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Patterns of care and survival impact of adjuvant chemoradiotherapy for oropharyngeal cancer with intermediate-risk features

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Abstract

Background: Survival outcomes for adjuvant chemoradiotherapy (aCRT) and adjuvant radiotherapy (aRT) were compared in patients with oropharyngeal squamous cell carcinoma (OPSCC) with intermediate-risk features.

Methods: We identified 2164 patients with OPSCC in the National Cancer Database without positive margins or extracapsular extension and with at least one intermediate-risk feature: pT3-T4 disease, ≥two positive lymph nodes, level IV/V nodal disease, and/or lymphovascular invasion. We assessed predictors of aCRT use and covariables impacting overall survival.

Results: aCRT was commonly used for both human papillomavirus (HPV)-positive (62.0%) and HPV-negative (64.3%) patients with OPSCC. Higher N stage, level IV/V neck disease, and younger age strongly predicted aCRT utilization. There was no significant survival benefit associated with aCRT vs aRT in HPV-positive (hazard ratio [HR], 0.93; 95% confidence interval [CI], 0.62–1.38; $P = .71$) or HPV-negative (HR, 0.75; 95% CI, 0.51–1.10; $P = .15$) disease.

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Conclusions: Despite high rates of utilization, aCRT is not associated with better survival vs aRT for OPSCC with intermediate-risk features, including HPV-negative tumors.

Keywords

adjuvant chemoradiotherapy; human papillomavirus; National Cancer Database; oropharyngeal cancer; squamous cell carcinoma

1 | INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) accounts for approximately 4% of all cancers in the United States. The management of resectable disease often includes primary surgery with the addition of adjuvant radiotherapy (aRT) or adjuvant chemoradiotherapy (aCRT) in the presence of certain adverse pathological features. The utilization of aCRT has risen since the publication of two landmark studies, the European Organisation for Research and Treatment of Cancer (EORTC) 22931 and the Radiation Therapy Oncology Group (RTOG) 9501, which demonstrated improved disease-free survival with aCRT compared with aRT alone.[1,2] A pooled analysis indicated that the survival benefit was limited to patients with positive surgical margins (SM) or extracapsular extension (ECE).[3] Consequently, aCRT for intermediate-risk features (eg, advanced T classification and multiple positive lymph nodes) remains controversial. Current guidelines indicate that aCRT may be considered for such patients, with prior studies demonstrating substantial practice variation in aCRT use based on patient and clinical characteristics.[4,5] The oropharyngeal squamous cell carcinoma (OPSCC) subsite is among the strongest predictors of aCRT utilization.[5,6] However, the pooled analysis did not consider tumor sites separately. There is a paucity of data on the role of aCRT specifically in the intermediate-risk OPSCC population. We sought to evaluate the utilization and survival impact of aCRT compared to aRT in patients with OPSCC with intermediate-risk features using the National Cancer Database (NCDB).

2 | PATIENTS AND METHODS

2.1 | Data source

The NCDB is a joint program of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The NCDB is a nationwide, hospital-based registry with annual data collected from >1500 CoC-accredited facilities that represent >70% of newly diagnosed cancer cases in the United States.[7] Because the database uses publicly available information with no personal identifiers, full review by the University of California—Los Angeles Institutional Review Board was not required.

2.2 | Study population

We identified patients in the NCDB with OPSCC using histology codes and International Classification of Diseases for Oncology (3rd edition) topography codes, as previously described.[8] Analysis was limited to patients diagnosed from 2010 to 2014, as tumor human papillomavirus (HPV) data became available beginning in 2010. Patients were included if they (a) received treatment of surgery with aRT or surgery with aCRT, (b) did not have

the high-risk features of positive SM or ECE, and (c) had at least one of the following intermediate-risk pathological features: disease, pT3-T4 disease, ≥two positive lymph nodes, level IV or V nodal, and/or lymphovascular invasion (LVI). Patients were excluded if they had (a) treatment with palliative intent, (b) metastatic disease (M1 classification), (c) neoadjuvant chemotherapy, or (d) missing information for vital status, HPV status, SM, or ECE.

2.3 | Covariates

We assessed the following patient characteristics: age, sex, race, income, education, insurance, year of diagnosis, treatment facility type, and Charlson/Deyo comorbidity index. Median household income and percent of adults without a high school education by zip code of residence are estimated by the NCDB based on census data and categorized by quartile of the US population. The highest income and education quartiles were compared to all other quartiles. Primary health insurance coverage was grouped as Medicaid, Medicare, other (private care/managed care/governmental insurance), none, or unknown. Treatment variables included radiation dose, time from surgery to radiation, and treatment facility type. The time from surgery to radiation was modeled as a binary variable with a threshold of 42 days, the maximum duration for this interval as recommended by the National Comprehensive Cancer Network (NCCN).[4]

Treatment facility types were defined as academic, CoC-designated Comprehensive Community Cancer Program (CCCP), community, or other. Oncologic characteristics included primary tumor subsite (tonsil, base of tongue, soft palate/pharyngeal wall, and oropharynx not otherwise specified), HPV status, number of positive lymph nodes (≥two nodes vs <two nodes), level IV or V nodal disease, LVI, pathologic T classification, and pathologic N classification. We defined HPV-positive status as patients who tested positive for high-risk HPV, as determined by the collaborative stage site-specific factor 10 codes 20 to 60.

2.4 | Statistical analysis

The primary outcomes of interest were receipt of aCRT and overall survival (OS) after aCRT vs aRT. Chemotherapy was defined as single or multiagent chemotherapy during the first course of treatment and administered after surgery. All patients received aRT or aCRT after surgery. Patient OS was measured from the date of diagnosis to the date of death or last follow-up (through 2015). We assessed predictors of receiving aCRT using univariate and multivariable logistic regression including the aforementioned patient and oncologic characteristics. The impact of adjuvant therapy on OS was evaluated using Kaplan-Meier curves with comparisons using log-rank tests and multivariable Cox proportional hazard regression. Patients with HPV-positive and HPV-negative OPSCC were analyzed separately. Propensity score matching analysis was performed to control for potential differences in allocation of aCRT and aRT. Propensity scores for the likelihood of receiving aCRT were generated using all patient, tumor, and treatment characteristics. Patients receiving aRT were then matched with patients receiving aCRT using a caliper width of 0.001. Balance between the distribution of covariates within the two matched groups was confirmed by standardized differences, which were <0.2 for all covariates. The data analyses were performed using

Stata 14 (StataCorp, College Station, Texas). Statistical significance was set at $P < .05$, and all tests were two sided.

3 | RESULTS

The study cohort consisted of 2164 patients with OPSCC with intermediate-risk features. The majority of patients had HPV-positive tumors (72.7%, n = 1573). Among all patients, 1355 (62.6%) underwent aCRT and 809 (37.4%) underwent aRT. CRT utilization was similar among patients with HPV-positive disease (60.5%, n = 975) and HPV-negative disease (62.8%, n = 380). Further information on the distribution of patient and tumor characteristics by type of adjuvant therapy is presented in Table 1.

On multivariable logistic regression, the strongest predictors of having undergone aCRT were N2 to N3 disease (odds ratio [OR], 2.88; 95% confidence interval [CI] 1.68–4.94; $P < .001$), level IV or V nodal disease (OR, 2.02; 95% CI, 1.60–2.56; $P < .001$), radiation dose more than 66 Gy (OR, 2.45; 95% CI, 1.85–3.26; $P < .001$), and treatment at a CCCP (OR, 1.58; 95% CI, 1.23–2.02; $P < .001$; Table 2). Age ≥ 71 years (OR, 0.36; 95% CI, 0.23–0.56; $P < .001$), HPV-positive status (OR, 0.79; 95% CI, 0.63–0.99; $P = .04$), time from surgery to radiation >42 days (OR, 0.68; 95% CI, 0.55–0.82; $P < .001$), and diagnosis after 2013 (OR, 0.58; 95% CI, 0.45–0.76; $P < .001$) were associated with lower likelihood of having undergone aCRT.

The median patient follow-up was 48.6 months (interquartile range, 27.2–77.6 months), with a total of 275 deaths reported. On Kaplan-Meier analysis, the 3-year OS rates in HPV-positive OPSCC treated with aCRT or aRT were similar (92.5% vs 94.0%, respectively, $P = .88$, Figure 1). Likewise, in HPV-negative OPSCC, 3-year OS was comparable among treatment regimens (76.9% for aCRT vs 71.9% for aRT; $P = .37$). These patterns persisted in the multivariable Cox regression model, where the use of aCRT was not associated with improved survival in HPV-positive (hazard ratio [HR], 0.93; 95% CI, 0.62–1.38; $P = .71$) or HPV-negative (HR, 0.75; 95% CI, 0.51–1.10; $P = .15$) cancer (Table 3). Among other factors analyzed, advanced T classification and Charlson/Deyo score ≥1 were associated with worse survival in patients regardless of HPV status. Two or more positive nodes (HR, 2.59; 95% CI, 1.37–4.87; $P = .003$), time from surgery to radiation >42 days (HR, 1.89; 95% CI, 1.26–2.83; $P = .002$), and base of tongue (vs tonsil; HR, 1.78; 95% CI, 1.19–2.66; $P = .005$) or soft palate (vs tonsil; HR, 2.37; 95% CI, 1.17–4.78; $P = .02$) tumor subsites were associated with worse survival in patients with HPV-negative but not HPV-positive disease. Conversely, Medicaid (HR, 3.03; 95% CI, 1.86–4.92; $P < .001$) or Medicare (HR, 2.64; 95% CI, 1.37–5.09; $P = .004$) insurance, level IV or V nodes (HR, 1.64; 95% CI, 1.10–2.45; $P = .02$), and radiation doses higher (HR, 3.16; 95% CI, 1.96–5.13; $P < .001$) or lower (HR, 2.40; 95% CI, 1.47–3.90; P < .001) than 60 to 66 Gy were associated with worse survival in patients with HPV-positive but not HPV-negative disease. Highest education quartile was associated with improved survival (HR, 0.55; 95% CI, 0.33–0.91; $P = .02$) in the HPV-positive cohort only.

Propensity score matching identified a cohort of 1127 patients with HPV-positive OPSCC (529 receiving aCRT and 598 receiving aRT) and a cohort of 424 patients with HPV-negative OPSCC (213 receiving aCRT and 211 receiving aRT). For patients with HPV-

positive OPSCC, 3-year OS was 91.9% for aCRT and 94.0% for aRT ($P = .62$, Figure 2). In the HPV-negative cohort, 3-year OS was 73.7% for aCRT and 71.9% for aRT ($P = .84$). Multivariable analysis in the propensity matched subset revealed similar findings to the unmatched cohort, with receipt of aCRT associated with comparable survival to aRT in both HPV-positive (HR, 0.99; 95% CI, 0.64–1.56; $P = .98$) and HPV-negative (HR, 0.84; 95% CI, 0.55–1.29; $P = .42$) disease.

4 | DISCUSSION

We used a large national cancer registry to evaluate the patterns of use and survival impact of aCRT in patients with resected OPSCC without positive SM or ECE and with at least one of the following intermediate risk features: advanced pathological T classification, ≥two positive lymph nodes, level IV or V nodes, and/or LVI. aCRT was used for more than half of patients and was significantly associated with advanced N classification, HPV-negative disease, younger age, or diagnosis before 2013. We found no significant difference in OS with the use of aCRT vs aRT in either the HPV-positive group or HPV-negative group.

Current guidelines recommend the use of aCRT for resected, high-risk (positive SM and/or ECE) head and neck cancer, based largely on evidence from two landmark trials, RTOG 9501 and EORTC 22931.[1,2] In RTOG 9501, patients with ≥two positive lymph nodes, ECE, or positive SM were included.[1] In EORTC 22931, included patients had one of a wider range of risk factors (ECE, positive SM, stage III/IV disease, perineural invasion, LVI, or level IV or V nodes for an oral cavity or oropharyngeal primary).[2] Both studies showed improvement in locoregional control and disease-free survival with the addition of cisplatin to aRT and EORTC 22931 also demonstrated improved 5-year OS. Subsequent pooled analysis of these trials showed that the survival benefit of CRT was limited to those with positive SM or ECE.[3] Thus, the role of aCRT in patients with intermediate-risk disease has remained controversial. The generalizability of the trial results to all head and neck subsites also remains unclear. Oropharyngeal tumors, in particular, represented a minority of patients in both RTOG 9501 (42%) and EORTC 22931 (30%). Furthermore, RTOG 9501 had a statistically significant preponderance of patients with oropharynx cancer in the CRT arm. Neither trial-assessed HPV/p16 tumor status, a factor that would likely have a considerable impact on treatment responsiveness and oncologic outcomes. Thus, limitations of these trials ultimately leave practitioners without high-level evidence to reliably inform the selection of aCRT for patients with OPSCC with intermediate-risk features.

Although we did not demonstrate a significant survival difference between the two treatment groups, over half of patients in our study received aCRT. Selection of CRT appears to likely have been driven strongly by higher N stage classification, in accordance with prior research.[5,9] In fact, in another recent study, N2 classification was found to more strongly correlate with aCRT use than either ECE or positive margins, for which this treatment modality is considered the standard of care.[6] Younger age also strongly predicted prescription of aCRT. Current NCCN guidelines recommend consideration of aCRT in the case of intermediate-risk factors.[4] Our findings suggest that clinicians tend toward selecting more aggressive treatment for younger patients with concerning features like advanced nodal disease, despite the lack of proven survival benefit. Although the use of aCRT may have

been clinically appropriate and potentially beneficial in many of these patients, improved oncologic control must be balanced against the increased acute and long-term toxicities that may result from treatment intensification. The RTOG and EORTC trials demonstrated significantly increased incidence of severe acute toxicity from 34% in the RT group to 77% in the CRT group for the RTOG trial[1] and 21% to 42%, respectively, for the EORTC trial.[2] Receipt of concurrent CRT in both the definitive[10,11] and adjuvant[12] treatment settings has also been associated with increased risk of long-term swallowing dysfunction and gastrostomy tube dependence. In addition, treatment toxicities may necessitate breaks in the delivery of adjuvant therapy, with interruptions even as short as 1 week shown to have a significant negative impact on survival.[13,14] Consequences of intensified treatment in the form of increased toxic effects, noncancer death, or treatment delay may potentially outweigh any associated improvements in survival.

Our findings support prior studies that have called into question the benefit of aCRT for HPV-positive oropharynx cancer, including in the setting of ECE.[15–17] Skillington et al reviewed 195 patients with surgically managed, p16-positive OPSCC and demonstrated that aCRT compared to aRT was not associated with better disease-free survival (HR, 0.91; 95% CI, 0.59–1.42) or OS (HR, 1.46; 95% CI, 0.91–2.33).[15] Sinha et al analyzed 152 patients with HPV-positive OPSCC with nodal disease and found that aCRT did not improve disease-free survival in patients with ECE (HR, 0.25; 95% CI, 0.06–1.13).[16] An et al examined patients with HPV-positive oropharyngeal cancer with ECE in the NCDB and found no significant difference in the propensity-matched comparison of survival between the aCRT and aRT recipients (3-year OS, 89.3% vs 89.6%; $P = .44$).[17] The role of adjuvant therapy in HPV-positive OPSCC is the subject of several ongoing clinical trials.[18,19]

Few studies have compared adjuvant therapy modalities specifically in HPV-negative OPSCC. We extrapolate knowledge from analyses of other head and neck cancer sites, several of which have demonstrated a survival benefit of aCRT in select intermediate-risk groups. A recent NCDB study by Spiotto et al showed that aCRT compared to aRT was associated with better OS for patients with oral tongue cancer with ≥two positive nodes (HR 0.67; 95% CI, 0.52–0.87) or pT3–4 disease (HR 0.62; 95% CI, 0.39–0.98).[9] Trifiletti et al examined a multisubsite cohort (30% oropharynx) with negative SM and no ECE and found improved survival with aCRT (HR, 0.90; 95% CI, 0.86–0.94) that persisted when restricting their analysis to nonoropharyngeal primaries.[5] Chen et al demonstrated the benefit of aCRT compared to aRT (HR, 0.73; 95% CI, 0.58–0.93) in patients <70 years with intermediate-risk, T1–4 N2–3 head and neck cancer excluding HPV-positive OPSCC.[20] In contrast, Kirke et al, in examining patients with T4N0M0 multisite HNSCC, found similar survival among those receiving aCRT and aRT.[21] Their results highlight that the described benefit of aCRT for multisite, intermediate-risk HNSCC may only apply to carefully selected patient subgroups.

Our finding that OS is not significantly different between aCRT and aRT recipients with HPV-negative OPSCC with intermediate-risk features is novel and differs from what has been described in multisubsite HNSCC studies. There are a few possible explanations for this result. Our sample size was relatively smaller than in these other NCDB studies given limited availability of HPV data, potentially reducing our ability to detect small

survival differences. However, modest oncologic control benefits, even if present, may not outweigh the possible significant increases in treatment toxicity expected with the addition of chemotherapy. Second, the rate of aCRT use in our group of patients with HPV-negative cancer (61.0%) is considerably higher than rates described for oral cavity (43.1%), larynx (37.9%), and hypopharynx (51.0%) tumors in a similar database study.[5] More aggressive utilization of aCRT, perhaps motivated by historically high rates of locoregional recurrence in advanced oropharynx cancer, could diminish the relative benefit of aCRT.

We urge that our retrospective results should be interpreted with caution and viewed as hypothesis generating. The NCDB database is a valuable tool that facilitated our analysis of a large patient cohort; however, as with any large registry, the NCDB is subject to limitations including the potential for selection, information, and recall bias, as well as coding errors and missing information. Important cancer-specific outcomes such as locoregional recurrence and disease-specific survival are not collected by the NCDB. We also could not assess the impact of potential treatment-related toxicity, which is a critical consideration given the increased toxicity of aCRT compared to aRT. The NCDB does not record specific chemotherapy agents or dosing schedules. Although the randomized trials used 100 mg/m^2 bolus cisplatin every 3 weeks, patients in our cohort likely received various agents and dosages. Certain alternative regimens have been shown to be less efficacious than the high-dose cisplatin schedules used in the trials, and thus inclusion of patients receiving other regimens may have diminished any potential benefit of aCRT compared to aRT in our results. Finally, although our analysis adjusted for numerous clinical variables, there may be unmeasured biases that could confound our findings.

Clinical trials assessing aCRT for HNSCC are ongoing, many with a focus on HPV-positive OPSCC. One of the first of these trials, RTOG 1016, recently demonstrated inferior survival with the substitution of RT plus cetuximab for RT plus cisplatin for HPV-positive OPSCC.[22] In addition, we await the results of the ongoing study RTOG 0920, the largest prospective clinical trial assessing intermediate risk factors, which compares aRT to aRT plus cetuximab for patients who have undergone surgery for locally advanced head and neck cancer.[23]

5 | CONCLUSION

In conclusion, we report adjuvant treatment patterns and survival outcomes for 2164 patients with OPSCC with intermediate-risk features using a large national tumor registry. A majority of both patients with HPV-positive and HPV-negative OPSCC underwent aCRT. However, aCRT was not associated with a significant survival benefit compared to aRT, regardless of HPV status. Our findings emphasize the need for further research to characterize which patients are likely to benefit from aCRT, especially in the absence of positive SM or ECE.

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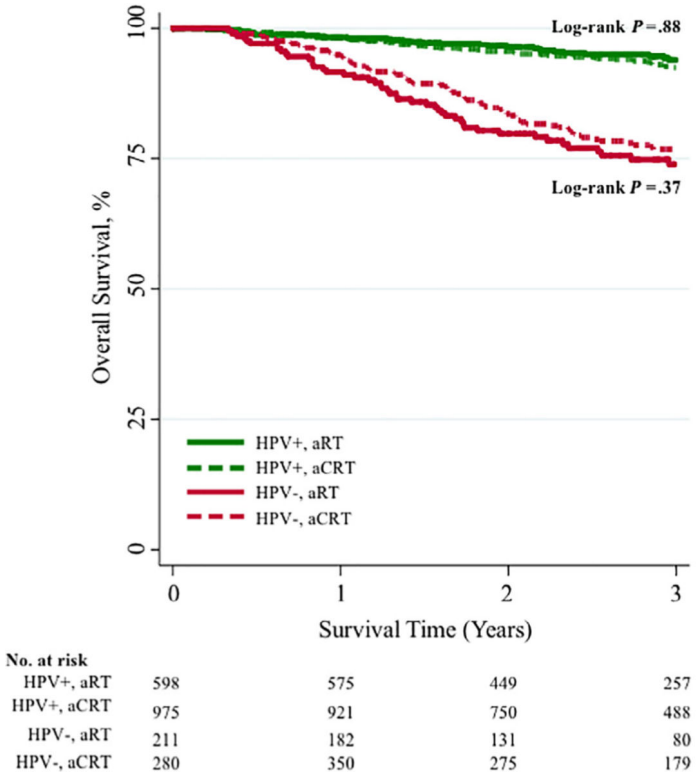

FIGURE 1.

Kaplan-Meier estimates of OS for patients with OPSCC with intermediate-risk features receiving aCRT vs aRT stratified by HPV status. aCRT, adjuvant chemoradiotherapy; aRT, adjuvant radiotherapy; HPV, human papillomavirus; OPSCC, oropharyngeal squamous cell carcinoma; OS, overall survival

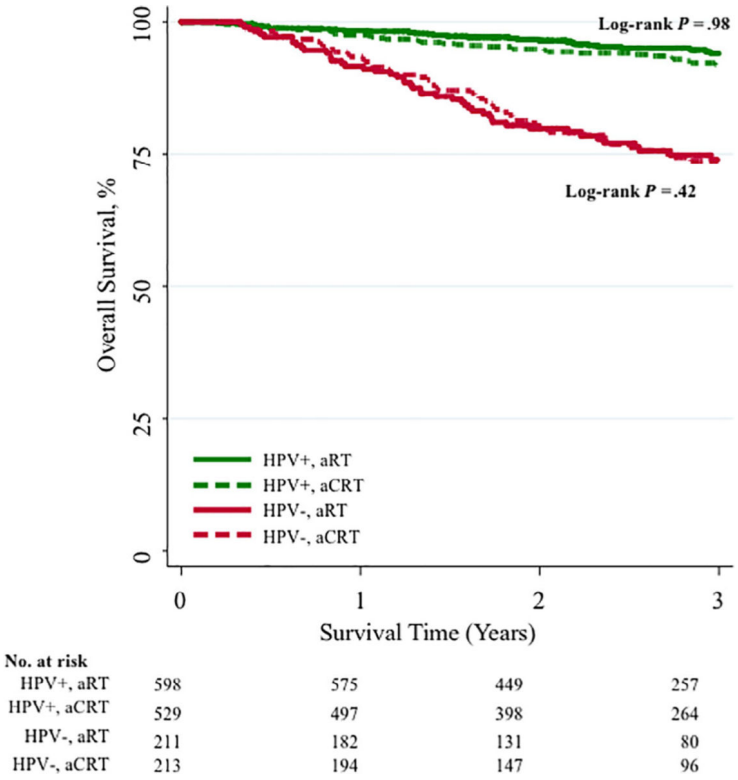

FIGURE 2.

Kaplan-Meier estimates of OS using propensity score matching of patients with OPSCC with intermediate-risk features receiving aCRT vs aRT stratified by HPV status. aCRT, adjuvant chemoradiotherapy; aRT, adjuvant radiotherapy; HPV, human papillomavirus; OPSCC, oropharyngeal squamous cell carcinoma; OS, overall survival

TABLE 1

Patient characteristics

Characteristic	Adjuvant RT (n = 809)	Adjuvant CRT (n = 1355)	*P* value
Sex			.65
Men	671 (82.9)	1134 (83.7)	
Women	138 (17.1)	221 (16.3)	
Age, y			<.001
≤50	159 (19.7)	330 (24.3)	
51–60	303 (37.4)	582 (43.0)	
61–70	254 (31.4)	361 (26.6)	
≥71	93 (11.5)	82 (6.1)	
Race			.44
White	748 (92.5)	1268 (93.6)	
Black	49 (6.0)	65 (4.8)	
Other	12(1.5)	22 (1.6)	
Education[a]			.82
Low	550 (68.0)	934 (68.9)	
Highest quartile	259 (32.0)	421 (31.1)	
Income[b]			.55
Low	474 (58.6)	823 (60.7)	
Highest quartile	335 (41.4)	532 (39.3)	
Insurance			.13
Medicaid	211 (26.1)	298 (22.0)	
Medicare	45 (5.6)	100 (7.4)	
Private/managed care/ other government	519 (64.2)	903 (66.6)	
None	25 (3.1)	43 (3.2)	
Unknown	9(1.1)	11 (0.8)	
Year of diagnosis			<.001
2010–2011	175 (21.6)	409 (30.2)	
2012–2013	372 (46.0)	591 (43.6)	
2014–2015	262 (32.4)	355 (26.2)	
Charlson/Deyo score			.10
0	648 (80.1)	1124(82.9)	
≥1	161 (19.9)	231 (17.1)	
Disease site			.003
Tonsil	475 (58.7)	902 (66.6)	
Base of tongue	265 (32.8)	354(26.1)	
Soft palate/pharyngeal wall	19 (2.3)	23 (1.7)	
Oropharynx, NOS	50 (6.2)	76 (5.6)	
HPV status			.32
Negative	211 (26.1)	380 (28.0)	
Positive	598 (73.9)	975 (72.0)	

Characteristic	Adjuvant RT (n = 809)	Adjuvant CRT (n = 1355)	*P* value
pT classification			.002
pT1–2	617 (76.3)	1034 (76.3)	
pT3–4	176 (21.8)	257 (19.0)	
Unknown	16 (2.0)	64 (4.7)	
pN classification			<.001
N0	69 (8.5)	37 (2.7)	
N1	91 (11.3)	81 (6.0)	
N2–3	612 (75.7)	1107 (81.7)	
Unknown	37 (4.6)	130 (9.6)	
≥Two positive nodes			<.001
No	230 (28.4)	280 (20.7)	
Yes	569 (70.3)	997 (73.6)	
Unknown	10 (1.2)	78 (5.8)	
Levels IV–V nodes			<.001
No	643 (79.5)	860 (63.5)	
Yes	134 (16.6)	428 (31.6)	
Unknown	32 (3.9)	67 (4.9)	
LVI			.05
No	417 (51.6)	645 (47.6)	
Yes	286 (35.4)	484 (35.7)	
Unknown	106 (13.1)	226 (16.7)	
Facility			<.001
Academic	581 (71.8)	839 (61.9)	
Comprehensive community	138 (17.1)	326(24.1)	
Community	29 (3.6)	61 (4.5)	
Other	61 (7.5)	129 (9.5)	
Radiation dose			<.001
≤59.99	176 (21.8)	287 (21.2)	
60.00–65.99	469 (58.0)	514 (37.9)	
66.00–69.99	91 (11.3)	281 (20.7)	
≥70.00	73 (9.0)	273 (20.2)	
Time from surgery to radiation >42 d	516(63.8)	722 (53.3)	<.001

Abbreviations: CRT, chemoradiotherapy; HPV, human papillomavirus; LVI, lymphovascular invasion; NOS, not otherwise specified; RT, radiation therapy.

[a]Education indicates the percent of people with no high school degree in the patient's zip code of residence.

[b]Income indicates the median household income in the patient's zip code of residence.

TABLE 2

Multivariable logistic regression for predictors of receipt of adjuvant CRT

Characteristic	OR (95% CI)	*P* value
Sex		
Men	1 (Reference)	…
Women	1.02 (0.78–1.32)	.88
Age, y		
≤50	1 (Reference)	…
51–60	0.93 (0.72–1.20)	.58
61–70	0.67 (0.50–0.91)	.01
≥71	0.36 (0.23–0.56)	<.001
Race		
White	1 (Reference)	…
Black	0.81 (0.53–1.25)	.34
Other	0.92 (0.42–1.98)	.83
Education[a]		
Low	1 (Reference)	…
Highest quartile	2.12 (0.03–146.01)	.73
Income[b]		
Low	1 (Reference)	…
Highest quartile	0.60 (0.03–11.99)	.74
Insurance		
Medicaid	1.26 (0.95–1.68)	.11
Medicare	1.38 (0.92–2.09)	.12
Private/managed care/other government	1 (Reference)	…
None	0.79 (0.46–1.38)	.41
Unknown	0.63 (0.23–1.69)	.36
Year of diagnosis		
2010–2011	1 (Reference)	…
2012–2013	0.68 (0.54–0.86)	.002
2014–2015	0.58 (0.45–0.76)	<.001
Charlson/Deyo score		
0	1 (Reference)	…
≥1	0.86 (0.67–1.10)	.22
Disease site		
Tonsil	1 (Reference)	…
Base of tongue	0.89 (0.72–1.11)	.32
Soft palate/pharyngeal wall	0.77 (0.38–1.54)	.46
Oropharynx, NOS	0.85 (0.56–1.29)	.44
HPV status		
Negative	1 (Reference)	…
Positive	0.79 (0.63–0.99)	.04

Characteristic	OR (95% CI)	*P* value
pT classification		
pT1–2	1 (Reference)	…
pT3–4	1.27 (0.97–1.66)	.08
Unknown	1.82 (0.89–3.69)	.10
pN classification		
N0	1 (Reference)	…
N1	1.37 (0.78–2.39)	.27
N2–3	2.88 (1.68–4.94)	<.001
Unknown	2.96 (1.55–5.63)	.001
≥Two positive nodes		
No	1 (Reference)	…
Yes	1.27 (0.93–1.74)	.13
Unknown	2.84 (1.38–5.84)	.005
Levels IV–V nodes		
No	1 (Reference)	…
Yes	2.02 (1.60–2.56)	<.001
Unknown	1.31 (0.82–2.08)	.26
LVI		
No	1 (Reference)	…
Yes	1.12 (0.90–1.39)	.31
Unknown	0.99 (0.74–1.33)	.97
Facility		
Academic	1 (Reference)	…
Comprehensive community	1.58 (1.23–2.02)	<.001
Community	1.30 (0.79–2.12)	.30
Other	1.35 (0.95–1.94)	.10
Radiation dose		
≤59.99	1.47 (1.15–1.87)	.002
60.00–65.99	1 (Reference)	…
66.00–69.99	2.45 (1.85–3.26)	<.001
≥70.00	2.34 (1.74–3.47)	<.001
Time from surgery to radiation	0.68 (0.55–0.82)	<.001
>42 d		

Abbreviations: CI, confidence interval; CRT, chemoradiotherapy; HPV, human papillomavirus; LVI, lymphovascular invasion; NOS, not otherwise specified; OR, odds ratio; RT, radiation therapy.

[a]Education indicates the percent of people with no high school degree in the patient's zip code of residence.

[b]Income indicates the median household income in the patient's zip code of residence.

TABLE 3

Multivariable Cox regression for overall survival stratified by HPV status

Characteristic	HPV-positive OR (95% CI)	*P* value	HPV-negative OR (95% CI)	*P* value
Sex				
Men	1 (Reference)	…	1 (Reference)	…
Women	0.83 (0.47–1.48)	.54	0.85 (0.57–1.27)	.43
Age, y				
≤50	1 (Reference)	…	1 (Reference)	…
51–60	1.55 (0.90–2.67)	.12	1.20 (0.71–2.02)	.49
61–70	0.97 (0.52–1.81)	.50	1.10 (0.60–2.02)	.75
≥71	1.12 (0.50–2.54)	.78	0.91 (0.42–1.97)	.82
Race				
White	1 (Reference)	…	1 (Reference)	…
Black	1.26 (0.53–3.00)	.60	0.86 (0.49–1.51)	.61
Other	2.17 (0.66–7.16)	.20	0.80 (0.19–3.39)	.77
Education[a]				
Low	1 (Reference)	…	1 (Reference)	…
Highest quartile	0.55 (0.33–0.91)	.02	1.35 (0.79–2.30)	.27
Income[b]				
Low	1 (Reference)	…	1 (Reference)	…
Highest quartile	1.35 (0.86–2.09)	.19	0.97 (0.60–1.55)	.89
Insurance				
Medicaid	3.03 (1.86–4.92)	<.001	1.48 (0.90–2.42)	.12
Medicare	2.64 (1.37–5.09)	.004	1.34 (0.77–2.32)	.30
Private/managed care/other government	1 (Reference)	…	1 (Reference)	…
None	0.38 (0.05–2.77)	.34	1.31 (0.46–3.76)	.62
Unknown	1.85 (0.25-13.91)	.55	*c*	*c*
Year of diagnosis				
2010–2011	1 (Reference)	…	1 (Reference)	…
2012–2013	1.36 (0.89–2.08)	.16	0.86 (0.58–1.27)	.44
2014–2015	1.06 (0.57–1.99)	.85	1.01 (0.60–1.68)	.98

Characteristic	HPV-positive OR (95% CI)	*P* value	HPV-negative OR (95% CI)	*P* value
Charlson/Deyo score				
0	1 (Reference)	…	1 (Reference)	…
≥1	1.58 (1.05–2.38)	.03	1.54 (1.03–2.31)	.03
Disease site				
Tonsil	1 (Reference)	…	1 (Reference)	…
Base of tongue	1.40 (0.92–2.13)	.12	1.78 (1.19–2.66)	.005
Soft palate/pharyngeal wall	1.50 (0.19–11.75)	.70	2.37 (1.17–4.78)	.02
Oropharynx, NOS	1.11 (0.47–2.61)	.81	0.99 (0.53–1.86)	.98
pT classification				
pT1–2	1 (Reference)	…	1 (Reference)	…
pT3–4	2.41 (1.62–3.60)	<.001	2.58 (1.73–3.85)	<.001
Unknown	0.45 (0.06–3.61)	.45	1.97 (0.69–5.66)	.21
pN classification				
N0	1 (Reference)	…	1 (Reference)	…
N1	0.91 (0.26–2.51)	.71	1.14 (0.53–2.46)	.73
N2–3	0.91 (0.33–2.48)	.85	0.64 (0.27–1.51)	.31
Unknown	0.80 (0.24–2.70)	.73	0.84 (0.32–2.16)	.71
≥Two positive nodes				
No	1 (Reference)	…	1 (Reference)	…
Yes	1.11 (0.61–2.03)	.73	2.59 (1.37–4.87)	.003
Unknown	0.52 (0.12–2.29)	.39	2.56 (0.82–8.02)	.11
Levels IV–V nodes				
No	1 (Reference)	…	1 (Reference)	…
Yes	1.64 (1.10–2.45)	.02	1.32 (0.94–2.14)	.096
Unknown	1.28 (0.51–3.24)	.60	1.10 (0.49–2.43)	.82
LVI				
No	1 (Reference)	…	1 (Reference)	…
Yes	1.36 (0.92–2.01)	.12	1.48 (1.00–2.17)	.05
Unknown	1.16 (0.66–2.03)	.60	0.78 (0.45–1.37)	.39
Facility				
Academic	1 (Reference)	…	1 (Reference)	…

Characteristic	HPV-positive OR (95% CI)	*P* value	HPV-negative OR (95% CI)	*P* value
Comprehensive community	1.18 (0.74–1.86)	.49	0.77 (0.50–1.19)	.24
Community	1.80 (0.81–4.00)	.15	0.77 (0.30–1.96)	.59
Other	0.94 (0.46–1.92)	.86	0.87 (0.45–1.68)	.67
Radiation dose				
≤59.99	2.40 (1.47–3.90)	<.001	1.10 (0.69–1.76)	.68
60.00–65.99	1 (Reference)	…	1 (Reference)	…
66.00–69.99	3.17 (1.96–5.13)	<.001	1.46 (0.92–2.31)	.11
≥70.00	1.62 (0.89–2.93)	.12	1.20 (0.71–2.05)	.49
Time from surgery to radiation >42 d	1.01 (0.69–1.48)	.95	1.89 (1.26–2.83)	.002
Treatment				
Adjuvant RT	1 (Reference)	…	1 (Reference)	…
Adjuvant CRT	0.93 (0.62–1.38)	.71	0.75 (0.51–1.11)	.15

Abbreviations: CI, confidence interval; CRT, chemoradiotherapy; HPV, human papillomavirus; LVI, lymphovascular invasion; NOS, not otherwise specified; OR, odds ratio; RT, radiation therapy.

[a]Education indicates the percent of people with no high school degree in the patient's zip code of residence.

[b]Income indicates the median household income in the patient's zip code of residence.

[c]Due to small number of patients, analysis was not performed on this group.