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Clinical Outcomes for Patients Presenting with N3 Head and Neck Squamous Cell Carcinoma: Analysis of the National Cancer Database

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Abstract

Background—There is a paucity of data regarding head and neck squamous cell carcinomas and N3 nodal disease (N3 HNSCC).

Methods—Retrospective analysis of N3 HNSCC identified in the National Cancer Database was performed.

Results—We identified 4,867 N3 HNSCC patients treated with primary surgery or CRT. Propensity-adjusted median survival was 54.2 and 44.8 months for surgery and CRT, respectively ($p = 0.06$). Oropharyngeal primary subsite demonstrated a survival advantage with surgery versus CRT with propensity-adjusted median survivals of 86.0 and 61.9 months, respectively ($p < 0.05$).

Conclusion—Management of N3 HNSCC relies largely on chemoradiotherapy. N3 patients with non-oropharynx primary tumors exhibit 5-year overall survival approaching 30% independent of initial treatment modality. Patients with oropharynx primaries exhibit improved outcomes with surgery largely influenced by the HPV-negative subset. These data represent the most comprehensive analysis of N3 HNSCC outcomes and serve as a foundation for future research and clinical management.

Keywords

Head and Neck Cancer; N3 nodal staging; Surgery; Radiation; National Cancer Database

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INTRODUCTION

The optimal treatment of patients with head and neck squamous cell carcinoma who present with N3 nodal disease (N3 HNSCC) is ill-defined and randomized trials designed to define standards of care for locally advanced HNSCC infrequently include this patient cohort^[1]. Given the lack of N3-specific data, patients are commonly treated according to recommendations for those with N2 disease. However, data suggests that N3 disease is associated with a worse outcome^[2–18]. Therefore, a better understanding of the prognostic implications of N3 nodal disease and clinical outcomes of differing management approaches in the context of the primary tumor site will enable more appropriate management of this uncommon disease presentation.

Treatment of N3 HNSCC is typically driven by disease characteristics and institutional patterns of care. Given the paucity of N3 HNSCC patients, individual series lack significant statistical power to perform meaningful regression analyses to determine factors associated with surgery and radiotherapeutic approaches. Published series are unable to account for confounders such as performance status, primary tumor site, and HPV status because of limited sample size. Therefore, survival outcomes may be significantly impacted by the various selection factors that guide patients to receive primary surgery versus chemoradiotherapy. Thus, larger data sets are valuable to better understand treatment effects in the context of patient and disease characteristics.

We previously reported our institutional experience regarding clinical outcomes of N3 HNSCC [under review]. Similar to other series, we demonstrated 5-year rates of locoregional and distant control of approximately 75% and 60% at 5 years, respectively^[3, 9, 11, 12, 17, 19]. Further, we demonstrated an improvement in locoregional control with surgery and a trend toward improved survival in patients with p16-positive oropharyngeal primary tumors.

Here, we sought to determine factors associated with patterns of care and report on clinical outcomes using the NCDB. Specifically, we report on survival data of patients undergoing either definitive surgery or chemoradiotherapy approaches in the context of differing primary tumor sites.

MATERIAL AND METHODS

Study design and patient cohort

We performed a retrospective, observational, cohort study using the National Cancer Database (NCDB)^[20]. We identified 5,675 patients with squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, and larynx treated with curative intent between 2004–2012 with either clinical or pathological N3 nodal disease defined by any node measuring greater than 6 cm in greatest dimension per the American Joint Commission on Cancer Staging, 7th edition. Patients were excluded for incompletely staged or metastatic disease. Overall survival is the only available outcomes data.

The NCDB records all first course treatments defined as therapy administered before disease progression or recurrence^[20]. Treatment groups were designated as surgery or chemoradiotherapy (CRT). The surgery group included patients undergoing resection of the primary site. Of the 1,464 surgical patients treated with primary surgery, 78.4% underwent planned neck dissection. Eleven and 89% of patient received neoadjuvant or adjuvant therapy, respectively, consisting of chemotherapy, radiotherapy, or CRT. The CRT group was defined as patients receiving external beam (photon or proton) radiotherapy with chemotherapy, either concurrently or sequentially, and not undergoing resection of the primary tumor. Neck dissection was performed in 21% of CRT patients. Patient receiving surgery alone, radiotherapy alone, or CRT with a dose less than 50 Gy or above 99 Gy were excluded as they were assumed to represent palliative therapy or erroneous cataloguing of the actual treatment dose, respectively. Patients receiving brachytherapy, radioisotopes, or with missing information with regard to definitive treatment type were excluded.

The final cohort consisted of 1,464 patients receiving surgery and 3,403 patients treated with CRT, and 808 patients that underwent treatment not characterized as described.

Independent variables

Patient characteristics included age, gender, and Charlson/Deyo comorbidity score. Patient demographics included race, insurance status, income, and location. Treatment facilities were divided into location and facility volume. Facility volume was divided into high and non-high with high representing those facilities in the top quartile of cases performed. Tumor characteristics included subsite, tumor size, and T-stage.

Statistical analysis

The primary outcome was overall survival defined as the date of diagnosis to date of death or last known follow-up. All baseline demographics and patient characteristics were analyzed by Pearson chi-square tests except for age, radiation dose, and tumor size, which were considered continuous variables and therefore analyzed with Wilcoxon signed-rank test. Multivariate logistic regression was applied to patient and tumor characteristics to further examine factors associated with receipt of treatment.

Propensity score-weighted Kaplan-Meier estimators and Cox proportional hazards models were used to compare overall survival. We estimated the probability of receiving CRT for each patient according to relevant observed covariates using multivariable logistic regression. Covariates were chosen by stepwise selection in the logistic model. We evaluated the distribution of propensity scores for each treatment group and confirmed sufficient overlap in the distributions. We then grouped patients into quintiles according to their estimated propensity scores and used the Cochran-Mantel-Haenszel test and linear regression to verify that measured covariates were balanced across all strata. Our Kaplan-Meier estimators incorporated inverse probability of treatment weights (IPTW) based on the propensity score to account for confounding due to measured covariates. We also undertook multivariate analysis using Cox proportional hazards models to determine those associated with overall survival. Factors found to be significant in univariate analysis were included and further chosen by stepwise selection. A second Cox proportional hazards model that

included IPTW was further performed within the oropharyngeal group, which was used as baseline HR for later sensitivity analysis.

We conducted a sensitivity analysis within the oropharyngeal group to assess the potential effects of an unknown or unmeasured confounder on hazard ratio (HR) estimates of the association between treatment and survival. Baseline HR for this analysis was from the IPTW Cox model. We recalculated HRs and 95% confidence intervals (CIs) for the association of treatment with overall survival under hypothesized conditions, varying both the prevalence of the unmeasured confounder as well as the relative hazard of death associated with the confounder.

Propensity score analyses and survival analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC). Sensitivity analyses were performed using R 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria). All p-values were two-sided, and a p = 0.05 was considered statistically significant.

RESULTS

Patient characteristics

Baseline demographics and patient characteristics are listed in Table 1. Factors associated with non-surgical management from binary logistic regression are shown in Table 2. Patients and treatment characteristics associated with CRT included increasing age, non-private/unknown insurance, oropharynx and hypopharynx primary site, increasing tumor size, and greater than stage T1. Factors that were more likely to predict for a non-CRT approach included high volume centers, stage T1, and treatment between years 2010–2012 compared to treatment in 2004–2006.

Outcomes analysis

Median follow-up time is 27 months for all patients and 32 months and 25 months for surgery and CRT, respectively. Unadjusted median survival (MS) for all patients receiving surgery was 72.2 months and 36.7 months for CRT. Adjusted Kaplan-Meier curves for all patients utilizing IPTW revealed no difference in overall survival between the surgery and CRT groups (p = 0.06) (Figure 1). Propensity score-adjusted MS for surgery and CRT were 54.7 months and 45.7 months, respectively. On subset analysis of primary tumor site, oropharynx gained a significant benefit in overall survival with surgery (MS surgery: 86.0 months; 95% CI 73.7–117.2, MS CRT: 61.9 months; 95% CI 52.0–75.1; p < 0.05) while oral cavity, hypopharynx, and larynx did not. Subgroup analysis of oropharyngeal primary tumors revealed a trend in improved survival with surgery compared to CRT for the HPV-negative cohort (p = 0.06) whereas there was no difference between surgery and CRT for HPV-positive tumors (p = 0.38) (Figure 2A–F).

Multivariate analysis using Cox proportional hazard model to evaluate disease and patient characteristics associated with survival demonstrated that increasing age, non-white race, non-private/unknown insurance, increasing tumor size, and T4 stage were associated with decreased overall survival. Conversely, oropharyngeal primary and increasing radiation dose were associated with improved overall survival (Table 3).

Similarly, we performed subset analysis for the oropharynx group given its impact on survival and prevalence in the data set. On multivariate analysis that only included patients with known HPV status age, non-white race, non-private/unknown insurance and T4 stage were associated with worse overall survival while treatment year 2010–2012, academic facility, and HPV-positive disease was associated with improved overall survival (Table 4).

The NCDB does not record whether or not the N3 lymph node is resectable. For patients with N3 HNSCC, the prevalence of unresectable nodal disease has been reported to be ~ 20%–30% and impacts both disease free and overall survival outcomes^[17]. Therefore, a sensitivity analysis utilizing assumed prevalence and hazard ratios was performed to assess the impact of the unmeasured nodal confounder (UC) on overall survival. Sensitivity analysis within the oropharyngeal groups demonstrate that the significant survival advantage associated with surgery was lost at an UC prevalence of 30% in the CRT group with an assumed hazard ratio of 1.5 (Table 5).

DISCUSSION

There is limited randomized data to guide management of patients with N3 HNSCC given their infrequent inclusion in prospective clinical trials. Therefore, small institutional series have been the mainstay in describing treatment patterns and clinical outcomes^[3, 9, 11, 12, 17, 19]. Though informative, such small series lack sufficient power to fully describe disease characteristics and treatment outcomes. Therefore, we utilized the NCDB to evaluate this patient cohort in order to provide additional information to help direct treatment recommendations.

We hypothesized that the trend in management of N3 HNSCC over the past decade would favor a non-surgical approach based on the increased use of CRT for other head and neck sites with bulky invasive disease such as clinical T4a larynx primaries^[21] and the favorable outcomes of patients with HPV-positive oropharyngeal primary tumors treated with CRT^[22]. Although 70% of patient received CRT, treatment in more recent years was unexpectedly associated with decreasing odds of receiving CRT. A similar reduction in the odds of receiving CRT was noted for clinical T1 tumors that were HPV positive. Given that only approximately 20–30% of N3 HNSCC patients have unresectable nodal disease^[17], it is likely that treatment decisions are often based on resectability of the primary tumor not the nodal disease which in the case of HPV positive oropharyngeal tumors, would be feasible given their typically low T-stage^[8]. This paradigm likely holds true for oral cavity tumors, which were more likely to receive surgery in this analysis.

Patients treated at high volume centers were more likely to undergo surgery. The reason for this is unclear. Unlike clinical T4a laryngeal cancer that is more often treated with surgery at high volume centers compared to lower volume centers as is recommended by randomized data^[21, 23], the use of surgery in N3 disease likely represents a comfort level for surgeons performing major oncologic surgery rather than high level evidence. In this setting, approximately 25% of patients received care at high volume centers. Despite previous studies that demonstrated better outcomes for patients treated at high volume centers^[24],

here, treatment at a high-volume center did not maintain significance in multivariate analysis regarding overall survival.

Individual series of patients with N3 HNSCC have reported similar rates of locoregional and distant control approximating 70% and 60%, respectively^[3, 9, 11, 12, 17]. The impact of surgery and CRT on clinical outcomes has been reported. In the largest study including 100 patients, surgery resulted in a 5-year OS of 68% compared to just 32% for CRT ($p = 0.047$)^[17]. This considerable difference in outcome however does not control for various prognostic factors. Indeed, 76% of patients in the surgery group were T0, T1, or T2 staged tumors while radiotherapy was used for only 46% of similarly staged tumors.

Patient selection bias can have a very powerful impact on comparative clinical results. Although certain factors are considered objective and readily measureable (i.e., tumor size), some are clearly less objective with high inter-observer variability (i.e., tumor resectability). Indeed, many criteria that may have association with outcome are frequently not captured in clinical reports (i.e., weight loss or performance status decline in the months preceding cancer treatment) and may be particularly significant for HNSCC patients. These issues underscore the tremendous caution warranted in making comparisons of outcome for non-randomized patient cohorts who are selected to undergo distinct treatment approaches. Similar precaution is warranted for comparison of treatment outcomes across different time periods. For example, some have postulated that the introduction of intensity modulated radiation therapy (IMRT) is responsible for increasing tumor control rates in HNSCC, whereas detailed analyses controlling for the different eras of treatment delivery suggest that factors beyond IMRT likely explain this outcome improvement^[25]. Sensitivity analyses that explore the impact of various confounders can be valuable to illuminate these potential sources of bias as described further below. However, there is no substitute for randomized clinical trial comparisons and the low incidence of N3 nodal disease suggests we are unlikely to mount comparative trials for this patient cohort.

In this report, we analyzed 4,867 patients with N3 HNSCC undergoing either surgery or CRT. For all patients, there was no significant difference in overall survival for patients undergoing surgery, compared to those receiving CRT. There was an improvement in survival for patients with oropharyngeal primaries undergoing surgery but not for oral cavity, hypopharyngeal, or laryngeal primaries. The benefit of surgery in the oropharynx group was highly influenced by patients with HPV-negative disease. The difference in outcomes between surgery and CRT for HPV-negative tumors is unclear. One possibility is that the difference stems from persistent, non-surgically salvageable, disease in the CRT group given the rapid separation in the survival curves. Another possibility is the presence of unresectable nodal disease. In a previous series, all patients with unresectable disease (20% of the patient cohort) underwent radiotherapy, and if excluded from the radiotherapy group, the significant association between treatment modalities was lost ($p=0.07$)^[17]. To evaluate the impact of this unknown confounder on the outcomes of patients with oropharyngeal cancer, we performed a sensitivity analysis assuming that unresectable nodal disease was the major confounder and that its prevalence resulted in worse outcomes in the group undergoing CRT. Prevalence was assigned at 0% for the surgical group and 10% to 40% for the CRT given reported data^[17]. Hazard ratio assumptions were kept below 1.5 to prevent

over-estimating the impact of this finding. The results of the sensitivity analysis suggest that the significance associated with surgery could be affected by such a confounder. For example, if the presence of unresectable nodal disease was present in 30% of patients and conferred a hazard of 1.5, the significance of surgery is lost. Other confounders that may affect the results include the lack of granularity in the Charlson/Deyo score, which for example a non-surgical candidate with congestive heart failure, prior myocardial infarction, and a severe liver disease would be scored as 2 while a surgical candidate with hypertension, diabetes, and rheumatoid arthritis would also be scored as 2. Finally, unaccounted for in this analysis is the possibility of patients receiving surgery but did not undergo recommended adjuvant therapy given peri-operative morbidity, mortality, or patient refusal as we only included patients that went on to receive definitive treatment consistent with surgery with adjuvant therapy or primary chemoradiotherapy. Limitations of this analysis are inherent to the nature of the data available in the NCDB. The major limitation is the lack of outcomes data. Despite recording overall survival, NCDB does not include disease-free and cancer-free survival and does not include data regarding local, regional, or distant disease control. Follow-up patterns and outcome of salvage operations are not recorded in NCDB. Finally, patient performance status is not recorded. These factors, and our inability to assess many other features that may have prompted the selection of patients for surgery versus CRT, underscore the limitations of making comparisons between distinct treatment approaches from retrospective datasets such as the NCDB.

Patients with N3 HNSCC uncommonly accrue to clinical trials meant to establish therapeutic standards of care. Thus, retrospective analyses are often valuable to provide additional perspective regarding the natural history of the disease and outcomes of different therapy approaches. However, in the absence of randomized controlled trials, the inherent selection bias that allocates patients to receive surgery or chemoradiotherapy as initial therapy will undoubtedly confound direct comparison of these treatment approaches on ultimate outcome.

In an attempt to diminish confounders, we utilized the NCDB to analyze a large number of patients with N3 HNSCC. Here we demonstrate that overall survival for patients treated with either primary surgery or CRT achieve similar 5-year survival rates of 30–50% depending on the primary tumor site. Consistent with the literature, patients with oropharyngeal HPV-positive tumors fare considerably better than HPV-negative N3 HNSCC patients. Acknowledging the limitations described above, patients with HPV-negative oropharyngeal tumors appear to fare better with the inclusion of surgery in this review. The reason for this benefit is not clear and deserves further examination. In conclusion, we demonstrate similar survival outcomes for patients with N3 HNSCC using either surgery or CRT as the initial treatment approach. These data provide support to practitioners to select surgery or CRT based on clinical practice expertise and individual patient desires.

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Figure 1. Adjusted Kaplan-Meier curves with inverse probability of treatment weighting for all patients. Median survival for surgery and CRT groups was 54.2 and 44.8 months, respectively ($p = 0.06$).

Figure 2.

Adjusted Kaplan-Meier curves with inverse probability of treatment weighting for individual head and neck subsites. Median survival for (A) oral cavity (surgery 20.9 months and CRT 23.59 months, $p = 0.35$), (B) oropharynx (surgery 86.0 months and CRT 61.9 months, $p < 0.05$), (C) hypopharynx (surgery 26.9 months and CRT 21.8 months, $p = 0.55$), (D) larynx (surgery 20.2 months and CRT 23.8 months, $p = 0.75$), 3-year overall survival for (E) HPV-negative oropharynx (surgery 80% and CRT 46%, $p = 0.06$) and (F) HPV-positive oropharynx (surgery 82% and CRT 81%, $p = 0.38$).

Table 1

Baseline Demographics and Patient Characteristics

	All patients	Surgery with Adjuvant Therapy	Chemoradiotherapy	p-value Before adjustment	After propensity adjustment
Total patients	4,867	1,464	3,403		
Age, years					
Median (range)	57 (21–90)	55 (21–90)	57 (21–90)	<0.001	0.74
Mean (Std. Dev.)	57.3 (9.6)	55.9 (9.6)	57.9 (9.5)		
Sex					
Male	4,180 (85.9)	1,275 (87.1)	2,905 (85.4)	0.11	
Female	687 (14.1)	189 (12.9)	498 (14.6)		
Race					
White	3,903 (80.2)	1,225 (83.7)	2,678 (78.7)		NA
Black	817 (16.8)	185 (12.6)	632 (18.6)	<0.001	
Other	147 (3.0)	54 (3.7)	93 (2.7)		
Charlson/Deyo comorbidity score					
0	4,041 (83.0)	1,206 (82.4)	2,835 (83.3)		
1	653 (13.4)	209 (14.3)	444 (13.0)	0.47	
2	173 (3.6)	49 (3.3)	124 (3.6)		
Insurance type					
No insurance	554 (11.4)	146 (10.0)	408 (12.0)		
Private	2,043 (42.0)	732 (50.0)	1,311 (38.5)		
Medicaid	891 (18.3)	215 (14.7)	676 (19.9)		0.13
Medicare	1,156 (23.8)	308 (21.0)	848 (24.9)	<0.001	
Other government.	132 (2.7)	33 (2.3)	99 (2.9)		
Unknown	91 (1.9)	30 (2.0)	61 (1.8)		
Income					
<\$48,000	2,455 (50.4)	693 (47.3)	1,762 (51.8)		
\$48,000	2,333 (47.9)	752 (51.4)	1,581 (46.5)	<0.01	0.61
Unknown	79 (1.6)	19 (1.3)	60 (1.8)		
Location					
Urban (< 250,000)	3,367 (69.2)	1,004 (68.6)	2,363 (69.4)	0.83	

	All patients	Surgery with Adjuvant Therapy	Chemoradiotherapy	p-value Before adjustment	After propensity adjustment
Non-urban (<250,000)	1,345 (27.6)	413 (28.2)	932 (27.4)		
Unknown	155 (3.2)	47 (3.2)	108 (3.2)		
Facility					
Non-academic	2,258 (47.5)	658 (46.6)	1,600 (47.8)		
Academic	2,498 (52.5)	754 (53.4)	1,744 (52.2)	0.23	
Unknown	111 (2.3)	52 (3.6)	59 (1.7)		
Facility volume					
Non-high volume center	3,601 (74.0)	1,027 (70.2)	2,574 (75.6)	<0.001	0.65
High volume center (26+)	1,266 (26.0)	437 (29.8)	829 (24.4)		
Head and neck subsite					
Oral cavity	425 (8.7)	191 (13.0)	234 (6.9)		
Oropharynx	3,275 (67.3)	995 (68.0)	2,280 (67.0)		
Hypopharynx	538 (11.1)	115 (7.9)	423 (12.4)	<0.001	0.99
Larynx	629 (12.9)	163 (11.1)	466 (13.7)		
HPV status					
Negative	325 (6.7)	110 (7.5)	215 (6.3)		
Positive	515 (10.6)	199 (13.6)	316 (9.3)	0.16	
Unknown	4,027 (82.7)	1,155 (78.9)	2,872 (84.4)		
Radiation dose (cGy)					
Median	7000	6600	7000	<0.001	NA
Tumor size (mm)					
Median (range)	33 (178)	30 (155)	36 (178)		
Mean (Std. Dev.)	37.86 (22.55)	33.56 (21.78)	40.45 (22.62)	<0.001	0.96

Table 2

Predictors of primary chemoradiotherapy management of N3 HNSCC.

	Odds Ratio	(95% CI)	p-value
Age, years (continuous)	1.02	(1.01–1.03)	<0.001
Year			
2004–2006	1.00	(0.98–1.25)	0.12
2007–2009	1.11	(0.73–0.94)	<0.01
2010–2012	0.83		
Insurance type			
Private	1.00		
Non-private/Unknown	1.14	(1.04–1.24)	<0.01
Facility volume			
Non-high	1.00		
High	0.80	(0.72–0.88)	<0.001
Head and neck subsite			
Oral cavity	1.00	(1.16–1.56)	<0.001
Oropharynx	1.35	(1.16–1.85)	<0.01
Hypopharynx	1.47	(0.84–1.32)	0.70
Larynx	1.05		
Tumor size (cm) (continuous)	1.06	(1.01–1.11)	<0.05
T stage			
0	1.00		
1	0.79	(0.65–0.95)	<0.05
2	1.65	(1.41–1.93)	<0.001
3	1.95	(1.63–2.33)	<0.001
4	2.32	(1.91–2.81)	<0.001

Table 3

Univariate and multivariate analysis for all patients using Cox proportional hazards model.

	Univariate Analysis			Multivariate Analysis		
	HR	(95% CI)	p-value	HR	(95% CI)	p-value
Age, years (continuous)	1.02	1.02–1.03	<0.001	1.02	1.01–1.02	<0.001
Sex						
Male	1.00					
Female	1.13	1.01–1.26	0.034			
Race						
White	1.00			1.00		
Non-white	1.57	1.43–1.73	<0.001	1.42	1.24–1.61	<0.001
Year						
2004–2006	1.00					
2007–2009	1.02	0.92–1.12	0.761			
2010–2012	0.88	0.79–0.98	0.021			
Charlson/Deyo score						
0	1.00			1.00		
1	1.23	1.10–1.39	<0.001	1.14	0.98–1.33	0.094
2	1.43	1.17–1.75	<0.001	1.26	0.98–1.62	0.067
Insurance type						
Private	1.00			1.00		
Non-private/Unknown	2.05	1.88–2.24	<0.001	1.57	1.39–1.78	<0.001
Income						
<\$48,000	1.00					
\$48,000	0.79	0.73–0.86	<0.001			
Location						
Urban (>250,000)	1.00					
Non-urban (<250,000)	0.99	0.91–1.09	0.902			
Facility						
Non-academic	1.00					
Academic	0.91	0.84–0.99	0.031			
Facility volume						

	Univariate Analysis			Multivariate Analysis		
	HR	(95% CI)	p-value	HR	(95% CI)	p-value
Non-high	1.00					
High	0.89	0.81–0.98	0.021			
Head and neck subsite						
Oral cavity	1.00			1.00		
Oropharynx	0.49	0.43–0.56	<0.001	0.56	0.47–0.67	<0.001
Hypopharynx	1.02	0.87–1.20	0.815	0.96	0.78–1.18	0.681
Larynx	1.00	0.85–1.17	0.974	0.89	0.72–1.10	0.273
HPV Status						
Negative	1.00			1.00		
Positive	0.40	0.29–0.54	<0.001	0.53	0.35–0.80	0.002
Unknown	0.97	0.79–1.19	0.783	0.96	0.74–1.24	0.769
Radiation dose (Gy) (continuous)	0.99	0.99–1.00	<0.001	0.99	0.99–1.00	<0.001
Tumor size (mm) (continuous)	1.01	1.01–1.01	<0.001	1.00	1.00–1.01	0.005
Treatment						
Primary surgery	1.00			1.00		
Primary CRT	1.44	1.31–1.58	<0.001	1.27	1.11–1.46	<0.001
T stage						
0	1.00			1.00		
1	0.81	0.68–0.96	0.016	0.83	0.66–1.06	0.134
2	1.06	0.91–1.23	0.480	0.91	0.74–1.13	0.397
3	1.56	1.34–1.82	<0.001	1.21	0.98–1.51	0.080
4	2.09	1.80–2.43	<0.001	1.42	1.14–1.76	0.002
IPTW hazard model Treatment						
Primary surgery	1.00					
Primary CRT	1.13	1.05–1.22	0.002			

Table 4

Univariate and multivariate analysis for all oropharynx patients using Cox proportional hazards model.

	Univariate Analysis			Multivariate Analysis		
	HR	(95% CI)	p-value	HR	(95% CI)	p-value
Age, years (continuous)	1.03	1.02–1.03	<0.001	1.02	1.01–1.03	<0.001
Sex						
Male	1.00					
Female	1.13	0.96–1.33	0.127			
Race						
White	1.00			1.00		
Non-white	1.75	1.53–1.99	<0.001	1.54	1.28–1.84	<0.001
Year						
2004–2006	1.00			1.00		
2007–2009	0.99	0.87–1.13	0.894	0.91	0.77–1.08	0.260
2010–2012	0.87	0.76–1.01	0.074	0.74	0.59–0.93	0.010
Charlson/Deyo score						
0	1.00					
1	1.15	0.97–1.35	0.104			
2	1.67	1.29–2.17	<0.001			
Insurance type						
Private	1.00			1.00		
Non-private/Unknown	2.21	1.97–2.48	<0.001	1.93	1.64–2.27	<0.001
Income						
<\$48,000	1.00					
\$48,000	0.73	0.66–0.82	<0.001			
Location						
Urban (250,000)	1.00					
Non-urban (<250,000)	1.03	0.91–1.17	0.604			
Facility						
Non-academic	1.00			1.00		
Academic	0.89	0.79–0.99	0.032	0.84	0.73–0.98	0.022
Facility volume						

	Univariate Analysis			Multivariate Analysis		
	HR	(95% CI)	p-value	HR	(95% CI)	p-value
Non-high	1.00					
High	0.94	0.83–1.06	0.306			
HPV status						
Negative	1.00			1.00		
Positive	0.46	0.32–0.68	<0.001	0.46	0.28–0.74	0.002
Unknown	0.92	0.69–1.22	0.554	0.62	0.42–0.92	0.017
Radiation dose (Gy) (continuous)	0.99	0.99–1.00	0.002	0.99	0.99–1.00	0.004
Tumor size (mm) (continuous)	1.01	1.01–1.02	<0.001	1.00	1.00–1.01	0.012
Treatment						
Primary surgery	1.00			1.00		
Primary CRT	1.62	1.43–1.84	<0.001	1.29	1.06–1.56	0.009
T stage						
0	1.00			1.00		
1	0.85	0.68–1.05	0.129	0.94	0.68–1.29	0.690
2	0.96	0.79–1.17	0.703	0.83	0.62–1.11	0.197
3	1.50	1.23–1.84	<0.001	1.17	0.87–1.59	0.306
4	2.25	1.85–2.72	<0.001	1.49	1.09–2.03	0.012
IPTW hazard model Treatment						
Primary surgery	1.00					
Primary CRT	1.22	1.10–1.35	<0.001			

Table 5

Sensitivity analysis of the effects of an unmeasured confounder (UC) on the HR of death after treatment for all patients and oropharynx patients. The baseline HRs are from IPTW models for all patients and oropharynx patients, respectively.

Prevalence of UC in Primary CRT group	Prevalence of UC in Primary Surgery group	UC HR	Primary CRT Treatment HR adjusted for UC (95% CI)	
			All Patients	Oropharynx Patients
0.1	0	1.1	1.12 (1.04–1.21)	1.21 (1.09–1.34)
0.1	0	1.25	1.10 (1.02–1.19)	1.19 (1.08–1.32)
0.1	0	1.5	1.08 (1.00–1.16)	1.16 (1.05–1.29)
0.2	0	1.1	1.11 (1.03–1.20)	1.20 (1.08–1.33)
0.2	0	1.25	1.08 (1.00–1.16)	1.16 (1.05–1.29)
0.2	0	1.5	1.03 (0.95–1.11)	1.11 (1.00–1.23)
0.3	0	1.1	1.10 (1.02–1.18)	1.19 (1.07–1.31)
0.3	0	1.25	1.05 (0.97–1.13)	1.14 (1.03–1.26)
0.3	0	1.5	0.98 (0.91–1.06)	1.06 (0.96–1.18)
0.4	0	1.1	1.09 (1.01–1.17)	1.17 (1.06–1.30)
0.4	0	1.25	1.03 (0.95–1.11)	1.11 (1.00–1.23)
0.4	0	1.5	0.94 (0.87–1.02)	1.02 (0.92–1.13)
0.5	0	1.1	1.08 (1.00–1.16)	1.16 (1.05–1.29)
0.5	0	1.25	1.00 (0.93–1.08)	1.09 (0.98–1.20)
0.5	0	1.5	0.90 (0.84–0.98)	0.98 (0.88–1.08)