 2021 (95% CI, 2.6 – 2.7).[1] The etiology of head and neck cancer is multifactorial with known risk factors including tobacco use, alcohol use, human papilloma virus-infection (HPV; oropharyngeal cancer), and prior history of cancer.[2–5] For oropharyngeal cancer, HPV-status is an important consideration as prior meta-analyses have demonstrated that HPV-positive oropharyngeal cancer is associated with improved overall survival and disease-free survival compared to non-HPV related oropharyngeal cancers.[6,7]

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Abbreviations	
BOP	bleeding on probing
BW	Brigham and Women's Hospital
CAL	clinical attachment loss
CEJ-GM	cementoenamel junction to the gingival margin
CMC	Atrium Health Carolinas Medical Center
DMFS	decayed, missing, filled surfaces
Gy	Gray
HNC	head and neck cancer
HPV	human papillomavirus
HR	hazard ratio
NYU	New York University
OH-QOL	oral health-related quality-of-life
OraRad	Clinical Registry of Dental Outcomes in Head and Neck Cancer Patients
ORN	osteoradionecrosis
RR	risk ratio
RT	radiation therapy
SCC	squamous cell carcinoma
TNM	tumor, node, metastasis
UConn	University of Connecticut
UNC	University of North Carolina
UPenn	University of Pennsylvania

Radiation and surgery are the primary treatment modalities for oral and oropharyngeal cancers, but these may be combined with adjuvant chemotherapy. HNC treatment is a complex decision-making process that balances the size of the primary cancer, extent of nodal involvement, presence of metastatic disease, and patient stability and willingness to undergo surgery. Radiation therapy (RT) may be used pre- or post-surgery. Curative RT typically starts 6 to 7 weeks after surgery (if performed) and consists of daily fractions of 2 Grays (Gy) 5 d per week for 5 to 7 w for 50 to 70 Gy total.[8] Radiation may be unilateral or bilateral depending on primary tumor site and nodal involvement. Tissues in the field of radiation are subject to short- and long-term side effects of RT. Oral cavity short-term effects include oral mucositis, xerostomia (dry mouth), candidiasis, and taste changes, and long-term effects include xerostomia, increased caries rate, periodontal disease, trismus, dysphagia, and osteoradionecrosis.[8–13]

Survival of oral and oropharyngeal cancer has continued to improve with advancements in cancer therapies such that the 5-y survival rate is 69% (95% CI, 68.0% – 69.0%) and the 10-y survival rate is 56.6% (95% CI, 55.5% – 57.7%).[1] With increased years of survival, more HNC survivors are experiencing the long-term sequelae of cancer treatment including osteoradionecrosis (ORN), the associated morbidity of which can negatively impact quality-of-life, functional status, and nutritional status.[11,14–16] With known negative sequelae of treatment and improving survival, understanding the long-term implications of HNC therapies are increasingly critical for preserving quality-of-life in survivorship.

To better understand the oral complications of patients undergoing cancer therapies, the Oral Care Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology completed a series of 9 systematic reviews.[9,12,13,17–25] The findings from these reviews were not only that oral complications commonly arise following cancer therapies, but also that gaps exist in the understanding of the burden of illness and the risk factors associated with oral complications following cancer therapies. To address the lack of knowledge on oral sequelae from cancer therapies, the Clinical Registry of Dental Outcomes in Head and Neck Cancer Patients (OraRad) study (ClinicalTrials.gov NCT02057510) was funded by NIH and implemented. This multicenter prospective study evaluated the risks of and complications resulting from HNC therapy (the complete methodology has been previously published).[26] OraRad specifically assessed oral complications of external beam RT with curative intent for head and neck squamous cell carcinoma (SCC), salivary gland cancer, or at least 45 Gy for non-SCC, or non-salivary gland malignancy.[26,27] A total of 572 eligible participants (aged 18 or older) were enrolled between April 2014 and October 2018 across 6 clinical sites: Brigham and Women's Hospital (BW), University of Pennsylvania (UPenn), Atrium Health Carolinas Medical Center (CMC), University of Connecticut (UConn), New York University (NYU), and University of North Carolina (UNC).[26] Data were collected at baseline and at follow-up visits 6-, 12-, 18-, and 24-month following completion of RT.[26,27] By the 24-mo follow-up visit, 11% (62) of the 572 participants enrolled were deceased and 1% (5/572) withdrew consent to participate, leaving 505 participants remaining.[26,28] Of these remaining participants, 83% attended their 24-mo follow-up visits.[26,28]

Patients were assessed at the baseline visit prior to RT but after pre-RT dental evaluation and completion of recommended dental extractions, if applicable.[26] Pre-RT dental recommendations were not directed by the OraRad study protocol, rather they followed site specific internal guidelines at each treatment site.[26] Chosen HNC treatments were also determined according to institutional standards at each site and not dictated by the OraRad study protocol.[26] Data collection at the baseline visit included demographics, patient history (including tobacco and alcohol use history), oral health history, oral cancer characteristics (eg, tumor, node, metastasis [TNM] staging) and treatments, and radiation treatment details (eg, dose, number of fractions).[26]

Baseline dental examinations were completed by calibrated examiners with recent panoramic radiographs (within last 6 mo) available at the time of examination.[26] Calibration of examiners was completed prior to enrollment and repeated annually in person for decayed, missing, filled surfaces (DMFS) and periodontal measures. Dental disease characteristics collected included: number of teeth present, DMFS, probing depths, and clinical attachment loss (CAL).[26] For assessment of RT impact on salivary flow, stimulated whole salivary flow rate was collected at baseline.[26] Comprehensive oral examinations were performed at all follow-up visits, periodontal assessment was repeated only at the 12- and 24-mo visits, and salivary flow rates were reassessed only at the 6- and 18-mo visits.[26] Outcomes assessed include tooth failure, exposed bone, osteoradionecrosis, compliance with recommended oral hygiene practices, compliance with prescription fluoride, dental caries and DMFS, salivary flow rates, periodontal disease, trismus, dysphagia, oral pain, and quality-of-life.[26]

OraRad RESULTS

Exposed Bone and Osteoradionecrosis

OraRad used the American Association of Oral and Maxillofacial Surgeons diagnosis and staging criteria for medication-related osteonecrosis of the jaw as an agreed upon system for ORN of the jaw had not been established.[28] Staging is based on clinical and radiographic findings and on patient symptoms such that the early stages (Stage 1 and 2) have similar radiographic changes (alveolar bone loss not due to periodontal disease, changes to trabeculation, osteosclerotic regions, thickening of periodontal ligament, etc.) and exposed bone/fistula that probes to the bone, Stage 2 is differentiated by the presence of symptoms and signs of infection and/or inflammation, and Stage 3 is unique in that one of the following is present: exposed necrotic bone extending past the region of the alveolar bone (eg, the zygoma in the maxilla), extraoral fistula, oroantral communication, osteolysis past the alveolar bone (ie, to sinus floor, inferior floor of the mandible), and pathologic fracture.[10]

Of the 572 participants enrolled in OraRad, 182 participants (31.8%) had 1 or more teeth extracted by the baseline visit, while 24 others (4.2%) had hopeless teeth that were not extracted.[28] All patients received RT with an average dose of 66 Gy, and the most frequent sites for RT were the oropharynx (49%), oral cavity (15%), salivary gland (10%), and larynx/hypopharynx (7.5%).[28] Changes in dentition, including tooth loss events (extractions/exfoliations, newly "hopeless" status), were documented at follow-up visits.[28] Exposed bone is a defining feature of Stages 1 to 3 of osteonecrosis and was evaluated in the OraRad population in both spontaneous (without inducing extraction/exfoliation/hopeless teeth) and non-spontaneous iterations.[28] Exposed bone was detected in 35 participants, with 11 cases being spontaneous (1 of these with 2 sites of exposed bone) and 24 being non-spontaneous (1 of these with 2 sites of exposed bone).[28] Twenty percent of exposed bone cases (7/35) were present at a given site at more than one study visit, qualifying them as persistent exposed bone.[28] The mandible was the most frequently reported site for exposed bone (76%), and 5 of the 7 persistent exposed bone sites were in the posterior mandible (remaining 2 were in the posterior maxilla).[28] Five of the 7 participants with persistent exposed bone continued to have exposed sites at the 24-mo follow-up visit (or at last visit if prior), and 6 of the 7 participants with persistent exposed bone ultimately had confirmed diagnoses of ORN.[28]

Confirmed diagnosis of ORN was made for 18 participants, but actual incidence may have been higher than the reported 3.1% (18/572) due to lack of follow-through on subsequent referrals or lack of documentation on referral results.[28] The majority of confirmed ORN cases (13) were diagnosed as Stage 2 at their worst, with the remaining 5 were diagnosed as Stage 1 at their worst.[28] There were no Stage 3 ORN cases diagnosed. Of the Stage 2 cases, 9 cases were fully resolved, 1 improved to Stage 1, and 3 remained at Stage 2.[28] Treatments completed for confirmed ORN cases included chlorhexidine rinses, antibiotics, surgical debridement, sequestrectomy, pentoxifylline and vitamin E, analgesics, hyperbaric oxygen therapy, and surgical resection.[28] Treatments were not statistically associated with ORN resolution.[28]

The authors concluded that there are risk factors for exposed bone and ORN.[28] Current tobacco users (28/570 participants reporting tobacco use) were at elevated risk of exposed bone (17.9% had exposed bone) compared to the former tobacco users (5.8%) and never users (5.2%) (**Table 1**).[28] Exposed bone was most frequently identified in participants with the oral cavity as primary radiation site (13.4%), but not at the level of statistical significance (see **Table 1**).[28] Concurrent chemotherapy was not significantly associated with exposed bone frequency, but there was a non-significant, slightly higher incidence of exposed bone for participants receiving concurrent chemotherapy (6.6% vs 5.3%, $P=.59$) (see **Table 1**).[28] Extractions prior to RT were associated with increased incidence of exposed bone during follow-up, the number of pre-RT extractions were associated with an increased risk of developing exposed bone, and dose to primary radiation site were correlated with likelihood of having exposed bone (see **Table 1**).[28,29] The presence of hopeless teeth not extracted prior to RT was the greatest predictor of exposed bone at a tooth location (risk ratio [RR], 18.7; $P=.0002$).[29] As both dental extractions prior to RT and presence of hopeless teeth not extracted prior to RT were associated with exposed bone, the relative risks, and modifiable characteristics are critical considerations.[28,29] In this study,

Table 1
Tests of association of potential predictors with exposed bone outcomes

Potential Predictor	*P*-value: Any Exposed Bone vs None	*P*-value: Exposed Bone, No Sequestrum	Description of the Association Odds Ratios (ORs) Are for Exposed Bone vs No Exposed Bone
Pre-RT extraction or hopeless teeth at BL[a]	.008	.043	Any vs none: Extraction 10.4%, hopeless 8.3%, neither 3.8% No sequestrum: Extraction 5.0%, hopeless 0%, neither 1.4%
Any extraction or hopeless teeth by V24[b]	<.0001	.0013	Any vs none: Lost 12.2%, hopeless 0%, neither 2.8%. No sequestrum: Lost 5.6%, hopeless 0%, neither 0.6%.
N teeth extracted pre-RT prior to BL	.006	.060	Any vs none: OR per tooth 1.11 (95% CI 1.04–1.18) No sequestrum: OR per tooth 1.11 (95% CI 1.01–1.21)
N teeth present at BL	.11	.49	Any vs none: OR per additional tooth present 0.96 (95% CI 0.91–1.01) No sequestrum: OR per additional tooth present 0.97 (95% CI 0.89–1.05)
Total RT dose to primary site[c]	.039	.31	Any vs none: OR per 10 Gy higher dose 1.97 (95% CI 1.03–4.12). No sequestrum: OR per 10 Gy higher dose 1.64 (95% CI 0.59–4.58).
Primary RT site[d]	.087	.70	Any vs none: oral cavity 13.4%, larynx/hypopharynx 7.5%, oropharynx 5.7%, other 5.3%, salivary gland 1.9%. No sequestrum: oral cavity 3.7%, larynx/hypopharynx 0%, oropharynx 2.3%, other 4.2%, salivary gland 1.9%.
Definitive vs Post-operative RT	.58	1.00	Any vs none: definitive 6.9%, post-operative 5.4% No sequestrum: definitive 2.3%, post-operative 2.5%
RT type (IMRT vs Proton)	.71	1.00	Any vs none: IMRT 6.3%, proton 3.2% No sequestrum: IMRT 2.6%, proton 0%
Follow-up fluoride[e]	.85	.76	Any vs none: compliant 5.8%; non-compliant 6.9% No sequestrum: compliant 2.0%; non-compliant 2.8%

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Table 1
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Potential Predictor	*P*-value: Any Exposed Bone vs None	*P*-value: Exposed Bone, No Sequestrum	Description of the Association Odds Ratios (ORs) Are for Exposed Bone vs No Exposed Bone
Follow-up brush/floss[e]	1.00	.24	Any vs none: compliant 6.3%; non-compliant 6.7% No sequestrum: compliant 1.2%; non-compliant 3.2%
Tobacco, ever v. never v. current	.048	.0047	Any vs none: Never 5.2%, Former 5.8%, Current 17.9% No sequestrum: Never 2.0%, Former 1.7%, Current 14.3%
Chemotherapy (Y/N)	.59	.78	Any vs none: chemotherapy 6.6%; none 5.3% No sequestrum: chemotherapy 2.8%; none 1.9%
Anti-resorptive (Y/N)	.31	.37	Any vs none: anti-resorptive 11.1%; none 6.0% No sequestrum: anti-resorptive 5.6%; none 2.4%
Enrollment site (clinic)	.0024	.018	Any vs none: CMC 13.5%, UConn 11.3%, BW 5.7%, UNC 3.2%, UPenn 2.7%, NYU 1.3%. No sequestrum: CMC 5.8%, UConn 7.6%, BW 1.3%, UNC 0%, UPenn 0.7%, NYU 1.3%.
Whole mouth average (WMA) PD[f]	.10	.13	Any vs none: OR for +0.5 mm WMA PD 1.33 (95% CI 0.95–1.85)[g] No sequestrum: OR for +0.5 mm WMA PD 1.45 (95% CI 0.91–2.34)[g]
% sites PD≥4	.21	.16	Any vs none: OR for +13% points 1.23 (95% CI 0.91–1.68)[g] No sequestrum: OR for +13% points 1.37 (95% CI 0.92–2.06)[g]
% sites PD≥5	.10	.086	Any vs none: OR for +6% points 1.26 (95% CI 0.98–1.62)[g] No sequestrum: OR for +6% points 1.37 (95% CI 1.01–1.85)[g]
Whole mouth average (WMA) CAL	.13	.30	Any vs none: OR for +1 mm WMA CAL 1.29 (95% CI 0.94–1.78)[g] No sequestrum: OR for +1 mm WMA CAL 1.30 (95% CI 0.82–2.05)[g]

% sites CAL≥2	.098	.40	Any vs none: OR for +27% points 1.36 (95% CI 0.94–1.98)[g] No sequestrum: OR for +27% points 1.26 (95% CI 0.73–2.20)[g]
% sites CAL≥3	.24	.53	Any vs none: OR for +25% points 1.23 (95% CI 0.88–1.72)[g] No sequestrum: OR for +25% points 1.18 (95% CI 0.71–1.95[g]

Abbreviations: BL, baseline; CAL, clinical attachment loss; IMRT, intensity modulated radiation therapy; PD, probing depth; RT, radiation therapy.

[a] Had an extraction at BL vs had no extractions but had a tooth declared hopeless vs had no teeth extracted or declared hopeless.

[b] Some teeth exited the mouth (lost) versus no teeth exited the mouth but had a tooth declared hopeless versus no teeth lost or declared hopeless.

[c] n = 571, n = 536 for “none”, 35 for “any”; the other 1 had missing data.

[d] n = 533, n = 498 for “none”, 35 for “any”; the other 39 had “Other” or “Don’t know”.

[e] Brush/floss: Reported brushing at least 2x daily and flossing at least daily for all followup visits attended; Fluoride: reporting using prescription fluoride at least daily for all followup visits attended.

[f] WMA = “whole mouth average”; n = 533 for BL periodontal data, n = 503 for “none”, 30 for “any”.

[g] Odds ratios (ORs) are for an approximately 1 standard deviation increase in the predictor measure. Standard deviations are: WMA PD 0.52 mm; % sites PD≥4 13.0% points; % sites PD≥5 6.0% points; WMA CAL 0.99 mm; % sites CAL≥3 27.1% points; % sites CAL ≥3 25.2% points.

Table modified with permission from Treister, et al. Exposed bone in patients with head and neck cancer treated with radiation therapy: an analysis of the Observational Study of Dental Outcomes in Head and Neck Cancer Patients (OraRad). Cancer 2022;128(3):487–96. https://doi.org/10.1002/cncr.33948.

the only other significant pre-RT predictive factors for exposed bone were periodontal pocket depth equaling 5 mm (RR, 4.7; *P*=.016) and pocket depth 6 mm or greater (RR, 5.4; *P*=.003).[29] Pre-RT dental extractions in participants who did not develop exposed bone were completed an average of 26.2 d prior to RT, while the pre-RT extractions in participants who did develop exposed bone were completed an average of 19.6 d prior to RT (*P*=.21).[29]

There is inherent risk of spontaneous exposed bone following head and neck radiation, but additional risk is conferred by current tobacco use, pre-RT dental extractions, presence of "hopeless" teeth, higher radiation dose to the primary site, and pre-RT extractions less than 3 w prior to RT start.[28,29] These findings have application in pre-treatment patient counseling in that they further support pre-treatment tobacco cessation for best outcomes. The results regarding pre-RT dental extractions and retention of "hopeless" teeth illustrate the double-edge sword that is poor dentition in the peri-radiation period. Extractions pre-radiation increase risk of exposed bone, but these studies suggest that postponing the inevitable by allowing hopeless teeth to remain may be the greater risk.[28–30]

Tooth Failure

One objective of pre-radiation dental clearances for patients undergoing head and neck radiation is to minimize tooth loss following radiation and thereby minimize risk of exposed bones and osteoradionecrosis.[27–29] The factors related to tooth failure post-radiation are therefore of great interest and may be considered either "tooth-level" or "non-tooth related" factors.[27,29] Tooth failure in the OraRad Study was defined as a tooth being extracted or declared hopeless after RT as extraction may be avoided post-radiation due to risk of ORN.[27,29] A hopeless tooth was defined as a tooth with any of the following: non-restorable (fractured, extensive decay), retained root tips, and/or persistent/uncontrolled odontogenic or periodontal infection.[27,29] Tooth-level factors assessed include caries, periodontal measures, and mobility, amongst others.[29]

Lalla and colleagues found that tooth-level risk factors could predict tooth failure within 2 y after RT.[29] The greatest pre-RT predictor of tooth failure was the presence of hopeless teeth not extracted prior to RT (hazard ratio [HR], 17.1; *P*<.0001), which was also the greatest predictor of exposed bone at a tooth location in this study (RR, 18.7; *P*=.0002) (**Table 2**).[29] The presence of untreated caries was predictive of tooth failure within 2 y following RT with an HR of 5.0 (*P*<.0001) but was not a predictor of exposed bone (see **Table 2**).[29] Pre-radiation periodontal factors were found to be predictive of tooth failure in the 2 y following RT, specifically periodontal pocket equaling 5 mm or greater (HR, 2.2; *P*=.006), periodontal pocket 6 mm or greater (HR, 3.4; *P*=.001), furcation score of 2 (HR, 3.3.; *P*=.003), gingival recession >2 mm (HR, 2.8; *P*=.002), and any mobility (HR, 2.2; *P*=.008) (see **Table 2**).[29]

Additional factors considered in relation to tooth failure were treatment related (eg, location of primary RT, dose of RT, and concurrent chemotherapy), oral hygiene habits, number of baseline teeth, routine dental care history, and saliva flow (**Table 3**).[27] For the OraRad population, the estimated fraction of tooth failure was 17.8% (95% CI, 14.3%-21.3%) at the 2-y mark post-radiation.[27] The number of failed teeth was higher for participants who had fewer teeth to begin with (*P*<.0001) and for participants who were not compliant with daily routine oral hygiene (ie, brushing 2x/day and flossing daily) (*P*=.03).[27] These findings suggest that patient behavior plays a role in tooth failure following RT in that tooth loss/fewer teeth at baseline (a surrogate marker for poor oral hygiene habits prior to RT) and non-compliance with oral hygiene prior to and following RT are associated with greater tooth failure.[27] Further support for this was that the patients who became oral hygiene compliant (ie, were not oral

Table 2
Predictors of tooth failure within 2 y after radiation therapy

	Unadjusted[a]			Adjusted[b]		
Comparison	**Hazard Ratio**	**95% CI**	***P* Value**	**Hazard Ratio**	**95% CI**	***P* Value**
Retained Hopeless Teeth vs Other Teeth Present[c]	47.8	21.6 – 105.9	< .0001	17.1	7.9 – 37.1	< .0001
Untreated Caries vs Teeth Without Caries	10.0	5.3 – 18.\9	< .0001	5.0	2.7 – 9.3	< .0001
Deepest Periodontal Pocket, mm						
≥ 6 vs < 4	6.0	2.5 – 14.3	< .0001	3.4	1.6 – 7.0	.001
5 vs < 4	3.5	1.9 – 6.3	< .0001	2.2	1.3 – 4.0	.006
4 vs < 4	2.1	1.3 – 3.2	.001	1.7	1.1 – 2.5	.018
Furcation Score						
2 vs 0	6.7	3.1 – 14.3	< .0001	3.3	1.5 – 7.3	.003
1 vs 0	1.6	0.7 – 3.6	.31	1.4	0.6 – 3.1	.40
Gingival Recession, Cementoenamel Junction to Gingival Margin Distance, mm						
< −2 vs ≥ 0	8.3	4.5 – 15.5	< .0001	2.8	1.5 – 5.2	.002
−1 or −2 vs ≥ 0	2.8	1.6 – 5.0	.0006	2.8	0.99 – 3.2	.053
Mobility, Any Grade vs None	5.9	3.1 – 11.3	< .0001	2.2	1.2 – 4.0	.008
Bleeding on Probing, Yes vs No	1.5	0.7 – 3.1	.28	1.0	0.5 – 1.9	.98

[a] These analyses include the same participants and teeth included in the adjusted analyses.
[b] Adjusted analyses omitted teeth with missing data for adjusters. With exceptions as noted, analyses were adjusted for these person-level characteristics: baseline number of teeth (5 categories: ≤ 14, 15–24, 25–26, 27, 28); age (continuous); whether the person had untreated caries at baseline; alcohol use (<12 drinks per year vs ≥ 12 drinks per year); radiation type (any intensity-modulated radiation therapy [RT] vs proton); smoking (never, former, or current); clinic; compliance change baseline to follow-up (4 categories, defined in the Methods section); radiation dose; nadir of saliva after RT as a percentage of baseline. Exceptions were as follows. For the tooth-level predictor untreated caries, the person level adjuster "whether the person had untreated caries at baseline" was not included. For furcation score, only teeth with furcations were included, and a further adjuster was added, premolar versus molar.
[c] For this comparison only, teeth were at risk at baseline if they were present in the mouth, and only newly missing teeth were counted as events.
Table modified with permission from Lalla, et al. Tooth-level predictors of tooth loss and exposed bone after radiation therapy for head and neck cancer, J Am Dent Assoc 2023;154(6):519–28.e4.

Table 3
Non-tooth level predictors of oral sequelae

Factor	Oral Sequelae
Demographics/Patient	
Alcohol Use	Tooth Failure[27]
Tobacco Use	Exposed Bone/ORN†[28]
Lack of Dental Insurance	DMFS*[31]
Older Age	DMFS*[31]
Professional Dental Care Compliance	Tooth Failure,[27] DMFS*[31]
Cancer/Treatment	
Oral Cavity Primary	DMFS[31]
Larynx/Hypopharynx Primary	Gingival Recession[29]
Higher RT dose to Parotids	Tooth Failure[27]
Higher RT dose to Mandible	Exposed Bone/ORN†,[28] DMFS*[31]
Post-radiation Therapy Factors	
Prescription Fluoride Compliance	DMFS*[31]
Lower Salivary Flow with Baseline Caries	Tooth Failure[27]
Oral Hygiene Compliance	Tooth Failure,[27] DMFS*[31]

The demographic or patient related, cancer or treatment related, and post-radiation therapy factors that increase risk of adverse oral sequelae are listed above with their corresponding oral sequelae as identified through the OraRad papers.
*Decayed, missing, filled surface.
†Osteoradionecrosis of the jaw.

hygiene compliant at baseline but were at follow-up) had the fewest teeth fail, while those participants who were non-compliant with oral hygiene at both baseline and follow-up had the greatest rates of tooth failure.[27] The effects of RT are also associated with increased tooth failure, as more teeth failed with increasingly reduced salivary flow rates (P=.013).[27] Risk of tooth failure due to reduced salivary flow was highest for patients with untreated dental caries at baseline.[27]

The authors hypothesized that patients who had received routine dental care in the year prior to initiating radiation for HNC would have fewer failed teeth in the post-radiation period.[27] The results, however, were not as anticipated. For participants with fewer than 14 teeth at baseline, 57% of those who also reported routine care within 1 y prior to RT had a tooth failure event during the follow-up visits while only 25% of those who denied dental care within the preceding year had a tooth failure event.[27] For participants who had more teeth at baseline (25 – 26 teeth), nearly one-fifth (19%) of those reporting routine dental care within the year prior to RT reported a tooth-failure event, but none of those who had not had routine dental care experienced a tooth-failure event.[27] Tooth-failure event rates were similar between those who did and did not receive routine dental care in the other number of teeth at baseline categories.[27]

One possible explanation for this phenomenon is that controlling for baseline number of teeth, patients with worse dental problems are more likely to have pursued dental care in the year prior to beginning RT and are also more likely to experience tooth-failure following RT.[27] In this explanation, rather than considering dental visits in the year before radiation to be indicative of good oral hygiene behavior, they could be viewed as a surrogate for tooth-level risk factors (eg, periodontal disease, dental caries) that require routine dental treatment.

As discussed, patients who are not compliant with recommended oral hygiene behaviors are more likely to lose teeth following head and neck radiation.[27] A question asked by Lim and colleagues was whether these habits were modifiable and what happens when patients do adopt better oral hygiene habits.[32] Of the 518 HNC patients with follow-up visits in OraRad, 296 self-reported being oral hygiene non-compliant at their baseline visit, and 44 (14.9%) became oral hygiene compliant at all follow-up visits.[32] When compared with those participants who did not become compliant at all, some, or any of their follow-up visits, the group who became oral hygiene compliant differed on a few key factors.[32] Participants were more likely to become oral hygiene compliant post-radiation when they had primary surgical site of larynx and hypopharynx ($P=.042$), primary oral cavity radiation site ($P=.004$), surgery before RT ($P=.008$), limited mouth opening before RT ($P=.001$), compliant fluoride use ($P=.023$), and dental insurance ($P=.026$).[32]

Patients who became oral hygiene compliant after surgery and radiation may have done so because their tumor did not allow for oral hygiene (ie, lesion limited access for hygiene, lesion bled during brushing, and pain from lesion), and that, for these patients, range-of-motion might have improved post-surgery.[32] Similarly, those who began RT with a lower range-of-motion may have been more motivated to attempt oral hygiene.[32] Access to dental care, however, may be the more actionable topic to consider, as having dental insurance and compliant fluoride use are the only modifiable factors unrelated to disease process.[32] There is a financial burden associated with dental care; dental insurance may be considered a surrogate measure for higher socioeconomic status that would facilitate patient participation in dental care.[32,33] Merely encouraging oral hygiene compliance for HNC patients may not be enough for successful outcomes if resources are insufficient to facilitate oral hygiene compliance.

Periodontal Disease

As previously discussed, periodontal disease (ie, tooth mobility, deep probing depths, and gingival recession) is a predictor of tooth failure.[28,29] Periodontal disease is also a possible oral complication following head and neck radiation, and some aspects of periodontal health have been found to be impacted by radiation in a dose-related fashion.[11,34] In the study conducted by Lalla and colleagues, measurements of pocket depth, bleeding on probing (BOP), clinical attachment loss (CAL), and cementoenamel junction to the gingival margin (CEJ-GM) were considered in relation to each other, radiation dose to mandible, and incidence of dental caries across baseline, 12-, and 24-mo visits.[34] They found that the estimated average whole mouth mean percentage of sites with BOP did not differ significantly across visits, indicating that this measure of periodontal disease is not impacted by head and neck radiation.[34] Periodontal pocket depth (as estimated average whole mouth mean) decreased significantly ($P=.001$) between baseline (2.24 mm, SE 0.02) and 12-mo (2.24 mm, SE 0.02), then holding steady at the 24-mo assessment (2.23 mm, SE 0.02).[34] Likewise, mean percentage of all sites with pocket depth of 4 mm decreased significantly ($P=.001$) from baseline (11.1%, SE 0.5%) to 12-mo (8.9%, SE 0.6%) then remaining stable at the 24-mo visit (8.8%, SE 0.6%).[34] Although lower probing depths typically represent improved periodontal health, the findings regarding CAL and gingival recession indicate otherwise in the post-RT patient.[34]

Degree of clinical attachment was found to worsen significantly ($P=.005$) at each follow-up visit with the estimated average whole mouth mean CAL being 1.92 mm (SE 0.04) at baseline, and 2.00 mm (SE 0.04) and 2.11 mm (SE 0.05) at 12- and 24-mo respectively.[34] Sites with CAL 2 mm (represented by mean percentage) increased from baseline (53.1%, SE 1.2%) to 12-mo (54.3%, SE 1.2%) significantly (P=.001), increased from baseline to 24-mo (57.5%, SE 1.3%) significantly (P=.001), but percentages did not differ significantly from 12- to 24-mo (P=.17).[34] Gingival recession is represented here by average whole mouth mean distance from the CEJ-GM and can be a value less than 0 mm, which represents gingival margin being apical to the CEJ.[34] The CEJ-GM was reduced significantly (P=.001) from baseline (0.43 mm, SE 0.04) to 12-mo (0.24 mm, SE 0.04) and to 24-mo (0.11 mm, SE 0.04), and reduction from 12- to 24-mo was also significant (P=.001).[34] The mean percentage of sites with CEJ-GM distance less than 0 mm significantly (P=.02) increased from baseline (23.3%, SE 1.0%) to 12-mo (28.5%, SE 1.0%), from baseline to 24-mo (30.5%, SE 1.1%), and from 12- to 24-mo[34] Greater increase in percentage of mandibular sites with CEJ-GM distance less than 0 mm was significantly (P=.003) associated with higher mean radiation dose to the mandible.[34] A dose-dependent relationship was observed such that the percentage of mandibular sites with recession increased by 2.0% (SE 0.7%) from baseline to 12-mo (P=.006) and by 2.3% (SE 0.8%) from baseline to 24-mo for every additional 10 Gy of mandibular radiation.[34] Change in average mandibular CEJ-GM distance was not associated (P=.25) with mean radiation dose to the mandible.[34]

These findings demonstrate that while pocket probing depths improve after RT, overall periodontal health does not. Gingival recession and CAL increasing at all visits following RT means that post-RT patients have a reduced periodontium supporting remaining teeth. The proposed mechanism of action for this effect is that increases in local matrix metalloproteinases and interleukin 6 due to RT mimic the pro-inflammatory conditions of periodontal disease leading to bone loss.[34] Reduced periodontium puts patients at risk of increased tooth mobility and tooth loss due to periodontal disease. Increased CAL and gingival recession also mean increased exposed tooth surface, including root surface when the CEJ-GM distance is less than 0 mm.[34] The dental root surface is more vulnerable to decay than the coronal structure, leading to the question of whether gingival recession post-RT is associated with dental caries development.[34]

In assessing this relationship, the authors found that increased gingival recession is associated with increased dental caries post-RT.[34] Whole mouth DMFS was significantly associated (P<.01) with both mean percentage of CEJ-GM distance less than 0 mm sites and with mean CEJ-GM distance.[34] In addition, the whole mouth proportion of decayed or filled facial/buccal surfaces was found to be greater (P<.001) with greater gingival recession (both mean CEJ-GM distance and mean percentage of sites with CEJ-GEM distance < 0 mm).[34] The aforementioned relationships become more notable over time such that at baseline, a 1 mm smaller CEJ-GM distance (ie, 1 mm more recession) was associated with 0.88% (SE 0.41%, P=.032) more DMFS total and with 1.25% (SE 0.63%, P=.048) more decayed or filled facial/buccal surfaces.[34] At 24-mo follow-up, a 1 mm smaller CEJ-GM distance was associated with 2.83% (SE 0.44%, P<.001) more DMFS total and with 4.36% (SE 0.69%, P<.001) more decayed or filled facial/buccal surfaces.[34] Thus, the negative impact of RT on periodontal health has broader implications with regards to caries risk and tooth loss due to caries following HNC-RT.[34]

Dental Caries

Dental caries was assessed in the OraRad study using a dental explorer and the surrogate measure of DMFS (decayed, missing, and filled surfaces) was recorded for the anterior and posterior teeth (excluding third molars) at the baseline and all follow-up visits.[27,29,31] Over these follow-ups, DMFS increased from baseline at each follow-up visit.[31] The average DMFS increase from baseline to each subsequent visit was as follows: +1.11, 6 mo; +2.47, 12 mo; +3.43, 18 mo; and +4.29, 24 mo ($P<.0001$).[31] Notably, DMFS increase varied according to select patient factors.[31] Reduction in salivary flow alone was not significantly associated with increased DMFS ($P>.1$) but was associated with increased DMFS in the subset of patients (n = 164) who had salivary gland hypofunction at baseline.[31] The following patient characteristics were found to correspond to a smaller increase in DMFS: daily prescription fluoride use compliance ($P=.0004$), daily oral hygiene compliance (defined as brushing twice daily, flossing daily; $P=.015$), dental insurance ($P=.004$), and greater than high school education ($P=.001$).[31] Again, we see that patient behavior impacts oral health outcomes following head and neck radiation.[31]

In the study by Mougeot and colleagues on the microbiome of HNC patients, the relative abundance of greater than 600 bacterial species was assessed across oral flora samples of 31 patients with HNC.[35] The DMFS score was used to differentiate between groups that had increases in tooth decay (as represented by increased DMFS score) and that had no increase in tooth decay (as represented by unchanged DMFS score) from baseline to 6- and 18-mo post-radiation follow-up visits.[35] They identified changes in microbiome beta-diversity at both follow-up time points.[35] At the 6-mo follow-up, relative abundance of *Streptococcus mutans* (classically associated with dental caries) increased in both the increased DMFS score and no change in DMFS score groups.[35] Also at the 6-mo follow-up, relative abundance of *Prevotella melaninogenica* (associated with early childhood caries) increased in the increased DMFS score group.[35] A species associated with the oral flora of health, *Abiotrophia defectiva*, was found to have decreased relative abundance in the increased DMFS score group.[35] The *S. mutans* and *P. melaninogenica* results may seem contradictory, but the authors argue that they can be explained by considering similarities between radiation caries and early childhood caries.[35] Radiation caries predominantly involve the smooth surfaces of the incisors, premolars, and molars (surfaces that are more resistant to decay in the adult dentition) and early childhood caries also predominantly involve the smooth surfaces of teeth.[35–37]

The presence of untreated dental caries prior to head and neck radiation has been identified as one of the strongest predictors of tooth failure in the post-RT observation period (HR = 5.0, $P<.0001$).[29] Dental caries are treatable, but, given what is commonly a very short window between dental evaluation and the initiation of HNC RT, dental restorations have not historically been prioritized in the pre-radiation period.[29,38] These findings collectively suggest that dental caries should be treated prior to initiating HNC radiation and that oral hygiene compliance should be emphasized for best outcomes.[29]

Quality of Life

The after-effects of any kind of cancer treatment are numerous and with a lasting impact on survivors.[14,20,39] There is growing interest in how the sequelae of HNC therapy affect quality-of-life in survivorship.[15,40] Patton and colleagues assessed quality-of-life in the OraRad population using single item questions and composite scales from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-HNC specific module-35 items scale, which is a widely used and validated instrument.[41–43] In the OraRad cohort, the oral health-related quality-of-life (OH-QOL) scale is sensitive to demographic, tumor, and treatment variables up to 2 y after RT.[41] Notably, the OH-QOL scores were in general highest (ie, quality-of-life was worst) at the 6-mo post-radiation visit and declined somewhat by the 12-mo visit, but scores remained elevated over baseline at the 18- and 24-mo visits.[41]

The oral health-related factors that continued to impact quality-of-life at the 24-mo visit were sense problems (including taste), dry mouth, and sticky saliva, all of which were still significantly elevated at 24-mo post-radiation but were most elevated at 6-mo post-radiation.[41] This leads to the question of what factors are associated with clinically meaningful changes in sense problems, dry mouth, and sticky saliva and therefore worsened quality-of-life in HNC survivorship.

Additional patient, cancer, and treatment factors were associated with clinically meaningful changes that negatively impact quality-of-life.[41] For example, greater increase in sticky saliva and dry mouth were noted for men at the 12-mo and 6- and 12-mo visits, respectively.[41] Age also plays a role, with older individuals (>65 y old) having greater increase in senses problems from baseline to all follow-up visits than younger individuals (<50 y old), and a greater increase in dry mouth at 18-mo mark than younger individuals.[41] Oropharynx tumor site was associated with an increase in sticky saliva and dry mouth greater than that associated with larynx/hypopharynx, oral cavity, and salivary gland tumors.[41] Nodal involvement was significantly ($P<.001$) associated with increase in dry mouth from baseline to subsequent visits, and an increase in sticky saliva from baseline at the 6- and 24-mo visits.[41]

Treatment modality and total radiation dose are associated with a number of adverse oral health outcomes.[39,41] When total radiation dose to primary site was considered, increase in radiation per 10 Gy greater dose was significantly associated with increased dry mouth ($P=.0001$), increased sticky saliva ($P=.0004$), increased sense problems ($P=.0001$), and increased taste problems ($P=.0001$), although taste is included in the sense problems scale.[41] Different combinations of treatment modalities (surgery, radiation, and chemotherapy) had different impacts, most notable in the dry mouth findings.[41] Radiation alone and chemoradiation (without surgery) were associated with greater increase in dry mouth than radiation following surgery at all follow-up points, while combined surgery/radiation/chemotherapy was associated with dry mouth increase greater than only radiation following surgery at the 6-, 12-, and 18-mo visits.[41] Chemoradiation was associated with greater increase in dry mouth from baseline than all other treatment modalities, but at different follow-up time frames: surgery/radiation/chemotherapy (6- and 12-mo) and radiation alone (6-mo).[41] Chemoradiation was also associated with increased sticky saliva at the 6-mo visit when compared to all other modality combinations, and with increased problems with senses (6-mo) and taste (6- and 12-mo) compared to surgery followed by radiation.[41]

These findings have critical implications for ongoing developments in HNC therapy.[41] Prior studies on HNC treatment modalities have shown both that chemoradiation increases survival and that chemoradiation has higher local toxicity, which is supported by worse dry mouth, sticky saliva, and sense problems noted here for chemoradiation over other treatment modalities.[41,44,45] This study also identified worse oral health quality-of-life outcomes for patients who are men, over 65 y old, with oropharynx primary lesions, and/or nodal involvement.[41] Knowing individual and treatment-specific risk factors not only help providers prepare HNC patients for the sequelae of therapy, but also provide targets for future efforts to limit treatment toxicities.[41]

SUMMARY

Oral health care providers are in a unique position to care for HNC patients at all stages of treatment. The OraRad study identified treatment-, patient-, and cancer-based risk factors for specific oral health outcomes following head and neck RT, as well as the areas that may be targeted in future to improve supportive care for HNC patients.[8,26] Prior to HNC RT, the oral health care provider should consult a radiation oncologist for RT fields, consider extraction of teeth with poor long-term prognosis according to RT map (areas receiving > 50 Gy will be at higher risk of ORN), complete extractions at least 2 w prior to RT, and monitor for healing prior to RT start.[8] Patients with remaining teeth benefit from prescription-strength topical fluoride and restoration of dental caries prior to RT, and all benefit from counseling on the importance of oral hygiene considering risk of hyposalivation, gingival recession, trismus, caries, tooth loss, and osteoradionecrosis.[8] For the post-RT patient, oral hygiene instruction, increased hygiene visits, ongoing prescription fluoride, prompt restoration of decay, and management of periodontal disease are critical for maintenance of remaining teeth, especially in areas receiving greater than 50 Gy.[8] Referral to oral and maxillofacial surgery may be indicated in the event of tooth failure in the radiation field.[8] Best outcomes begin with evidence-based practices, and the collective OraRad study findings form a useful framework for mitigating risk of adverse oral health events for the HNC patients preparing for and following completion of radiation therapy.[8]

CLINICS CARE POINTS

- Head and neck radiation for oral cavity and oropharyngeal cancers has long-term effects on oral health.
- Unique risk for osteoradionecrosis of the jaw, elevated by dental extractions <2 w pre-RT or any time post-RT, and by presence of hopeless teeth not extracted prior to radiation.
- Elevated dental caries rates are related to hyposalivation, gingival recession, and shift in oral microbiome following head and neck radiation.
- Quality-of-life in survivorship is negatively impacted by negative oral health outcomes.
- Dental providers can support good patient outcomes by prioritizing dental extractions >2 w pre-RT, dental restorations pre-RT, fluoride treatment, oral hygiene compliance at home, and dental care following radiation.

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