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The prognostic impact of pathologic lymph nodes in HPV-positive oropharyngeal cancers

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ABSTRACT

Purpose: Recent pathologic staging of HPV-positive oropharyngeal squamous cell carcinomas (OPSCC) is solely dependent on number of pathologic nodes. Using a large dataset, we aimed to understand how increase in pathologic lymph nodes (LN) associated with overall survival.

Materials and methods: National Cancer Database was queried for HPV-positive OPSCC patients undergoing primary surgery with LN dissection between 2010 and 2013. Kaplan-Meier, univariate and multivariate Cox models were used to evaluate overall survival. Interaction between nodal status and radiotherapy was examined.

Results: Implications of pathologic LN on overall survival differed according to receipt of post-operative radiotherapy ($p\text{-value}_{interaction} = 0.008$). In patients who did not receive adjuvant radiotherapy, there were no significant differences in risk of death from 0 to 2 pathologic nodes (adjusted HR (aHR) 0.92, 95%CI 0.61–1.4). However, risk increased by 18% on average with each additional LN thereafter (aHR 1.18, 95%CI 1.1–1.27). Among radiotherapy patients, after adjusting for other variables, patients with 1 pathologic LN had 70% lower risk of death than those with 0 pathologic LN (aHR 0.30, 95%CI 0.14–0.64). Thereafter, risk increased on average by 7% with each additional LN (aHR 1.07, 95%CI 1–1.14).

Conclusion: The prognostic impact of pathologic nodes in resected HPV-positive OPSCC differs by receipt of radiotherapy, with better outcomes in post-operative radiotherapy treated patients with one pathologic LN than none. These findings suggest that LN involvement may improve anti-tumor immune responses following radiotherapy, or result in earlier detection and treatment of disease. These results merit further studies to corroborate these findings and establish the underlying mechanism.

Introduction

Human papillomavirus-driven oropharynx squamous cell cancer (OPSCC) is a distinct clinical entity with improved prognosis when compared to head and neck squamous cell carcinomas (HNSCC) unrelated to HPV [1,2]. Recognition of the improved prognosis and distinct characteristics has permitted us to reconsider the prognostic impact of traditional risk factors for head and neck cancers [3]. For example, the implication of extranodal extension (ENE), traditionally a high-risk pathologic factor, is being reconsidered for HPV-positive OPSCC [4]. Indeed, AJCC staging, which had not radically changed in prior iterations, has undergone a transformation in its most recent update. For the first time, HPV-positive cancers have their own staging [4]. Whereas prior schema accounted for size, number and laterality of clinically involved lymph nodes, the most recent AJCC clinical criteria for HPV-positive cancers only accounts for size and laterality. However, in pathologic staging, number of pathologic lymph nodes is the only determinant of risk [4,5]. Of note, previous studies suggest patients with five or more pathologic nodes have worse survival [4,6,7].

The prognostic impact of each additional lymph node on survival has not been explored in HPV-OPSCC yet, although similar data exist for HPV-unrelated head and neck cancers [8,9]. Using a large national database, this study aims to understand how the number of pathologic lymph nodes affects survival in HPV-positive OPSCC patient.

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Table 1
Baseline characteristics of the study population.

		Overall	No Radiotherapy	With Radiotherapy	
		N = 2611	N = 783	N = 1828	p-value
Age	Median (range)	58 (27–90)	59 (31–90)	57 (27–90)	< 0.001
Categorical Variables Count (%)					
Sex	Male	2191 (83.91)	644 (82.25)	1547 (84.63)	0.129
	Female	420 (16.09)	139 (17.75)	281 (15.37)	
Race	White	2472 (95.41)	733 (94.70)	1739 (95.71)	0.525
	Black	77 (2.97)	27 (3.49)	50 (2.75)	
	Other	42 (1.62)	14 (1.81)	28 (2.54)	
	Unknown	20	9	11	
Income	< $48,000	789 (30.35)	266 (34.1)	523 (28.74)	0.006
	> =$48,000	1811 (69.65)	514 (65.9)	1297 (71.26)	
	Unknown	11	3	8	
Residence	Metropolitan	2162 (84.55)	655 (85.18)	1507 (84.28)	0.567
	Urban/Rural	395 (15.45)	114 (14.82)	281 (15.72)	
	Unknown	54	14	40	
Charlson-Deyo Score	0	2137 (81.85)	614(78.42)	1523 (83.32)	0.003
	≥1	474 (18.15)	169 (21.58)	305 (16.68)	
Clinical T stage	≤T2*	2381 (91.82)	717 (92.16)	1664 (91.68)	0.683
	T3,T4	212 (8.18)	61 (7.84)	151 (8.32)	
	Unknown	18	5	13	
Clinical N stage	N0	386 (15.61)	237 (31.94)	149 (8.61)	< 0.001
	N1	645 (26.08)	195 (26.28)	450 (26.00)	
	N2	1394 (56.37)	298 (40.16)	1096 (63.32)	
	N3	48 (1.94)	12 (1.62)	36 (2.08)	
	Unknown	138	41	97	
Pathological N stage	N0	295 (11.75)	215 (28.44)	80 (4.56)	< 0.001
	N1	419 (16.69)	157 (20.77)	262 (14.93)	
	N2	1725 (68.70)	371 (49.07)	1354 (77.15)	
	N3	72 (2.87)	13 (1.72)	59 (3.36)	
	Unknown	100	27	73	
Margins	Negative	1945 (79.32)	669 (87.91)	1276 (75.46)	< 0.001
	Positive	507 (20.68)	92 (12.09)	415 (24.54)	
	Unknown	159	22	137	
No. pathologic LN	Median (range)	2 (0–19)	1 (0–19)	2 (0–19)	< 0.001
No. LN examined	Median (range)	30 (5–90)	31 (5–90)	30 (5–90)	0.107
Size of LN	≤4 cm	1730 (72.87)	585 (81.93)	1145 (68.98)	< 0.001
	> 4 cm	644 (27.13)	129 (18.07)	515 (31.02)	
	Unknown	237	69	168	
Lower LN involvement	No	1996 (93.27)	631 (95.17)	1365 (92.42)	0.019
	Yes	144 (6.73)	32 (4.83)	112 (7.58)	
	Unknown	471	120	351	
ENE	No	1532 (62.33)	558 (74.3)	974 (57.06)	< 0.001
	Yes	926 (37.67)	193 (25.7)	733 (42.94)	
	Unknown	153	32	121	

* Includes T0, TX, TIS, T1, T2.

Material and Methods

Data source

The National Cancer Database (NCDB), a joint project by the American Cancer Society and the Commission on Cancer of the American College of Surgeons, was queried for head and neck cancers diagnosed between 2004 and 2014. The database includes approximately 70% of cancers from 1500 hospitals across the United States in the form of de-identified data. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator. This study was deemed exempt from review by the Johns Hopkins Medicine Institutional Review Board as it does not involve Human Subjects Research.

Patient population

Adults aged 18 years or older who underwent primary surgical resection with neck dissection for OPSCC were included. OPSCC were captured using the following International Classification of Diseases third edition (ICD-O-3) topography codes C01.9, C02.4, C05.1, C05.2, C09.0, C09.1, C9.8-C10.0, C10.2, C10.3, C10.8, C10.9 and histology codes 8052, 8070–8076, 8078, 8083, 8084. Patients with less than 5 lymph nodes examined, receipt of neoadjuvant therapy, distant metastasis at presentation, greater than 20 pathologic nodes, or nodes measuring > 10 cm were excluded from anlaysis. HPV positivity was defined as those with high-risk HPV, including HPV16 and HPV18. Receipt of radiotherapy was defined as post-operative radiotherapy within 120 days of diagnosis. Analysis was limited to those diagnosed between 2010 and 2013, since HPV testing was limited prior to those years.

Statistical analysis

Baseline characteristics were summarized as median and range for continuous variables, and frequency and percentage for categorical variables. Overall survival was defined as time from diagnosis to death from any cause or loss to follow-up.

After detecting a paradoxical similarity in survival among patients with and without pathologic nodes, the impact of adjuvant radiotherapy was assessed by the interaction between radiotherapy and nodes. To do so, an inverse probability-score weighted (IPSW) Cox proportional hazard model was constructed, truncating IPSW at 95th percentile. Variables included in the propensity score model for the probability of receiving radiotherapy were age at diagnosis, gender,

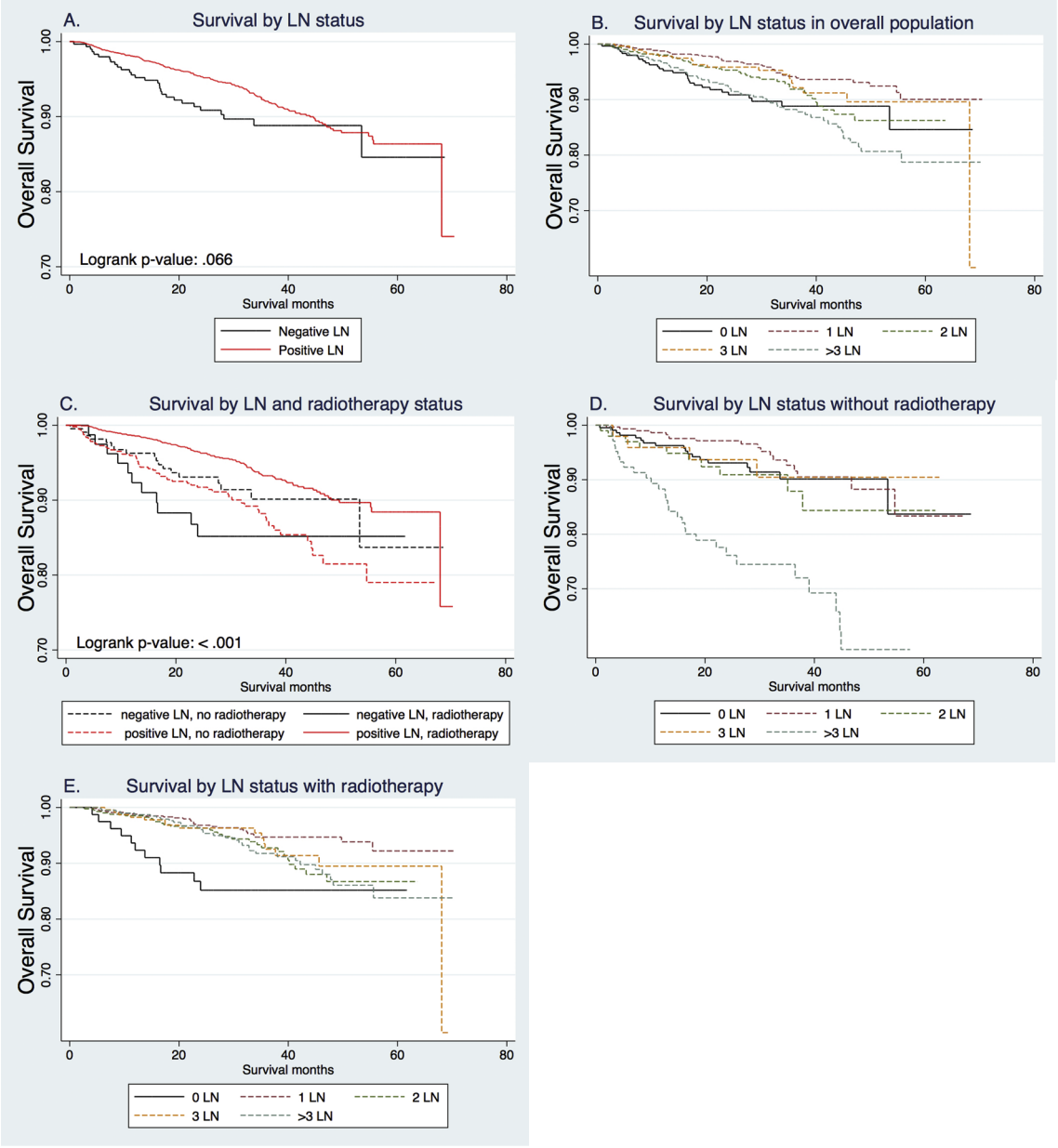

Fig. 1. The effect of number of pathologic lymph nodes on overall survival. Kaplan Meier survival curves comparing (a) the presence and absence of any pathologic nodes among all participants; (b) different number of positive lymph nodes in overall population; (c) the presence and absence of any pathologic nodes among all participants by receipt of adjuvant radiotherapy (Logrank p-value for difference in survival between those with and without pathologic nodes in non-radiated group is 0.269, while that of the radiated group is 0.004); (d-e) different number of positive lymph nodes in (d) patients not receiving post-operative radiotherapy and (e) those receiving post-operative radiotherapy.

race, Charlson-Deyo comorbidity score, AJCC 7th edition clinical T stage, margin status, number of lymph nodes examined, number of pathologic nodes, size of lymph nodes, lower lymph node involvement, and ENE. After finding statistically significant interaction between number of pathologic nodes and radiotherapy, all subsequent analyses were stratified by receipt of radiotherapy. Differences in baseline characteristics between groups with and without radiotherapy were compared via Wilcoxon rank-sum and Chi-squared tests for continuous and categorical variables, respectively.

To assess the association of pathologic nodes and lymph nodes examined with overall survival (OS), accounting for their nonlinear relationship, we first fit a univariate Cox proportional hazard model with restricted cubic spline (rcs) function for number of pathologic nodes and number of lymph nodes examined, respectively. To balance the smoothness and accuracy of the model fitting, minimum number of knots within a 4 unit difference from the lowest AIC was used [10]. For number of lymph nodes examined, rcs had 3 knots at 10th, 50th, and 90th percentiles in both radiotherapy and non-radiotherapy groups [11]. For number of pathologic nodes, four knots were used (at 0th, 10th, 50th, and 90th percentiles) in the radiotherapy group, and three knots (at 10th, 50th, and 90th percentiles) in the group without post-operative radiotherapy. To facilitate the interpretability of results, piecewise linear function of number of pathologic nodes and number of lymph nodes examined was constructed in our multivariable Cox models, using the break-points obtained from the change point detection method based on the rcs function [12]. The multivariable model of pathologic nodes was adjusted for age, Charlson-Deyo comorbidity score, T stage, surgical margins, number of LN examined, size of largest LN and ENE.

Statistical analyses were performed using IBM SPSS Statistics

package version 24 and Stata version 12, R package (Version 3.4.2; twang, survey, rms, SiZer). All tests were two-sided and considered significant if $p < 0.05$.

Results

Patient cohort

Inclusion criteria were met by 2611 patients (Supplementary Fig. 1). Baseline characteristics are summarized in Table 1. Median age at diagnosis was 58 (range: 27–90), and the majority were white (94.68%), male (83.91%), of higher income (70%), and resided in a metropolitan area (85%) with fewer comorbidities (Charlson-Deyo Score 0, 82%). The majority had a smaller primary tumor at presentation (T2 or less, 91.82%) and more advanced AJCC 7th edition clinical N stage (N2 or greater). Only 6.7% had clinical or pathologic evidence of lower cervical lymph node involvement at presentation. After surgery, 79.32% had negative surgical margins. The median number of lymph nodes examined was 30 (interquartile range (IQR) 20–43), with a median of 2 pathologic nodes (IQR 1–3). The largest lymph node was 4 cm or smaller among the majority (72.87%). Approximately 38% had ENE reported. In this study population, 70% received adjuvant radiotherapy (within 120 days of surgery) and 44% received both radiotherapy and chemotherapy. Patients who received adjuvant therapy differed from those who did not by age, income, co-morbidities, clinical and pathologic N stage, lower level lymphadenopathy, number of pathologic lymph nodes, size of largest lymph nodes and ENE (p-value < 0.05 for each, Table 1).

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.oraloncology.2018.12.005.

Survival analysis

Median follow-up for the study population was 30.36 months. Interestingly, overall survival was better among those with present compared to absent pathologic lymph nodes, a factor historically associated with worse prognosis (Logrank p-value 0.066, Fig. 1A; B). This was surprising and therefore we evaluated whether this was related to treatment. Indeed, among patients who did not receive radiotherapy, survival did not show significant correlation with pathologic lymph node status, but among those who did receive radiotherapy, the presence of pathologic lymph nodes was associated with significantly improved survival (Logrank p-value$_{overall}$ < 0.001 p-value$_{non\text{-}radiated}$ 0.269 p-value$_{radiated}$ 0.004, Fig. 1C). Given the differences in the relationship between lymph nodes and receipt of radiotherapy, we evaluated whether there was statistical interaction between number of pathologic lymph nodes and receipt of radiotherapy. After adjustment for baseline characteristics by IPSW, there was a statistically significant interaction (p-value$_{interaction}$ 0.008). Therefore, survival analyses were stratified by receipt of radiotherapy (Fig. 1D and E).

Primary surgical therapy without adjuvant radiotherapy

In univariate analysis, among patients who did not receive radiotherapy (Table 2), factors associated with significantly worse overall survival included: older age (HR 1.02, 95%CI 1.00–1.05, p-value 0.03), more advanced T stage (HR 3.32, 95%CI 1.89–5.83, p-value < 0.001), positive surgical margins (HR 2.50, 95%CI 1.47–4.25, p-value 0.001), lymph node larger than 4 cm (HR 2.11, 95%CI 1.28–3.49, p-value 0.003), lower lymph node involvement (HR 3.20, 95%CI 1.58–6.47, p-value 0.001), and ENE (HR 2.41, 95%CI 1.53–3.8, p-value < 0.001).

The effect of number of lymph nodes examined and number of pathologic lymph nodes was next evaluated using restricted cubic spline model to determine change points (Fig. 2), followed by piecewise linear spline Cox regression. Among those who did not receive radiotherapy, change point at 2 pathologic lymph nodes was identified. When considering the prognostic effect of each additional pathologic lymph node, risk of death was stable for zero to 2 lymph nodes, suggesting that risk of death was similar for patients with either 0, 1 or 2 pathologic lymph nodes (HR 1.10, 95%CI 0.79–1.53, p-value 0.562). However, with each additional pathologic lymph node after 2, risk of death significantly increased by 22% (HR 1.22, 95%CI 1.16–1.29, p-value < 0.001). On multivariate analysis, risk of death significantly increased per additional pathologic lymph node > 2 (adjusted HR (aHR) 1.18, 95%CI 1.10–1.27, p-value < 0.001). Other independent prognostic factors in non-radiated patients included advanced T stage (aHR 2.93, 95%CI 1.50–5.73, p-value 0.002), positive margins (aHR 2, 95%CI 1.11–3.58, p-value 0.02), and lymph node size (aHR 2.14, 95%CI 1.20–3.81, p-value 0.01).

Table 2
Univariate and multivariate associations of clinical characteristics and overall survival among patients who did not receive radiation therapy.

	HR (95% CI)	p-value	adjusted HR (95% CI)	p-value
Age	1.02 (1.00–1.05)	0.030	1.01 (0.99–1.03)	0.354
Sex			–	
Male	1.0			
Female	1.04 (0.59–1.82)	0.894		
Race		0.346	–	
White	1.0			
Black	1.17 (0.37–3.73)	0.784		
Other	2.66 (0.84–8.47)	0.098		
Income			–	
< $48,000	1.0			
> =$48,000	0.61 (0.39–0.95)	0.030		
Residence			–	
Metropolitan	1.0			
Urban/Rural	0.91 (0.48–1.73)	0.782		
Charlson-Deyo Score				
0	1.0	0.274	1.0	
≥1	1.32 (0.80–2.18)		1.04 (0.59–1.84)	0.891
Clinical T stage				
≤T2*	1.0		1.0	
T3,T4	3.32 (1.89–5.83)	< 0.001	2.93 (1.50–5.73)	0.002
Margins				
Negative	1.0		1.0	
Positive	2.50 (1.47–4.25)	0.001	2.00 (1.11–3.58)	0.020
Number of pathologic LN§				
0–2	1.10 (0.79–1.53)	0.562	0.92 (0.61–1.40)	0.698
> 2	1.22 (1.16–1.29)	< 0.001	1.18 (1.10–1.27)	< 0.001
Number of LN examined§				
0–35	0.99 (0.96–1.01)	0.328	0.99 (0.95–1.02)	0.353
> 35	1.01 (0.99–1.03)	0.602	0.99 (0.97–1.02)	0.673
Size of LN				
< 4 cm	1.0		1.0	
> 4 cm	2.11 (1.28–3.49)	0.003	2.14 (1.20–3.81)	0.010
Lower LN involvement			–	
No	1.0			
Yes	3.20 (1.58–6.47)	0.001		
ENE				
No	1.0		1.0	
Yes	2.41(1.53–3.80)	< 0.001	1.27(0.67–2.42)	0.464

§ HR reported as change in HR per additional LN.
* Includes T0, TX, TIS, T1, T2.

Primary surgical therapy with adjuvant radiotherapy

Among patients who received radiotherapy, univariate factors associated with worse overall survival included older age (HR 1.04, 95%CI 1.02–1.06, p-value < 0.001), lower income (HR 0.61, 95%CI 0.42–0.88, p-value 0.009), urban/rural residence (HR 1.72, 95%CI

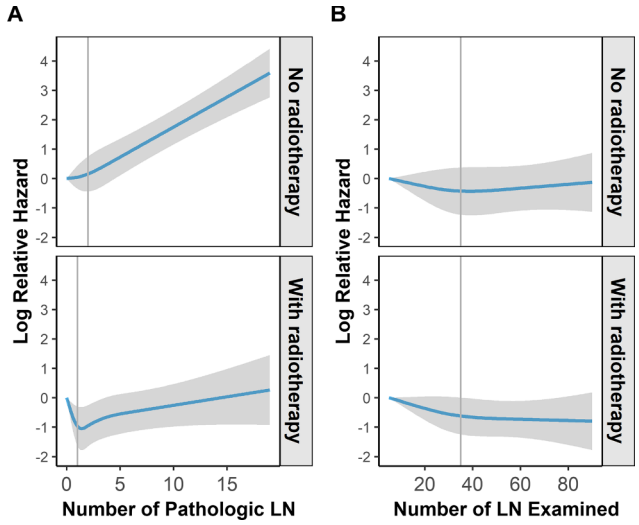

Fig. 2. Stratified graph of unadjusted log relative hazard on overall survival by (**A**) number of pathologic lymph nodes with 0 as a reference value and (**B**) number of lymph nodes examined with 5 as a reference value. For pathologic lymph nodes (LN), change points were determined at 2 LN and 1 LN in the non-irradiated and irradiated groups, respectively. For number of LN examined, change point was found at 35 LN in both groups.

1.12–2.65, p-value 0.014), Charlson Deyo comorbidity index of 1 or greater (HR 2.08, 95%CI 1.39–3.1, p-value < 0.001), more advanced T stage (HR 2.98, 95%CI 1.87–4.75, p-value < 0.001), lower lymph node involvement (HR 1.88, 95%CI 1.02–3.45, p-value 0.042), and ENE (HR 1.67, 95%CI 1.15–2.44, p-value 0.008). Among those who received radiotherapy, change point at 1 for pathologic lymph node was identified. The presence of one pathologic lymph node reduced the risk of death by 76% compared to zero lymph node (HR 0.34, 95% CI 0.18–0.65, p-value < 0.001). The risk of death for each additional lymph node after the first increased on average by 8% (HR 1.08, 95%CI 1.03–1.14, p-value 0.003). On multivariate analysis, risk of death increased with age (aHR 1.04, 95%CI 1.01–1.06, p-value 0.002), comorbid conditions (aHR 1.86, 95%CI 1.17–2.95, p-value 0.008), higher T stage (aHR 2.24, 95%CI 1.30–3.88, p-value 0.004), and ENE (aHR 1.9, 95%CI 1.18–3.06, p-value 0.008). The presence of one pathologic node was independently associated with a 70% reduction in risk of death (aHR 0.30, 95%CI 0.14–0.64, p-value 0.002). For each additional pathologic lymph node risk of death increased by 7% (aHR 1.07, 95%CI 1–1.14, p-value 0.039; Table 3).

With regard to the number of lymph nodes examined, the change point was 35 in both non-radiated and radiated groups. Of note, risk of death was not significantly associated with number of lymph node examined in either group (Tables 2 and 3).

Discussion

In patients with HPV-positive OPSCC undergoing primary surgical resection without adjuvant therapy, risk of death was similar in those with 0–2 pathologic lymph nodes, but increased by 18% for each additional node thereafter. This is consistent with general oncologic principles that with increased cervical metastases, prognosis is reduced and with survival trends in squamous cell carcinomas of the larynx, hypopharynx and oral cavity, primarily HPV-negative sites [8,9,13]. By contrast, in the adjuvant radiotherapy group, patients with one pathologic lymph node had a 70% lower risk of death than those with no pathologic lymph nodes (aHR 0.30, 95% CI: 0.14–0.64), and beyond one lymph node, risk of death increased on average by 7% with each additional pathologic lymph node (aHR 1.07, 95% CI: 1.00–1.14), after accounting for other prognostic factors. While these findings require further validation, in this specific patient population, they challenge our accepted general oncologic principle that prognosis worsens with increasing number of pathologic lymph nodes [13].

Recent pathologic staging guidelines indicate that risk of death significantly increased for HPV positive OPSCC patients with 5 or more pathologic lymph nodes [7]. The analysis by Haughey et al was multi-institutional and comprised of heterogeneously treated patients, analogous to the present analysis. In concordance with our study, they found patients with AJCC N0 pathologic staging, indicating no nodal metastasis, to have worse survival than those with N1 pathologic staging [7].

In another paper, Sinha et al found best survival in those with 0 pathologic nodes [6]. However, their analysis did not stratify by receipt of radiotherapy, used disease-specific survival rather than overall survival, and had a smaller sample size. It is unlikely that therapy alone sufficiently explains the divergent results, as most patients received radiotherapy in that study. The relative rarity of HPV positive tumors with no nodal metastases means present study, which benefits from a much larger sample size, offers more insight into this population and allows studying whether the prognostic effect of nodal status depends on adjuvant radiotherapy (p-value for interaction of radiotherapy and lymph nodes positivity = 0.008). Furthermore, using overall survival in lieu of disease-specific survival cannot be the sole explanation, as previous similar studies using overall survival from NCDB on other sites of head and neck cancers found results consistent with the general oncologic principles [8,9]. This suggests that our remarkable findings are likely due to the unique site and viral pathology of oropharyngeal cancers.

Interestingly, other prognostic factors besides lymph nodes are also dependent on therapy. In the absence of radiation, size of largest lymph node, size of primary tumor and positive margins are independent and significant indicators of poor survival, while ENE is not. In patients receiving radiotherapy, size of primary tumor and ENE are associated with survival, while size of lymph node and margins are not. Taken together, this indicates that without radiotherapy, size of lymph node and positive margins remain prognostically important. However, adjuvant treatment offsets them, and makes ENE prognostically relevant. Hence, there is the need to carefully account for radiotherapy in future analyses of risk stratification.

What may explain the results observed in this study? Characteristic of HPV-positive oropharyngeal cancers is presentation with nodal disease despite small primary tumors [1,14,15]. This has been thought to be a reflection of these tumors arising within lymphoid tissue, which can be considered another lymph node. HPV-positive tumors are immune-rich [16–18] with high tumor infiltrating lymphocytes (TILS), one of the features that may drive the observed improved prognosis of these patients. While the minority of patients present without evidence of lymph node involvement (11% in this study), the finding that their survival is worse when treated with radiotherapy is unexpected and may be related to reduced endogenous immune response to primary tumor. However, in light of all the scientific and therapeutic advances in cancer immunology and immunotherapy, including for oropharyngeal cancer, one can develop a plausible and testable hypothesis to explain our findings. The success of immunotherapy is due in significant part to activation of tumor-specific T cells [19]. Radiation to tumors has been shown in animal models to release tumor antigens allowing them to be more efficiently presented to T cells in tumor-draining lymph nodes [20]. The immune system may be more capable of recognizing and reacting to tumor in lymph node rather than primary site. It is thus quite possible that the presence of at least a limited number of metastatic foci in tumor draining lymph nodes can itself result in expansion of a pool of tumor specific T cells that are “primed” for further activation upon post-operative radiation when there is residual tumor in the radiation field. This additive or synergistic immune priming effect of lymph node metastases and radiation could help prevent relapse from minimal residual disease and improve ultimate outcome.

Additionally, as asymptomatic disease at the primary site

Table 3
Univariate and multivariate associations of clinical characteristics and overall survival among patients who received radiation therapy.

	HR (95% CI)	p-value	adjusted HR (95% CI)	p-value
Age	1.04 (1.02–1.06)	< 0.001	1.04 (1.01–1.06)	0.002
Sex			–	
Male	1.0			
Female	1.09 (0.67–1.79)	0.724	–	
Race		0.342		
White	1.0			
Black	0.30 (0.04–2.18)	0.237		
Other	1.02 (0.25–4.15)	0.980		
Income			–	
< $48,000	1.0			
> =$48,000	0.61 (0.42–0.88)	0.009		
Residence			–	
Metropolitan	1.0			
Urban/Rural	1.72 (1.12–2.65)	0.014		
Charlson-Deyo Score				
0	1.0		1.0	
≥1	2.08 (1.39–3.10)	< 0.001	1.86 (1.17–2.95)	0.008
Clinical T stage				
≤T2*	1.0		1.0	
T3,T4	2.98 (1.87–4.75)	< 0.001	2.24 (1.30–3.88)	0.004
Margins				
Negative	1.0		1.0	
Positive	1.29 (0.85–1.95)	0.238	1.12 (0.70–1.78)	0.645
Number of pathologic LN§				
0–1	0.34 (0.18–0.65)	0.001	0.30 (0.14–0.64)	0.002
> 1	1.08 (1.03–1.14)	0.003	1.07 (1–1.14)	0.039
Number of LN examined§				
0–35	0.98 (0.96–1.00)	0.087	0.98 (0.95–1.01)	0.162
> 35	1.00 (0.98–1.02)	0.670	0.99 (0.97–1.01)	0.351
Size of LN				
< 4 cm	1.0		1.0	
> 4 cm	0.76 (0.49–1.20)	0.240	0.88 (0.54–1.44)	0.620
Lower LN involvement			–	
No	1.0			
Yes	1.88 (1.02–3.45)	0.042		
ENE				
No	1.0		1.0	
Yes	1.67 (1.15–2.44)	0.008	1.9 (1.18–3.06)	0.008
Post-op chemo w/in 120 d			–	
No	1.0			
Yes	1.22 (0.82–1.80)	0.322		

§ HR reported as change in HR per additional LN.
* Includes T0, TX, TIS, T1, T2.

frequently remains unnoticed, the presence of clinically evident nodal disease may hasten patient lag time to seek medical attention and undergo definitive therapy, which possibly contributed to improved survival outcome in this cohort. In fact, our data show that 10% of patients with lower T stage (≤T2) as compared to 23% of patients with stage T3/T4 tumors presented with nodal metastasis.

The implications of this paper are that staging and prognostic discussions of nodal disease should be done in the context of the receipt of radiotherapy or not. Additionally, the risk factors driving prognosis differ by receipt of radiotherapy. In HPV-positive disease in its purest form, ENE may not be relevant, while it is in radiated tumors. The findings caution against generalizing conclusions regarding stage and prognosis from heterogeneous datasets as prognosis differs by receipt of adjuvant therapy. Understanding the clinical significance of pathologic lymph nodes and other risk factors in the context of therapy is important as the field embarks on therapeutic changes specific to HPV-positive patients.

There are several limitations to the present study primarily related to its retrospective nature such as heterogeneity between institutions, in addition to the quality and type of variables in the NCDB. For instance, variables such as smoking, alcohol consumption, and recurrence are not included in the database. Furthermore, the means of assessing HPV positivity (p16 immunohistochemistry, in-situ hybridization or polymerase chain reaction for HPV DNA) may differ between patients. Certain treatment details and the reasons affecting the clinical decision of giving radiotherapy or not may also be missing, which may result in unobserved confounders that are not addressed in the analysis. Indeed, patients with no pathologic nodes who received radiotherapy were more likely to present at more advanced T stages than patients with positive nodes who were assigned to radiotherapy (data not shown). The database captures all-cause mortality rather than disease-specific deaths, which may not accurately reflect whether mortality was disease-related. Moreover, it does not report other measures of outcome such as progression-free survival, local or regional control. Additional prospective studies should be conducted to corroborate our findings and establish an explanatory mechanism to these observations.

Conclusion

To our knowledge, this is the first study demonstrating differential survival benefit in HPV positive OPSCC with metastatic regional lymph nodes, after stratifying by adjuvant radiotherapy. A number of factors may explain these, including tumor-specific immune responses as well as treatment escalation or earlier treatment initiation for those presenting with nodal disease. Further studies are needed to elucidate the biology of these findings.

Conflict of interest

None declared.

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