Epidemiologic factors in patients with advanced head and neck cancer treated with radiation therapy

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Abstract

Background: Approximately 50% of patients with head and neck cancer (HNC) initially were seen with advanced disease. We aimed to evaluate the association of epidemiologic factors with advanced HNC at diagnosis.

Methods: The OraRad multicenter prospective cohort study enrolled HNC patients receiving curative-intent radiation therapy. Factors assessed for association with advanced HNC presentation at diagnosis included demographics, social and medical history, cancer characteristics, human papilloma virus (HPV) status, and dental disease measures.

Results: We enrolled 572 participants; 77% male and mean (SD) age of 61.7 (11.2) years. Oropharyngeal squamous cell carcinomas (88% HPV-related) were seen with smaller tumors, but more frequent nodal involvement. Private medical insurance and no Medicaid were associated with smaller tumors. A higher dental disease burden was associated with larger tumors.
Conclusions: Insurance status, cancer type/location, and dental disease are associated with advanced HNC and may represent potentially modifiable factors or factors to be considered in the screening process of new lesions.

Keywords: baseline features, dental health, epidemiology, head and neck cancer, radiotherapy

1 | Introduction

Approximately 63,000 new cases of head and neck cancer (HNC) are diagnosed annually in the United States, with estimated 13,360 deaths each year and an overall 5-year survival rate of 65%. About 50% of all HNC patients were seen with late-stage (advanced) cancer at diagnosis, which is characterized as larger tumor size (T3 or T4) or nodal involvement (≥N1) in the HNC staging (tumor, node, metastases [TNM]) classification. Numerous factors have been associated with more advanced HNC at diagnosis including demographics (age, sex, and race), socioeconomic status, insurance status, marital status, tumor location, and access to care. Additionally, human papilloma virus (HPV)-related oropharyngeal carcinomas have been noted to involve smaller tumors, but more extensive nodal disease.

The OraRad study (Clinical Registry of Dental Outcomes in Head and Neck Cancer Patients) is a multicenter prospective study of 572 HNC patients receiving curative-intent radiation therapy (RT). The study was designed to address gaps in our knowledge of dental and oral outcomes and dental management strategies. This analysis evaluated the association of epidemiologic factors with more advanced cancers on presentation in the well-characterized OraRad cohort.

Table 1: Demographics of study cohort

| Variable          | All sites | BWH     | UPENN   | CMC     | UConn   | NYU     | UNC     | P-Value |
|-------------------|-----------|---------|---------|---------|---------|---------|---------|---------|
| N                 | 572       | 158     | 146     | 104     | 53      | 80      | 31      |         |
| Sex               |           |         |         |         |         |         |         | .1512   |
| Male              | 440 (76.9%) | 124 (78.5%) | 119 (81.5%) | 77 (74.0%) | 44 (83.0%) | 54 (67.5%) | 22 (71.0%) |         |
| Female            | 132 (23.1%) | 34 (21.5%) | 27 (18.5%) | 27 (26.0%) | 9 (17.0%) | 26 (32.5%) | 9 (29.0%) |         |
| Age               | 61.7 (11.2) | 63.1 (9.4) | 61.0 (10.3) | 61.4 (12.2) | 60.9 (11.3) | 62.1 (13.9) | 58.7 (11.5) | .3322   |
| Highest grade     |           |         |         |         |         |         |         | .0014   |
| ≤High school      | 158 (27.6%) | 26 (16.5%) | 42 (28.8%) | 34 (32.7%) | 19 (35.8%) | 31 (38.8%) | 6 (19.4%) |         |
| >High school      | 412 (72.0%) | 131 (82.9%) | 104 (71.2%) | 70 (67.3%) | 33 (62.3%) | 49 (61.3%) | 25 (80.6%) |         |
| Decline           | 2 (0.3%) | 1 (0.6%) | 0 (0.0%) | 0 (0.0%) | 1 (1.9%) | 0 (0.0%) | 0 (0.0%) |         |
| Marital status    |           |         |         |         |         |         |         | .0010   |
| Not married       | 173 (30.2%) | 41 (25.9%) | 32 (21.9%) | 42 (40.4%) | 20 (37.7%) | 33 (41.2%) | 5 (16.1%) |         |
| Married           | 398 (69.6%) | 117 (74.1%) | 114 (78.1%) | 62 (59.6%) | 33 (62.3%) | 46 (57.5%) | 26 (83.9%) |         |
| Decline           | 1 (0.2%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (1.2%) |         |
| Race              |           |         |         |         |         |         |         | .0005   |
| White only        | 474 (82.9%) | 150 (94.9%) | 134 (91.8%) | 78 (75.0%) | 47 (88.7%) | 38 (47.5%) | 27 (87.1%) |         |
| African American only | 45 (7.9%) | 2 (1.3%) | 6 (4.1%) | 18 (17.3%) | 3 (5.7%) | 13 (16.2%) | 3 (9.7%) |         |
| Other             | 53 (9.3%) | 6 (3.8%) | 6 (4.1%) | 8 (7.7%) | 3 (5.7%) | 29 (36.2%) | 1 (3.2%) |         |
| Ethnicity         |           |         |         |         |         |         |         | <.0001  |
| Hispanic          | 29 (5.1%) | 2 (1.3%) | 1 (0.7%) | 6 (5.8%) | 5 (9.4%) | 15 (18.8%) | 0 (0.0%) |         |
| Non-Hispanic      | 543 (94.9%) | 156 (98.7%) | 145 (99.3%) | 98 (94.2%) | 48 (90.6%) | 65 (81.2%) | 31 (100.0%) |         |

Note: Table entries are n (%) except for age, which is average (SD).
Abbreviations: BWH, Brigham and Women’s Hospital; CMC, Atrium Health’s Carolinas Medical Center; NYU, New York University; UConn, University of Connecticut; UNC, University of North Carolina; UPENN, University of Pennsylvania.
2 | METHODS

2.1 | Patient cohort

The OraRad study, which has been described in detail elsewhere,\textsuperscript{10} enrolled HNC patients at six clinical centers: Brigham and Women's Hospital, University of Pennsylvania, Atrium Health's Carolinas Medical Center, University of Connecticut, New York University, and University of North Carolina with the Data and Coordinating Center at the University of Minnesota. IRB approval was obtained at all sites and participants were consented and enrolled before initiating curative-intent RT. Patients were eligible if age 18 or older; diagnosed with head and neck squamous cell carcinoma (SCC) or a salivary gland cancer (SGC), or with a non-SCC, non-

| Measure                  | All sites | BWH       | UPENN     | CMC       | UConn     | NYU       | UNC       | P-Value |
|--------------------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|---------|
| Tobacco use              |           |           |           |           |           |           |           |         |
| Never used               | 250 (43.7%) | 76 (48.1%) | 64 (43.8%) | 42 (40.4%) | 18 (34.0%) | 35 (43.8%) | 15 (48.4%) | .5470   |
| Ever used                | 322 (56.3%) | 82 (51.9%) | 82 (56.2%) | 62 (59.6%) | 35 (66.0%) | 45 (56.2%) | 16 (51.6%) |         |
| Alcohol use in past 12 months |           |           |           |           |           |           |           | .0031   |
| No/do not know/declined | 190 (33.2%) | 42 (26.2%) | 40 (27.4%) | 38 (36.5%) | 20 (37.7%) | 41 (51.2%) | 9 (29.0%)  |         |
| Yes                      | 382 (66.8%) | 116 (73.4%) | 106 (72.6%) | 66 (63.5%) | 33 (62.3%) | 39 (48.8%) | 22 (71.0%) |         |
| Drinks per week in past 12 months | 6.9 (10.4) | 6.1 (6.1) | 6.0 (6.5) | 10.3 (19.6) | 7.4 (9.1) | 4.6 (3.4) | 8.1 (10.6) | .0770   |
| Type of cancer           |           |           |           |           |           |           |           | .3293   |
| SCC                      | 469 (82.0%) | 132 (83.5%) | 120 (82.2%) | 88 (84.6%) | 44 (83.0%) | 58 (72.5%) | 27 (87.1%) |         |
| SGC                      | 66 (11.5%)  | 15 (9.5%)  | 19 (13.0%) | 10 (9.6%)  | 7 (13.2%)  | 11 (13.8%) | 4 (12.9%)  |         |
| Non-SCC/non-salivary     | 37 (6.5%)  | 11 (7.0%)  | 7 (4.8%)   | 6 (5.8%)   | 2 (3.8%)   | 11 (13.8%) | 0 (0.0%)   |         |
| Primary tumor site       |           |           |           |           |           |           |           | .0240   |
| Oropharynx               | 266 (46.5%) | 76 (48.1%) | 82 (56.2%) | 44 (42.3%) | 25 (47.2%) | 26 (32.5%) | 13 (41.9%) |         |
| Oral cavity              | 87 (15.2%)  | 26 (16.5%) | 12 (8.2%)  | 21 (20.2%) | 6 (11.3%)  | 19 (23.8%) | 3 (9.7%)   |         |
| Larynx/hypopharynx      | 40 (7.0%)   | 10 (6.3%)  | 6 (4.1%)   | 9 (8.7%)   | 8 (15.1%)  | 5 (6.2%)   | 2 (6.5%)   |         |
| Salivary gland           | 56 (9.8%)   | 12 (7.6%)  | 18 (12.3%) | 10 (9.6%)  | 6 (11.3%)  | 6 (7.5%)   | 4 (12.9%)  |         |
| Other                    | 89 (15.6%)  | 24 (15.2%) | 23 (15.8%) | 15 (14.4%) | 5 (9.4%)   | 19 (23.8%) | 3 (9.7%)   |         |
| Unknown                  | 34 (5.9%)   | 10 (6.3%)  | 5 (3.4%)   | 5 (4.8%)   | 3 (5.7%)   | 5 (6.2%)   | 6 (19.4%)  |         |
| Cancer classification    |           |           |           |           |           |           |           | .7570   |
| T                        |           |           |           |           |           |           |           |         |
| 1 or 2                   | 343 (60.0%) | 99 (62.7%) | 94 (64.4%) | 62 (59.6%) | 29 (54.7%) | 42 (52.5%) | 17 (54.8%) |         |
| 3 or 4                   | 178 (31.1%) | 45 (28.5%) | 46 (31.5%) | 34 (32.7%) | 21 (39.6%) | 25 (31.2%) | 7 (22.6%)  |         |
| M                        |           |           |           |           |           |           |           | .0005   |
| 0                        | 536 (93.7%) | 144 (91.1%) | 146 (100.0%) | 103 (99.0%) | 50 (94.3%) | 71 (88.8%) | 22 (71.0%) |         |
| 1                        | 10 (1.7%)   | 5 (3.2%)   | 0 (0.0%)   | 1 (1.0%)   | 2 (3.8%)   | 1 (1.2%)   | 1 (3.2%)   |         |
| X                        | 26 (4.5%)   | 9 (5.7%)   | 0 (0.0%)   | 0 (0.0%)   | 1 (1.9%)   | 8 (10.0%)  | 8 (25.8%)  |         |
| N                        |           |           |           |           |           |           |           | .4503   |
| 00                       | 137 (24.0%) | 32 (20.3%) | 33 (22.6%) | 24 (23.1%) | 17 (32.1%) | 23 (28.7%) | 8 (25.8%)  |         |
| 01/02/2a/2b/2c/03        | 427 (74.7%) | 123 (77.8%) | 112 (76.7%) | 80 (76.9%) | 36 (67.9%) | 53 (66.2%) | 23 (74.2%) |         |

Note: Table entries are n (%) or average (SD).
Abbreviations: BWH, Brigham and Women’s Hospital; CMC, Atrium Health’s Carolinas Medical Center; NYU, New York University; SCC, squamous cell carcinoma; SGC, salivary gland cancer; TNM, tumor, node, metastasis; UConn, University of Connecticut; UNC, University of North Carolina; UPENN, University of Pennsylvania.
SGC malignancy of the head and neck region; receiving curative-intent RT of at least 4500 cGy to the head and neck region; had at least 1 natural tooth remaining after any pre-RT dental extractions; and had no prior curative-intent RT to the head and neck region. The baseline visit was scheduled before RT, after the pre-RT dental evaluation and after any recommended dental treatment was completed (eg, extractions). Participants underwent a baseline dental examination completed by calibrated examiners, and panoramic radiographic evaluation. A total of 572 participants were enrolled between April 2014 and October 2018 and eligible for follow-up post-RT. The current manuscript focuses on epidemiologic factors associated with presentation of advanced cancer (primary outcome).

2.2 | Primary outcome

The primary outcome was presentation with advanced cancer (based on American Joint Committee on Cancer [AJCC] seventh edition TNM staging) at diagnosis. Participants were defined for this purpose to have advanced cancer based on presenting with larger tumor size (T3 or T4) or any nodal metastases (N1, N2, or N3), whereas patients presenting with smaller tumor sized (T1 or T2) and absence of nodal metastases (N0) were considered early-stage HNC.

### Table 3: Public assistance and insurance status

| Variable                  | All sites | BWH | UPENN | CMC | UConn | NYU | UNC | P-Value |
|---------------------------|-----------|-----|-------|-----|-------|-----|-----|---------|
| N                         | 572       | 158 | 146   | 104 | 53    | 80  | 31  |         |
| Public assistance         |           |     |       |     |       |     |     | .0005   |
| No                        | 521 (91.1%) | 155 (98.1%) | 138 (94.5%) | 90 (86.5%) | 42 (79.2%) | 66 (82.5%) | 30 (96.8%) |
| Yes                       | 49 (8.6%)  | 1 (0.6%)  | 8 (5.5%) | 14 (13.5%) | 11 (20.8%) | 14 (17.5%) | 1 (3.2%)  |
| Declined                  | 2 (0.3%)  | 2 (1.3%)  | 0 (0.0%) | 0 (0.0%)   | 0 (0.0%)   | 0 (0.0%)   | 0 (0.0%)  |
| Type of medical insurance |           |     |       |     |       |     |     | <.0001  |
| No insurance              |           |     |       |     |       |     |     |         |
| No                        | 552 (96.5%) | 158 (100.0%) | 145 (99.3%) | 97 (93.3%) | 53 (100.0%) | 72 (90.0%) | 27 (87.1%) |
| Yes                       | 20 (3.5%)  | 0 (0.0%)  | 1 (0.7%) | 7 (6.7%)   | 0 (0.0%)   | 8 (10.0%)  | 4 (12.9%)  |
| Private insurance:        |           |     |       |     |       |     |     | .0005   |
| No                        | 137 (24.0%) | 23 (14.6%) | 8 (5.5%) | 37 (35.6%) | 18 (34.0%) | 44 (55.0%) | 7 (22.6%)  |
| Yes                       | 435 (76.0%) | 135 (85.4%) | 138 (94.5%) | 67 (64.4%) | 35 (66.0%) | 36 (45.0%) | 24 (77.4%) |
| Medicare                  |           |     |       |     |       |     |     | .0092   |
| No                        | 428 (74.8%) | 123 (77.8%) | 119 (81.5%) | 66 (63.5%) | 43 (81.1%) | 53 (66.2%) | 24 (77.4%) |
| Yes                       | 144 (25.2%) | 35 (22.2%) | 27 (18.5%) | 38 (36.5%) | 10 (18.9%) | 27 (33.8%) | 7 (22.6%)  |
| Medicaid                  |           |     |       |     |       |     |     | <.0001  |
| No                        | 512 (89.5%) | 149 (94.3%) | 144 (98.6%) | 96 (92.3%) | 40 (75.5%) | 52 (65.0%) | 31 (100.0%) |
| Yes                       | 60 (10.5%)  | 9 (5.7%)  | 2 (1.4%) | 8 (7.7%)   | 13 (24.5%) | 28 (35.0%) | 0 (0.0%)   |
| Dental insurance          |           |     |       |     |       |     |     | <.0001  |
| No                        | 206 (36.0%) | 43 (27.2%) | 36 (24.7%) | 56 (53.8%) | 21 (39.6%) | 37 (46.2%) | 13 (41.9%) |
| Yes                       | 366 (64.0%) | 115 (72.8%) | 110 (75.3%) | 48 (46.2%) | 32 (60.4%) | 43 (53.8%) | 18 (58.1%) |

Note: Table entries are n (%).
Abbreviations: BWH, Brigham and Women’s Hospital; CMC, Atrium Health’s Carolinas Medical Center; NYU, New York University; UConn, University of Connecticut; UNC, University of North Carolina; UPENN, University of Pennsylvania.
TABLE 4  Associations of characteristics with presentation of advanced head and neck cancer (defined as TNM values of T3/T4 and N ≥ 1)

| Characteristic                        | T1/2 | T3/4 | P-Value | N0   | N ≥ 1 | P-Value |
|---------------------------------------|------|------|---------|------|-------|---------|
| N*                                    | 343  | 178  | .216    | 104  | 307   | .379    |
| Education                             |      |      |         |      |       |         |
| (≤ vs > high school)                  | 254  | 122  | .685%   | 104  | 307   | .719%   |
| Dental insurance                      | 221  | 111  | .649%   | 80   | 280   | .656%   |
| Routine dental care                   | 256  | 124  | .746%   | 97   | 312   | .731%   |
| Freq. of brushing (<1x/day vs >1x/day) | 256  | 119  | .516%   | 102  | 306   | .717%   |
| Freq. of flossing (<1x/day vs ≥1x/day) | 177  | 90   | .506%   | 73   | 218   | .511%   |
| Enrollment sites                      |      |      | .757    | .450 |       |         |
| Married (vs not)                      | 239  | 121  | .670%   | 88   | 306   | .717%   |
| Ethnicity                             | 12   | 12   | .29%    | 9    | 20    | .379    |
| Race                                  |      |      | .469    | .301 |       |         |
| White                                 | 290  | 143  | .845%   | 109  | 360   | .843%   |
| African American                      | 25   | 16   | .73%    | 14   | 28    | .666%   |
| Other                                 | 28   | 19   | .82%    | 14   | 39    | .911%   |
| Private insurance                     | 272  | 123  | .793%   | 99   | 331   | .775%   |
| Medicaid                              | 29   | 27   | .85%    | 15   | 44    | .103%   |
| Public assistance                     | 25   | 20   | .73%    | 14   | 34    | .800%   |
| Primary tumor site^a                   |      |      | .003    | <.0001|       |         |
| Oropharynx                            | 193  | 71   | .563%   | 22   | 242   | .567%   |
| Oral cavity                           | 55   | 30   | .160%   | 33   | 54    | .126%   |
| Larynx/hypopharynx                    | 19   | 20   | .55%    | 19   | 20    | .47%    |
| Salivary gland                        | 29   | 24   | .85%    | 32   | 23    | .54%    |
| Other                                 | 47   | 33   | .13%    | 31   | 54    | .126%   |
| Type of cancer^b                       |      |      | .053    | <.0001|       |         |
| SCC                                   | 290  | 136  | .845%   | 80   | 387   | .906%   |
| SGC                                   | 38   | 27   | .111%   | 47   | 18    | .42%    |
| Non-SCC/SGC                           | 15   | 15   | .44%    | 10   | 12    | .52%    |
| Age                                   | 61.2 | 61.2 | .600-62.4 | 61.5 | 61.6 | .600-62.7 |
| Whole mouth avg PD                    | 2.3  | 2.4  | .23.4-2.5 | 2.3  | 2.4  | .23.4-2.4 |
| Whole mouth avg CAL                   | 1.8  | 2.1  | .17-1.9 | .005 | 1.9  | .17-2.0 |
| % sites CAL >= 2 mm                   | 0.50 | 0.57 | .48-0.53 | 0.13 | 0.52 | .48-0.57 |
| % sites PD >= 4 mm                    | 0.10 | 0.13 | .09-0.12 | 0.16 | 0.11 | .08-0.13 |
| Number of teeth at baseline           | 23.6 | 21.8 | .23.0-24.2 | 22.6 | 23.0 | .22.5-23.6 |
| Tobacco use                           | 189  | 106  | .55%    | 80   | 241   | .56%    |
| Alcohol use                           | 228  | 124  | .66%    | 88   | 291   | .68%    |
| DMFS score                            | 46.9 | 48.7 | .43.8-50.1 | 47.5 | 48.4 | .45.6-51.3 |

Abbreviations: CAL, clinical attachment level; PD, probing depth; SCC, squamous cell carcinoma; SGC, salivary gland cancer; TNM, tumor, node, metastasis.

^aNote that the percentages reflect the frequency based on all patients in each T or N category.

^bT score and N score were available for 521 and 564 participants, respectively.
examination to establish dental disease characteristics included number of teeth; decayed, missing, and filled surfaces (DMFS); and clinical attachment loss (CAL) and probing depth (PD). The burden of dental disease was based on the dental findings, with fewer teeth serving as a surrogate measure of prior dental disease resulting in tooth loss, while PD and CAL are indicators of periodontal disease and DMFS is an indicator of dental caries. HPV status was assessed and confirmed via p16 immunohistochemistry or HPV in-situ hybridization for patients presenting with SCC originating in the oropharynx.

### 2.4 Statistical considerations

Differences between enrollment centers were tested using Fisher’s exact test for categorical characteristics (eg, education) and one-way ANOVA for characteristics measured on continuous scales (eg, periodontal disease measures). Associations of tumor size and nodal metastases, and HPV status (all binary characteristics) with categorical characteristics were tested using Fisher’s exact test, and associations with characteristics measured on continuous scales were tested using two-sample t-tests. We also performed multivariate logistic regression analysis separately for tumor size stage (T1/2 vs T3/4) and for nodal involvement (N0 vs any nodal involvement), with P-values from likelihood-ratio tests. Characteristics with P < .05 in the univariate analyses were included in the multivariate analyses. All analyses were performed using JMP (Pro version 14.0, SAS Institute Inc., Cary, North Carolina).

### 3 RESULTS

A total of 572 HNC patients were enrolled in this cohort, with 77% male and mean (SD) age 61.7 (11.2) years (Table 1). The most common race was white (83%), with the proportion of patients of Hispanic origin consistent with national surveillance data (5%). Tobacco use (current or past) was reported by 56% of participants, 67% reported alcohol use in the past 12 months (Table 2). SCC was the most common histology (n = 469, 82%) with the oropharynx the most common primary location (n = 266, 47%). Most participants (60%) were seen with smaller tumors, while the majority (75%) had nodal metastases (Table 2).

The range of maximum RT dose that was delivered to the primary tumor site ranged from 636 to 7802 cGy with mean 6573 cGy; 7 out of 572 (1.22%) participants had ≤4500 cGy. The study enrolled 314 (54.9%) patients who had surgical resection before RT.

| Outcome                  | Predictor           | Effect estimate (log odds ratio) | SE   | P-Value |
|--------------------------|---------------------|----------------------------------|------|---------|
| T1/2 vs T3/4             | Private insurance   | -0.27                            | 0.29 | .37     |
|                         | Medicaid            | 0.33                             | 0.38 | .38     |
|                         | Whole mouth avg. PD | 0.29                             | 0.20 | .15     |
|                         | Whole mouth avg. CAL| 0.02                             | 0.12 | .85     |
|                         | # of teeth at baseline| -0.045                          | 0.021| .029    |

N0 vs N1

| Predictor | Effect estimate (log odds ratio) | SE | P-Value |
|-----------|----------------------------------|----|---------|
| Primary tumor site | —a | —a | <.0001 |
| Type of cancer     | —a | —a | <.0001 |

The cross-tab of primary tumor site and type of cancer has many cells with small counts, in many of which either all or none of the participants have nodal involvement. Thus, some coefficients in this multivariate logistic regression are estimated to be plus or minus infinity. The likelihood-ratio tests are nonetheless feasible and give the P-values in the table.

Seventy-six percent of participants had private primary medical insurance, 25% had Medicare and 11% had Medicaid; some participants had more than one type of insurance. Most participants (n = 366, 64%) had dental insurance (Table 3).

Several factors were associated with tumor size and nodal involvement. A total of 272 of 343 (79%) participants presenting with smaller tumors had private medical insurance compared to 123 of 178 (69%) participants with larger tumors (P = .012), whereas patients with Medicaid coverage tended to present with larger tumors (P = .025). Participants presenting with larger tumors also tended to present with a higher burden of dental disease including fewer teeth at baseline and more advanced periodontal disease measures (Table 4).

Few characteristics were associated with nodal involvement. Participants with SCC were more likely to have nodal involvement than participants with SGC or other non-SCC/SGC. This was especially the case for participants with oropharyngeal SCC, with the highest rate within the cohort presenting with nodal involvement (92%), but more frequently were seen with smaller tumors (73%) (Table 4). Dental disease measures were not associated with nodal involvement.

For tumor size stage (T1/2 vs T3/4), five characteristics that had P < .05 in the univariate analysis were included in the multivariate analysis as predictors: private insurance, Medicaid, whole mouth average PD,
whole mouth average CAL, and the number of teeth at baseline. We did not include percent of sites with CAL ≥ 2 mm because of its extremely high correlation with whole mouth average CAL. After adjusting for other predictors, only the number of teeth at baseline was significantly associated with the tumor size stage (Table 5).

For the nodal involvement stage (N0 vs any other N), two characteristics with $P < .05$ in the univariate analysis were included in the multivariate analysis as predictors: primary tumor site and type of cancer. Both characteristics were significantly associated with nodal involvement stage after adjusting for each other ($P < .0001$ for both; Table 5).

Numerous epidemiologic factors differed in the HPV-positive vs HPV-negative oropharyngeal SCC groups (Table 6). In the HPV-positive group, a number of factors were more common including higher education level and higher likelihood of private medical and dental insurance, and lower likelihood of Medicaid insurance or receipt of public assistance. Participants in the HPV-positive group were also more likely to be white and married, to use tobacco less, and to use alcohol more frequently. The HPV-positive group had less dental disease burden with more teeth at baseline and fewer sites with CAL ≥ 2 mm.

### Table 6: Associations of HPV status with patient characteristics

|                           | HPV-positive oropharyngeal cancer | HPV-negative oropharyngeal and non-oropharyngeal cancer | $P$-Value |
|---------------------------|----------------------------------|--------------------------------------------------------|-----------|
| N*                        | 236                              | 323                                                    |           |
| Sex (male)                | 210 (89.0%)                      | 219 (67.8%)                                           | <.0001    |
| Education (>high school)  | 181 (77.4%)                      | 222 (68.7%)                                           | .0273     |
| Age                       | 62.6 (61.1-64.0)                 | 61.0 (59.8-62.2)                                      | .1113     |
| Ethnicity                 | 9 (3.8%)                         | 18 (5.6%)                                              | .4257     |
| Race                      |                                  |                                                       |           |
| White                     | 219 (92.8%)                      | 245 (75.9%)                                           | <.0001    |
| African American          | 7 (3.0%)                         | 35 (10.8%)                                            |           |
| Other                     | 10 (4.2%)                        | 43 (13.3%)                                            |           |
| Married (vs not)          | 185 (78.4%)                      | 204 (63.4%)                                           | .0001     |
| Tobacco use               | 119 (50.4%)                      | 192 (59.4%)                                           | .0386     |
| Alcohol use               | 176 (74.6%)                      | 198 (61.3%)                                           | .0010     |
| Private insurance         | 205 (86.9%)                      | 222 (68.7%)                                           | <.0001    |
| Medicaid                  | 11 (4.7%)                        | 46 (14.2%)                                            | .0002     |
| Public assistance         | 9 (3.8%)                         | 38 (11.8%)                                            | .0006     |
| Dental insurance          | 162 (68.6%)                      | 197 (61.0%)                                           | .0739     |
| Routine dental care       | 179 (75.9%)                      | 227 (70.3%)                                           | .1509     |
| Freq. of brushing ($\leq 1x/day$ vs $>1x/day$) | 167 (70.8%)            | 238 (73.7%)                                           | .4453     |
| Freq. of flossing ($<1x/day$ vs $\geq 1x/day$) | 120 (50.9%)              | 165 (51.1%)                                           | 1.0000    |
| Whole mouth avg PD        | 2.4 (2.3-2.4)                    | 2.3 (2.3-2.4)                                         | .3340     |
| Whole mouth avg CAL       | 1.8 (1.7-1.9)                    | 2.0 (1.9-2.1)                                         | .0735     |
| % sites CAL $\geq 2$ mm   | 0.50 (0.46-0.53)                 | 0.55 (0.52-0.58)                                      | .0232     |
| % sites PD $\geq 4$ mm    | 0.12 (0.10-0.13)                 | 0.10 (0.09-0.12)                                      | .3167     |
| N teeth at baseline       | 23.8 (23.1-24.5)                | 22.3 (21.7-23.0)                                      | .0032     |
| DMFS score                | 47.3 (43.5-51.1)                 | 48.1 (44.8-51.4)                                      | .7443     |
| Enrollment sites          |                                  |                                                       | .0020     |

Note: Table entries are n (%) or group averages (95% confidence intervals).

Abbreviations: CAL, clinical attachment loss; DMFS, decayed, missing, filled surfaces; HPV, human papilloma virus; N, number; PD, probing depth.

*Although 572 patients were included in this cohort, data regarding HPV assessment of oropharyngeal SCC vs all other HNC was available for 559 patients.
4 | DISCUSSION

Prior studies have found numerous factors associated with presenting with advanced HNC such as demographics (age, sex, and race), socioeconomic status, insurance status, marital status, tumor location, and access to care.3,5-8 In the present cohort, we identified three main factors: insurance status, type/location of cancer, and dental disease measures. Lebo et al. identified Medicaid insurance and lack of medical insurance as key predictors in severity of disease presentation in patients with laryngeal cancer.8 Lack of medical insurance is often considered a surrogate measure for lack of routine screening and, perhaps, poor health. The findings from OraRad support this, with lack of medical insurance associated with more advanced HNC.

Adrien and colleagues3 found a higher rate of T3/T4 presentation in the hypopharynx vs the oral cavity, suggesting that cancers at anatomical sites that are not easily observed may be seen with larger tumors. In the present cohort, a higher rate of advanced cancer presentation was associated with larynx/hypopharynx (51%) compared to oral cavity (35%) and oropharyngeal region (27%), which is consistent with prior findings. The lower rate of advanced cancer presentation with tumors located with the oropharyngeal region and the oral cavity may be due to HNC in this area being more clinically observable as compared to laryngeal/hypopharyngeal cancers.

Patients presenting with larger tumors had higher dental disease burden. The association of oral health with stage of cancer presentation has not been reported in prior studies, though poor oral health as a risk factor for presentation of any HNC has been evaluated. In a large case-control study of HNC patients from the International Head and Neck Cancer Epidemiology Consortium, daily tooth brushing, absence of gum disease, annual dental visits and missing fewer than five teeth were associated with lower risk of HNC.12 A smaller case-control study of HNC patients from Taiwan found lack of regular dental visits, brushing teeth <2 times a day, gum bleeding and loss of more than 20 teeth were associated with higher risk of HNC.13 A Brazilian case-control study of HNC identified less than daily tooth brushing and sores caused by dentures as risk factors for HNC.14 A Swedish case-control study of oral and oropharyngeal SSCs identified poor oral hygiene, more than 5 defective teeth, more than 20 missing teeth and defective or malfunctioning dentures as risk factors for HNC.15 We did find that measures of oral health (fewer teeth and periodontal disease) were associated with advanced HNC presentation. The findings suggest that poor oral health (fewer teeth and periodontal disease) may be associated with advanced cancer at presentation, so routine dental care and increased screening among people with poor oral health are recommended. Multivariate analysis of the present cohort identified that number of teeth at baseline was the key predictor of presentation with larger tumors (T3/T4) vs smaller tumors (T1/T2). We did not find significant associations with other factors previously found to be associated with more advanced HNC such as older age, male sex, African American race, and not being married.3,5-8 The lack of associations with these factors in the present study may be related to inherent differences in study populations sampled and differences in sample size with prior studies.

Patients with HPV-positive oropharyngeal cancers have been shown to have risk factors and presentation differing from non-HPV-related HNCs, including younger age, higher socioeconomic status, white race,16 less tobacco exposure,17 less alcohol use,18 with smaller primary tumors and more nodal involvement.19 We found similar associations in the present cohort with a similar demographic presentation and measures consistent with higher socioeconomic status including private medical insurance, dental insurance, less public assistance, and less Medicaid. The association of insurance status with cancer presentation in the present study may not generalize beyond the United States as many industrialized countries have more universal health care systems. Some key differences in the OraRad study from prior publications included more alcohol use in the HPV-positive oropharyngeal group and no age difference between patients with HPV-positive oropharyngeal cancer vs all other HNC. This may represent the aging cohort of HPV-related cancers compared to non-HPV-related HNC as OraRad is a more recent cohort of HNC, compared to prior publications finding that HPV-related cancers are represented by a younger age range.

The current study identified several factors associated with presentation of more advanced HNC such as insurance status, type/location of cancer, and dental disease measures. Recognition of these factors associated with presentation of more advanced cancers offers potentially modifiable factors and actions such as improving poor oral health, whereas other factors (such as socioeconomic status factors and lesion site) can be considered in the screening process of new lesions.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.
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