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Impact of HPV-Status on Prognostic Potential of the AJCC Staging System for Larynx Cancer

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Abstract

Objective.—We evaluated the ability of the American Joint Committee on Cancer 7th edition (AJCC) staging system to prognosticate the overall survival of patients with human papillomavirus (HPV) positive laryngeal squamous cell carcinoma.

Study Design.—Retrospective analysis

Setting.—National Cancer Database (NCDB)

Subjects and Methods.—Patients diagnosed with laryngeal squamous cell carcinoma treated with curative intent were identified in the NCDB. Multivariate analysis was utilized to determine factors correlated with overall survival in the HPV-negative and HPV-positive cohorts. Unadjusted and propensity-score weighted Kaplan-Meier estimation was used to determine overall survival of HPV-negative and HPV-positive patients across AJCC stage groupings.

Results.—We identified 3,238 patients with laryngeal squamous cell carcinoma of which 2,812 were HPV-negative and 426 were HPV-positive. Overall survival adjusted for age, sex, and comorbidity status confirmed significant differences between all consecutive stage groupings (I vs

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Author Contributions

Stacey M. Davidson, acquisition of data, drafting of manuscript; **Huasing C. Ko**, acquisition of data, critical revision of manuscript for important intellectual content; **Paul M. Harari,** analysis and interpretation of data, critical revision of manuscript for important intellectual content; **Andrew M. Baschnagel**, critical revision of manuscript for important intellectual content; **Shuai Chen** statistical analysis; **Matthew E. Witek**, study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content. All authors gave final approval of the version to be published and are in agreement to be accountable for all aspects of the work.

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II, $p < 0.001$; II vs III, $p < 0.05$; III vs IVA, $p < 0.001$; IVA vs IVB, $p < 0.05$) in the HPV-negative cohort whereas only stage IVA and IVB ($p < 0.01$) exhibited a significant difference in overall survival for HPV-positive patients.

Conclusion.—The current AJCC staging system does not accurately distinguish risk of mortality for patients with HPV-positive disease. These data support the consideration of HPV status in estimating prognosis as well as clinical trial design and clinical decision making for patients with laryngeal squamous cell carcinoma.

Keywords

larynx; cancer; prognosis; human papillomavirus; squamous cell carcinoma

Introduction

HPV status is an independent prognostic factor for patients with oropharyngeal squamous cell carcinoma (OPSCC). Patients with HPV-positive OPSCC exhibit improved progression-free and overall survival compared to those with HPV-negative disease.[1-5] The marked difference in clinical outcomes between HPV-negative and HPV-positive OPSCC has dichotomized the intent of on-going clinical trials with therapy escalation being employed for the HPV-negative cohort[6] whereas current trials and those in development for the HPV-positive cohort are directed towards therapy de-intensification.[7] Moreover, validated datasets have demonstrated the inability of the 7th edition of the American Joint Committee on Cancer (AJCC) to accurately prognosticate patients with HPV-positive OPSCC.[8,9] The discordance in outcome in the current clinical staging criteria for HPV-positive compared with HPV-negative OPSCC patients prompted AJCC to established a separate TNM and overall staging system for this favorable cohort in its 8th edition. Taken together, identification of a favorable cohort within the OPSCC patient population has directed investigational treatment approaches and established new prognostic schemas.

There is a growing body of evidence supporting favorable outcomes for patients with HPV and/or p16 positive non-OPSCC compared to those with HPV/p16-negative cancers. For example, a pooled analysis of three cooperative group head and neck studies demonstrated that patients with p16-positive non-OPSCC exhibited improved progression-free and overall survival compared to those with p16-negative disease.[10] We recently reported outcomes of patients with non-OPSCC treated with definitive intent identified in the National Cancer Database (NCDB). Patients with HPV-positive SCC of the oral cavity, hypopharynx, and larynx shared comparable patient and disease characteristics as those with HPV-positive OPSCC as well as a similar marked improvement in overall survival.[11] Given these findings, we evaluated whether the current AJCC staging system was able to accurately prognosticate overall survival across disease stage groupings for patients with HPV-positive larynx cancer.

Materials and Methods

Data Source, Patient Selection, and Variable Definitions

We performed a retrospective, observational, cohort study using the NCDB that contains patient demographics, disease characteristics, and initial treatments under exemption by the

University of Wisconsin-Madison Institutional Review Board. Overall survival is the only available outcomes data. The laryngeal cancer cohort included patients with tumors categorized as glottic larynx, supraglottic larynx, subglottic larynx, overlapping laryngeal lesions, and larynx NOS. Overall stage was determined using the AJCC 7th edition for laryngeal carcinoma.[12] Patients diagnosed with Stage IVC disease, those that did not receive treatment, chemotherapy only, or less than 50 Gy or greater than 80 Gy of radiotherapy were excluded. Age was analyzed as a continuous variable. Charlson-Deyo comorbidity score was analyzed as either 0, 1 or ≥ 2. For purposes of univariate and multivariate analyses, we dichotomized race as white or non-white, insurance type a private or non-private/unknown, income as < $48,000 or ≥ $48,000, facility as community or academic, volume as high or low, and location as urban (≥ 250,000) or non-urban (< 250,000). HPV status was ascertained from testing of the primary tumor or regional lymph node. HPV-positive patients included were coded as non-16-non-18 high-risk HPV, HPV-16, HPV-18, HPV-16 and HPV-18, high-risk HPV-not stated, and HPV not otherwise specified. Product-limit survival estimates between patients with HPV-16 and/or HPV-18 high-risk were similar to those with HPV not otherwise specified and high-risk HPV not stated and therefore included in the analysis to provide statistical power (Supplemental figure 1). Patients with low-risk HPV-positive disease were excluded.

Statistical Analysis

Standard descriptive statistics were used to analyze the distribution of covariates throughout the cohort. Baseline demographics and patient characteristics were analyzed using Pearson chi-square tests, while continuous variables such as age and tumor size were analyzed with the Wilcoxon signed-rank test. Univariate and multivariate analyses using Cox proportional hazards methods were utilized to determine factors correlated with overall survival. Factors found to be significant in univariate analysis were included and further selected by stepwise method in multivariate analysis. T-stage and N-stage were also included in order to compare the accuracy of the AJCC 7th edition for HPV-positive and HPV-negative laryngeal tumors.[13] Note that insurance and treatment are statistically significant in univariate analysis but lose significance when adjusted by other variables in multivariate analysis due to confounding (Supplementary table 1).

Kaplan-Meier curves and log-rank test were used to compare overall survival among the different stage groups. In addition, propensity score-weighted Kaplan-Meier curves were adopted to account for covariate imbalance between stage groups. Our Kaplan-Meier estimators incorporated the inverse of the generalized multi-level propensity score. Because there are multiple groups, we estimated the generalized propensity score for each patient using multinomial logistic regression. The justification of using the multi-level propensity score has been previously documented.[14] Note that overall stage is not a ‘treatment’ in the conventional sense of causal inference since it is not able to be manipulated. This propensity score is a tool to balance the covariate distribution between stage groups for studies with either causal or non-causal purposes.[15] Covariates that were significantly associated with overall survival were included in the multinomial logistic model and further selected by stepwise selection. The final variables included for propensity adjustment were age, sex, and Charlson/Deyo comorbidity score.

Statistical analyses, including propensity score, survival, were performed using *SAS 9.4 (SAS Institute Inc., Cary, NC).* All p-values were two-sided, and a $p \leq 0.05$ was considered statistically significant.

Results

We identified 3,238 laryngeal cancer patients with 426 being positive for HPV who were treated with curative intent from 2010-2012. Baseline patient demographics, disease characteristics, and treatments rendered are listed in Table 1.

Clinical outcomes

Unadjusted Kaplan-Meier curves were used to compare overall survival among different clinical stage groups for HPV-negative (**p < 0.0001,** Figure 1A) and HPV-positive patients (**p < 0.001,** Figure 1B). Log-rank comparisons of overall survival between Stage I and II ($p < 0.001$), Stage III and IVA ($p < 0.01$), and Stage IVA and IVB ($p < 0.05$) were significantly different, whereas the difference in survival between Stage II and III did not meet statistical significance ($p = 0.10$). However, there were no significant difference between sequential clinical stage groupings for the HPV-positive cohort (Table 2).

Univariate and multivariate analyses for overall survival for patients with HPV-negative and HPV-positive laryngeal cancers were performed using Cox proportional hazards model. On multivariate analysis for the HPV-negative cohort, age ≥ 65 (HR 1.66; 95% CI 1.42 – 1.95), increasing Charlson/Deyo comorbidity of 1 (HR 1.31; 95% CI 1.10 – 1.55) and ≥ 2 (HR 1.76; 95% CI 1.35 – 2.30), increasing T-stage (T2 - HR 1.71; 95% CI 1.37 – 2.14), (T3 - HR 2.14; 95% CI 1.71 – 2.67), (T4 - HR 2.98; 95% CI 2.31 – 3.85), and N stage N2 or N3 (HR 1.65; 95% CI 1.37 – 1.95) were associated with worse overall survival while female sex (HR 0.75; 95% CI 0.62 – 0.91) was associated with improved survival (Table 3). Among the HPV-positive cohort, only T4 disease was associated with worse overall survival (HR 1.98; 95% CI 1.00-3.91) (Table 4).

Kaplan-Meier curves adjusted for age, sex, and Charlson/Deyo comorbidity score confirmed differences in overall survival in the HPV-negative cohort (**p < 0.0001,** Figure 1C), however, there were no differences in overall survival among the adjusted survival curves for the HPV-positive cohort (**p = 0.06,** Figure 1D). Log-rank comparisons between sequential clinical stage groupings for HPV-negative patients exhibited significant differences for all stages. Adjusted log-rank comparisons for the HPV-positive cohort only revealed a significant difference between stages IVA and IVB ($p < 0.01$) (Table 2).

Discussion

The need for accurate prognostication and modification of stage classification to reflect HPV status has recently been established for OPSCC. O'Sullivan *et al.* developed and validated a proposed staging system that better represented the distinct natural history and treatment response of HPV-positive tumors as compared to the AJCC 7th edition.[9] The ICON-S cohort study included HPV-positive non-metastatic OPSCC patients from across Europe and North America with a primary group and a validation cohort. The 5-year overall survival was

found to be not significantly different for AJCC 7th edition stage I, II, III, and IVA patients but was significantly lower for stage IVB. A new more accurate staging system was then developed using recursive partitioning analysis (RPA) and adjusted hazard ratio (AHR) modeling methods. The classification developed with the adjusted hazard ratio was practical and performed well in validation cohorts. Major changes as compared to the AJCC 7th edition include elimination of stage IV for non-metastatic disease and classification of stage III as T4 or N3.

Dahstrom *et al.* also recognized the disparity between the AJCC 7th edition and outcomes of HPV-positive OPSCC patients and proposed a new staging system using an RPA.[8] A separate RPA was then performed using the T categories for oropharyngeal carcinoma but the N categories for nasopharyngeal carcinoma, as this disease site is also associated with a viral etiology and has a unique N classification as compared to other head and neck malignancies. Increasing risk of death was demonstrated for increasing stage with even distribution of patients between groups for their proposed staging system in a single-center study, suggesting an alternate staging system may be more appropriate for HPV-positive OPSCC rather than the AJCC 7th edition.

Ultimately, the AJCC 8th edition staging manual has updated the staging system for OPSCC with a separate staging classification for HPV-positive tumors as compared to HPV-negative.[16] This will impact the way HPV-positive tumors are prognosticated and treated in the future with the potential for treatment de-escalation to reduce treatment morbidity and thereby improve quality of life. Treatment de-escalation is a very important concept for laryngeal carcinoma as well, given the significant impact of treatment on quality of life due to the critical function of the larynx for speech, swallowing, appearance, and psychosocial well-being, laryngeal cancer, and its treatment can greatly impact the quality of life of patients.[17,18] Early stage tumors can be treated definitively with single modality surgery or radiotherapy, whereas locally advanced disease requires more aggressive multimodality therapies.[19] To date, treatment recommendations are not tailored based on HPV status.

While the impact of HPV status on outcomes for OPSCC is well established, its prognostic significance on non-OPSCC malignancies has only recently been supported. A large observational cohort study by Ko *et al.* using the NCDB demonstrated that overall survival was significantly higher for HPV-positive non-OPSCC patients as compared to HPV-negative patients for both early and advanced stages. The adjusted 3-year overall survival for early-stage (stage I and II) HPV-positive larynx patients was reported as 79% as compared to 76% for HPV-negative patients. This difference was more pronounced for late-stage (stage III and IV) laryngeal cancer patients with an adjusted 3-year overall survival of 70% for HPV-positive patients as compared to 58% for HPV-negative patients.[11]

Building on the concept that HPV affects outcomes for non-OPSCC patients, this current study was designed to determine if the current AJCC 7th edition is adequate to accurately prognosticate patients with HPV-positive laryngeal cancer. Using the NCDB, we demonstrate that the clinical stage grouping defined by the 7th edition of the AJCC do not accurately discriminate the risk of mortality for patients with HPV-positive larynx cancer unlike those with HPV-negative disease. Although there were no changes in laryngeal T-

stage classifications in AJCC 8, a N3b designation was made for the majority of head and neck cancers to define lymph nodes with extra-nodal extension (ENE) regardless of size. As this definition requires is unambiguously defined by physical examination and radiographic evidence, it is unclear if this data could be extrapolated from the NCDB. Further, the ENE variable was rendered obsolete for patients diagnosed before 2010, which is prior to the dataset analyzed in this cohort of patients from 2010-2012.[20]

The retrospective nature of this study is a significant limitation. There are opportunities for cofounding factors to influence outcomes as patients in the different HPV cohorts were not well balanced in terms of staging or treatment, with a greater proportion of HPV-positive patients presented with more advanced disease and likely were treated more intensively as a result. Another limitation of this study is that smoking status is not captured in the NCDB. Continued or previous cigarette smoking is likely to be a significant cofounding factor for overall survival due to comorbidities or development of second primaries, and it is known that HPV-negative head and neck malignancies share the etiology of cigarette smoking and therefore it is probable that HPV-negative patients have a greater smoking history. Our findings suggest that the AJCC 7th edition staging system does not accurately prognosticate patients identified in the NCDB with HPV-positive laryngeal cancer. Given the sample size used in the current analysis, these finding will need to be validated with a larger external dataset prior to the consideration of novel staging systems such as have recently been accomplished for medullary thyroid cancers.[21]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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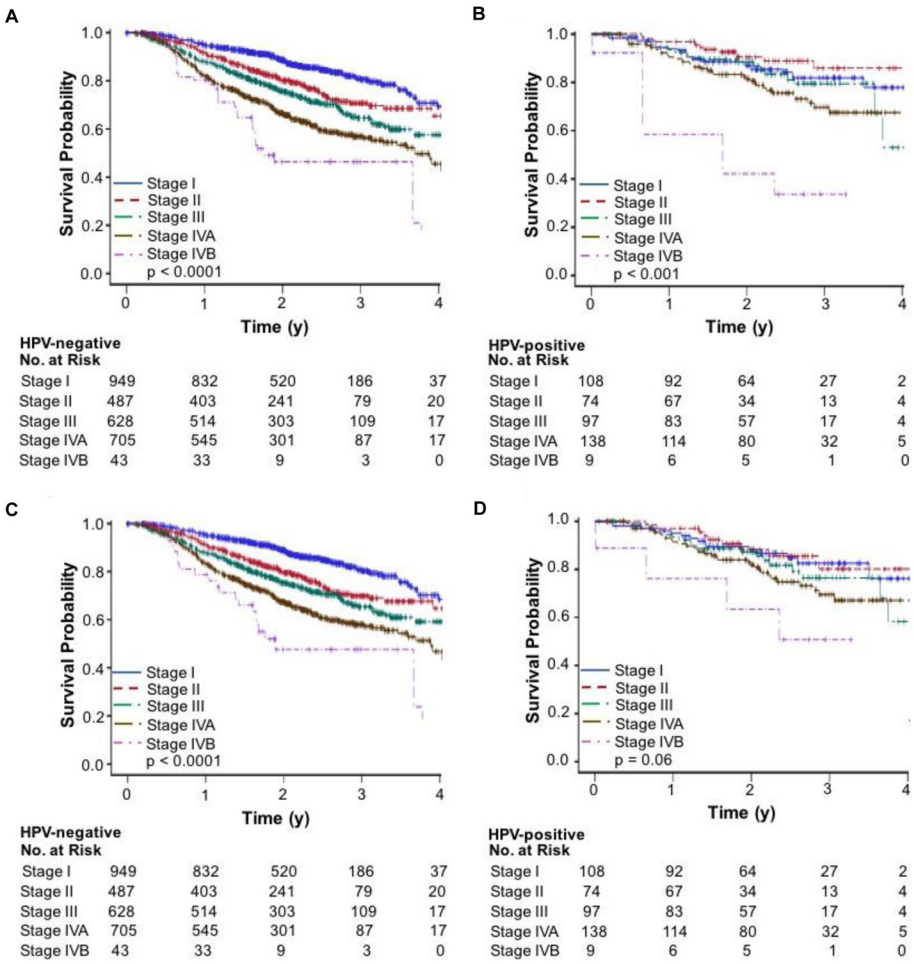

Figure 1.

Unadjusted survival curves for patients with HPV-negative (A) and HPV-positive (B) laryngeal cancer by AJCC stage. Propensity-score adjusted survival curves for patients with HPV-negative (C) and HPV-positive (D) laryngeal cancer by AJCC stage.

Table 1.

Baseline demographics and patient characteristics for all patients.

	HPV-negative	HPV-positive	All	p
Total patients	2,812	426	3,238	
Age, years				<0.001
Median (range)	64 (20-90)	60 (20-90)	63 (20-90)	
Mean (Std. Dev.)	63.9 (11.1)	59.8 (12.6)	63.4 (11.4)	
Tumor Size (mm)				0.55
Median (range)	25 (1-99)	25 (1-90)	25 (1-99)	
Mean (Std. Dev.)	26.6 (15.3)	27.2 (15.0)	26.7 (15.3)	
Age				<0.001
<65	1,502 (53.4)	273 (64.1)	1,775 (54.8)	
≥65	1,310 (46.6)	153 (35.9)	1,463 (45.2)	
Sex				<0.01
Male	2,196 (78.1)	306 (71.8)	2,502 (77.3)	
Female	616 (21.9)	120 (28.2)	736 (22.7)	
Race				0.86
White	2,201 (78.3)	346 (81.2)	2,547 (78.7)	
Black	387 (13.8)	50 (11.7)	437 (13.5)	
Hispanic	133 (4.7)	18 (4.2)	151 (4.7)	
Asian/Pacific islander	45 (1.6)	6 (1.4)	51 (1.6)	
Other	24 (0.9)	3 (0.7)	27 (0.8)	
Unknown	22 (0.8)	3 (0.7)	25 (0.8)	
Year of Diagnosis				0.29
2010	457 (16.2))	81 (19.0)	538 (16.6)	
2011	987 (35.1)	138 (32.4)	1,125 (34.7)	
2012	1,368 (48.7)	207 (48.6)	1,575 (48.6)	
Charlson/Deyo comorbidity score				0.94
0	2,005 (71.3)	307 (72.1)	2,312 (71.4)	
1	622 (22.1)	91 (21.4)	713 (22.0)	
≥2	185 (6.6)	28 (6.6)	213 (6.6)	
Insurance Type				0.17
Private	945 (33.6)	160 (37.6)	1,105 (34.1)	
Medicare	1,307 (46.5)	178 (41.8)	1,485 (45.9)	
Medicaid	311 (11.1)	48 (11.3)	359 (11.1)	
Other gov.	41 (1.5)	6 (1.4)	47 (1.5)	
No insurance	167 (5.9)	32 (7.5)	199 (6.2)	
Unknown	41 (1.5)	2 (0.5)	43 (1.3)	
Income				0.13
<$48,000	1,374 (48.9)	186 (43.7)	1,560 (48.2)	
≥$48,000	1,423 (50.6)	238 (55.9)	1,661 (51.3)	
Unknown	15 (0.5)	2 (0.5)	17 (0.5)	

	HPV-negative	HPV-positive	All	p
Location				0.88
Urban	2,028 (72.1)	303 (71.1)	2,331 (72.0)	
Non-urban	714 (25.4)	113 (26.5)	827 (25.5)	
Unknown	70 (2.5)	10 (2.4)	80 (2.5)	
Primary site				<0.001
Glottic larynx	1,335 (47.5)	148 (34.7)	1,483 (45.8)	
Supraglottic larynx	1,078 (38.3)	219 (51.4)	1,297 (40.1)	
Subglottic larynx	46 (1.6)	3 (0.7)	49 (1.5)	
Overlapping lesion of larynx	78 (2.8)	12 (2.8)	90 (2.8)	
Larynx NOS	275 (9.8)	44 (10.3)	319 (9.9)	
Facility				0.10
Academic	1,235 (43.9)	169 (39.7)	1,404 (43.4)	
Community	1,577 (56.1)	257 (60.3)	1,834 (56.6)	
Facility Volume				0.63
High volume	540 (19.2)	86 (20.2)	626 (19.3)	
Low volume	2,272 (80.8)	340 (79.8)	2,612 (80.7)	
Dose				0.07
None	453 (16.1)	65 (15.3)	518 (16.0)	
Low (50-65Gy)	572 (20.3)	65 (15.3)	637 (19.7)	
High (65-80Gy)	1,563 (55.6)	259 (60.8)	1,822 (56.3)	
Unknown	224 (8.0)	37 (8.7)	261 (8.1)	
Stage 1				
Primary Treatment				0.84
Surgery	247 (26.0)	37 (29.6)	284 (26.4)	
RT	464 (48.9)	61 (48.8)	525 (48.9)	
Surgery+RT	204 (21.5)	24 (19.2)	228 (21.2)	
CRT	27 (2.9)	2 (1.6)	29 (2.7)	
Surgery+CRT	7 (0.7)	1 (0.8)	8 (0.7)	
Stage 2				
Primary Treatment				0.84
Surgery	57 (11.7)	10 (12.7)	67 (11.8)	
RT	241 (49.5)	38 (48.1)	279 (49.3)	
Surgery+RT	71 (14.6)	15 (19.0)	86 (15.2)	
CRT	95 (19.5)	13 (16.5)	108 (19.1)	
Surgery+CRT	23 (4.7)	3 (3.8)	26 (4.6)	
Stage 3				
Primary Treatment				0.13
Surgery	81 (12.9)	13 (11.8)	94 (12.7)	
RT	49 (7.8)	11 (10.0)	60 (8.1)	
Surgery+RT	63 (10.0)	5 (4.6)	68 (9.2)	
CRT	354 (56.4)	59 (53.6)	413 (56.0)	
Surgery+CRT	81 (12.9)	22 (20.0)	103 (14.0)	

	HPV-negative	HPV-positive	All	p
Stage 4A				
Primary Treatment				0.12
Surgery	68 (9.7)	9 (6.0)	77 (9.0)	
RT	27 (3.8)	2 (1.3)	29 (3.4)	
Surgery+RT	71 (10.1)	10 (6.7)	81 (9.5)	
CRT	399 (56.6)	98 (65.3)	497 (58.1)	
Surgery+CRT	140 (19.9)	31 (20.7)	171 (20.0)	
Stage 4B				
Primary Treatment				0.10
Surgery	2 (4.7)	2 (22.2)	4 (7.7)	
RT	2 (4.7)	1 (11.1)	3 (5.8)	
Surgery+RT	0 (0.0)	0 (0.0)	0 (0.0)	
CRT	26 (60.5)	6 (66.7)	32 (61.5)	
Surgery+CRT	13 (30.2)	0 (0.0)	13 (25.0)	
T stage				<0.05
T1	1,016 (36.1)	123 (28.9)	1,139 (35.2)	
T2	716 (25.5)	126 (29.6)	842 (26.0)	
T3	726 (25.8)	121 (28.4)	847 (26.2)	
T4	353 (12.6)	55 (12.9)	408 (12.6)	
Unknown	1 (0.1)	1 (0.2)	2 (0.1)	
N stage				<0.001
N0	2,003 (71.2)	257 (60.3)	2,260 (69.8)	
N1	258 (9.2)	48 (11.3)	306 (9.5)	
N2	517 (18.4)	113 (26.5)	630 (19.5)	
N3	34 (1.2)	8 (1.9)	42 (1.3)	
Overall stage				<0.01
I	949 (33.8)	108 (25.4)	1,057 (32.6)	
II	487 (17.3)	74 (17.4)	561 (17.3)	
III	628 (22.3)	97 (22.8)	725 (22.4)	
IVA	705 (25.1)	138 (32.4)	843 (26.0)	
IVB	43 (1.5)	9 (2.1)	52 (1.6)	
	HPV-negative	**HPV-positive**	**All**	**p**
Total patients	2,812	426	3,238	
Age, years				<0.001
Median (range)	64 (20-90)	60 (20-90)	63 (20-90)	
Mean (Std. Dev.)	63.9 (11.1)	59.8 (12.6)	63.4 (11.4)	
Tumor Size (mm)				0.55
Median (range)	25 (1-99)	25 (1-90)	25 (1-99)	
Mean (Std. Dev.)	26.6 (15.3)	27.2 (15.0)	26.7 (15.3)	
Age				<0.001
<65	1,502 (53.4)	273 (64.1)	1,775 (54.8)	
≥65	1,310 (46.6)	153 (35.9)	1,463 (45.2)	

	HPV-negative	HPV-positive	All	p
Sex				<0.01
Male	2,196 (78.1)	306 (71.8)	2,502 (77.3)	
Female	616 (21.9)	120 (28.2)	736 (22.7)	
Race				0.86
White	2,201 (78.3)	346 (81.2)	2,547 (78.7)	
Black	387 (13.8)	50 (11.7)	437 (13.5)	
Hispanic	133 (4.7)	18 (4.2)	151 (4.7)	
Asian/Pacific islander	45 (1.6)	6 (1.4)	51 (1.6)	
Other	24 (0.9)	3 (0.7)	27 (0.8)	
Unknown	22 (0.8)	3 (0.7)	25 (0.8)	
Year of Diagnosis				0.29
2010	457 (16.2)	81 (19.0)	538 (16.6)	
2011	987 (35.1)	138 (32.4)	1,125 (34.7)	
2012	1,368 (48.7)	207 (48.6)	1,575 (48.6)	
Charlson/Deyo comorbidity score				0.94
0	2,005 (71.3)	307 (72.1)	2,312 (71.4)	
1	622 (22.1)	91 (21.4)	713 (22.0)	
≥2	185 (6.6)	28 (6.6)	213 (6.6)	
Insurance Type				0.17
Private	945 (33.6)	160 (37.6)	1,105 (34.1)	
Medicare	1,307 (46.5)	178 (41.8)	1,485 (45.9)	
Medicaid	311 (11.1)	48 (11.3)	359 (11.1)	
Other gov.	41 (1.5)	6 (1.4)	47 (1.5)	
No insurance	167 (5.9)	32 (7.5)	199 (6.2)	
Unknown	41 (1.5)	2 (0.5)	43 (1.3)	
Income				0.13
<$48,000	1,374 (48.9)	186 (43.7)	1,560 (48.2)	
≥$48,000	1,423 (50.6)	238 (55.9)	1,661 (51.3)	
Unknown	15 (0.5)	2 (0.5)	17 (0.5)	
Location				0.88
Urban	2,028 (72.1)	303 (71.1)	2,331 (72.0)	
Non-urban	714 (25.4)	113 (26.5)	827 (25.5)	
Unknown	70 (2.5)	10 (2.4)	80 (2.5)	
Primary site				<0.001
Glottic larynx	1,335 (47.5)	148 (34.7)	1,483 (45.8)	
Supraglottic larynx	1,078 (38.3)	219 (51.4)	1,297 (40.1)	
Subglottic larynx	46 (1.6)	3 (0.7)	49 (1.5)	
Overlapping lesion of larynx	78 (2.8)	12 (2.8)	90 (2.8)	
Larynx NOS	275 (9.8)	44 (10.3)	319 (9.9)	
Facility				0.10
Academic	1,235 (43.9)	169 (39.7)	1,404 (43.4)	
Community	1,577 (56.1)	257 (60.3)	1,834 (56.6)	

	HPV-negative	HPV-positive	All	p
Facility Volume				0.63
High volume	540 (19.2)	86 (20.2)	626 (19.3)	
Low volume	2,272 (80.8)	340 (79.8)	2,612 (80.7)	
Dose				0.07
None	453 (16.1)	65 (15.3)	518 (16.0)	
Low (50-65Gy)	572 (20.3)	65 (15.3)	637 (19.7)	
High (65-80Gy)	1,563 (55.6)	259 (60.8)	1,822 (56.3)	
Unknown	224 (8.0)	37 (8.7)	261 (8.1)	
Primary Treatment				<0.01
Surgery	455 (16.2)	66 (15.5)	521 (16.1)	
RT	783 (27.8)	95 (22.3)	878 (27.1)	
Surgery+RT	409 (14.5)	50 (11.7)	459 (14.2)	
CRT	901 (32.0)	163 (38.3)	1,064 (32.9)	
Surgery+CRT	264 (9.4)	52 (12.2)	316 (9.8)	
T stage				<0.05
T1	1,016 (36.1)	123 (28.9)	1,139 (35.2)	
T2	716 (25.5)	126 (29.6)	842 (26.0)	
T3	726 (25.8)	121 (28.4)	847 (26.2)	
T4	353 (12.6)	55 (12.9)	408 (12.6)	
Unknown	1 (0.1)	1 (0.2)	2 (0.1)	
N stage				<0.001
N0	2,003 (71.2)	257 (60.3)	2,260 (69.8)	
N1	258 (9.2)	48 (11.3)	306 (9.5)	
N2	517 (18.4)	113 (26.5)	630 (19.5)	
N3	34 (1.2)	8 (1.9)	42 (1.3)	
Overall stage				<0.01
I	949 (33.8)	108 (25.4)	1,057 (32.6)	
II	487 (17.3)	74 (17.4)	561 (17.3)	
III	628 (22.3)	97 (22.8)	725 (22.4)	
IVA	705 (25.1)	138 (32.4)	843 (26.0)	
IVB	43 (1.5)	9 (2.1)	52 (1.6)	

Table 2:

Univariate and multivariate analysis for overall survival of HPV-negative patients using Cox proportional hazards model.

	Univariate			Multivariate		
	HR	**(95% CI)**	**p-value**	**HR**	**(95% CI)**	**p-value**
Age						
<65	1.00			1.00		
≥65	1.35	1.17-1.57	<0.001	1.66	1.42-1.95	<0.001
Sex						
Male	1.00			1.00		
Female	0.81	0.67-0.97	<0.05	0.75	0.62-0.91	<0.01
Race						
White	1.00					
Non-white	1.03	0.86-1.23	0.77			
Year of Diagnosis						
2010	1.00					
2011	1.03	0.84-1.27	0.78			
2012	1.13	0.91-1.40	0.28			
Charlson/Deyo comorbidity score						
0	1.00			1.00		
1	1.52	1.28-1.80	<0.001	1.31	1.10-1.55	<0.01
≥2	1.97	1.52-2.56	<0.001	1.76	1.35-2.30	<0.001
Insurance Type						
Private	1.00					
Non-private/Unknown	1.49	1.25-1.76	<0.001			
Income						
<$48,000	1.00					
≥$48,000	0.90	0.78-1.05	0.18			
Location						
Urban	1.00					
Non-urban	1.16	0.98-1.38	0.08			
Facility						
Community	1.00					
Academic	0.87	0.74-1.01	0.06			
Volume						
Low	1.00					
High	0.83	0.68-1.01	0.06			
Dose						
None	1.00					
Low (50-65Gy)	0.89	0.69-1.16	0.40			
High (65-80Gy)	1.07	0.87-1.34	0.515			
Primary Treatment						
CRT	1.00					

	Univariate			Multivariate		
	HR	**(95% CI)**	**p-value**	**HR**	**(95% CI)**	**p-value**
Surgery	0.77	0.61-0.96	<0.05			
RT	0.57	0.46-0.70	<0.001			
Surgery+RT	0.56	0.43-0.71	<0.001			
Surgery+CRT	1.00	0.78-1.28	0.97			
T stage						
1	1.00			1.00		
2	1.84	1.48-2.28	<0.001	1.71	1.37-2.14	<0.001
3	2.34	1.90-2.88	<0.001	2.14	1.71-2.67	<0.001
4	3.30	2.61-4.16	<0.001	2.98	2.31-3.85	<0.001
N stage						
0	1.00			1.00		
1	1.57	1.23-1.99	<0.001	1.23	0.96-1.57	0.11
2/3	2.03	1.72-2.41	<0.001	1.65	1.37-1.98	<0.001

Table 3:

Univariate and multivariate analysis for overall survival of HPV-positive patients using Cox proportional hazards model.

	Univariate			Multivariate		
	HR	**(95% CI)**	**p-value**	**HR**	**(95% CI)**	**p-value**
Age						
<65	1.00					
≥65	1.35	0.86-2.12	0.19			
Sex						
Male	1.00					
Female	0.72	0.42-1.21	0.21			
Race						
White	1.00					
Non-white	1.21	0.71-2.05	0.49			
Year of Diagnosis						
2010	1.00					
2011	1.01	0.57-1.80	0.96			
2012	0.99	0.54-1.84	0.98			
Charlson/Deyo comorbidity score						
0	1.00					
1	1.24	0.74-2.10	0.41			
≥2	1.17	0.50-2.73	0.71			
Insurance Type						
Private	1.00					
Non-private/Unknown	1.80	1.09-2.97	0.02			
Income						
<$48,000	1.00					
≥$48,000	0.66	0.42-1.03	0.07			
Location						
Urban	1.00					
Non-urban	0.88	0.53-1.47	0.64			
Facility						
Community	1.00					
Academic	1.13	0.72-1.77	0.59			
Volume						
Low	1.00					
High	0.97	0.57-1.66	0.91			
Dose						
None	1.00					
Low (50-65Gy)	1.32	0.58-3.01	0.51			
High (65-80Gy)	1.47	0.74-2.90	0.27			
Primary Treatment						
CRT	1.00					

	Univariate			Multivariate		
	HR	**(95% CI)**	**p-value**	**HR**	**(95% CI)**	**p-value**
Surgery	0.95	0.47-1.94	0.89			
RT	1.32	0.72-2.42	0.27			
Surgery+RT	1.27	0.62-2.58	0.51			
Surgery+CRT	1.44	0.74-2.81	0.29			
T stage						
1	1.00			1.00		
2	0.68	0.33-1.37	0.29	0.62	0.30-1.27	0.19
3	1.46	0.81-2.62	0.21	1.27	0.67-2.39	0.47
4	2.28	1.21-4.31	0<.05	1.98	1.00-3.91	<0.05
N stage						
0	1.00			1.00		
1	1.20	0.58-2.48	0.62	1.20	0.57-2.52	0.63
2/3	1.61	1.00-2.690	0.05	1.38	0.82-2.33	0.23

Table 4:

P-values from log-rank rests for overall survival comparison.

	Unadjusted		Propensity-weighted Adjusted by Age, Sex. CDCC	
Compared overall stages	**HPV−**	**HPV+**	**HPV−**	**HPV+**
I vs II	<0.001	0.79	<0.001	0.38
II vs III	0.10	0.28	<0.05	0.16
III vs IVA	<0.01	0.47	<0.001	0.35
IVA vs IVB	<0.05	0.14	<0.05	<0.01