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The prognostic effect of anatomic subsite in HPV-positive oropharyngeal squamous cell carcinoma

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A B S T R A C T

Background: Since most HPV-associated disease occurs in the tonsillar-related areas (TRA) – palatine and lingual tonsils, the effect of HPV on survival in non-tonsillar oropharyngeal subsites (nTRA) is not well established. The objective of this study was to use a large population-based cohort to investigate the survival impact of HPV in nTRA subsites versus TRA subsites.

Methods: This SEER database study was conducted by stratifying the HPV-positive oropharyngeal cancer cohort into two primary groups, TRA and nTRA.

Results: HPV-positive squamous cell cancer was significantly more common in TRAs (73%) compared to nTRAs (31.2%, $p < 0.001$). After controlling for age, treatment, stage, race, and income, patients with HPV-positive disease in nTRAs had a worse cause-specific survival (CSS) than individuals with HPV-positive disease in TRAs (HR = 2.16, 95% CI 1.20–3.86, $p = 0.01$).

Conclusion: Patients with HPV-positive OPSCC in nTRAs had poorer survival outcomes compared to patients with HPV-positive OPSCC in TRAs.

1. Introduction

Human Papillomavirus (HPV)-positive oropharyngeal squamous cell carcinoma (OPSCC) has become an increasingly important disease entity in head and neck oncology. Though the overall incidence of head and neck cancers has decreased in recent years due to decreased rates of smoking, the incidence of HPV-positive OPSCC is increasing in the United States [1]. The typical OPSCC patient has changed from one that is older with significant smoking and alcohol history, to one that is younger with history of HPV infection. According to the Centers for Disease Control and Prevention (CDC), an estimated 3100 new cases of HPV-positive OPSCC are diagnosed in women and 12,600 in men each year [2]. This changing epidemiologic landscape has contributed to our knowledge about the underlying biology and clinical behavior of HPV-positive OPSCC, which in turn has led to significant changes in the practice of head and neck oncology, such as an updated oropharyngeal staging scheme in the 8th edition of AJCC [3]. Ongoing research will likely lead to further changes, including de-intensified treatment regimens and novel methods of disease detection [4].

The prevalence of HPV appears to be different across the four major subsites (soft palate, tonsillar fossa and pillars, base of tongue, posterior and lateral pharyngeal wall) of the oropharynx, occurring most commonly in the lingual tonsillar tissue of the base of tongue and the palatine tonsils. In a recent systematic review and meta-analysis, Haeggblom et al. demonstrated a marked difference in prevalence between the anatomic regions of the oropharynx (56% HPV prevalence in base of tongue/palatine tonsils and 19% in other sites) [5]. This difference in prevalence may be secondary to a fundamental histologic difference between these subsites [5–7]. In the tonsillar regions, the presence of highly specialized crypt lymphoepithelium has been shown to be a conducive environment for HPV-driven tumorigenesis. Conversely, the oral cavity and non-tonsillar areas in the oropharynx are lined by uninterrupted stratified squamous epithelium, which might serve as a barrier to HPV infection [6,8].

Given that the histopathological origin of SCCs arising from tonsillar tissue (largely non-keratinizing, and basaloid in appearance) has been observed to be different from SCCs arising from non-tonsillar tissue (largely keratinizing, and non-basaloid in appearance) [6], it is plausible that tumors arising from these distinct anatomical regions may represent different clinical and prognostic entities. To our knowledge, there have been no studies examining the prognostic differences between HPV-positive OPSCC in tonsillar related areas (TRA) versus non-tonsillar related areas (nTRA). Such a prognostic difference could have important clinical implications, as HPV-positive OPSCC is currently considered a single disease entity in oncologic practice and clinical trials [3].

In this context, the goals of this study are to examine the prevalence of HPV among the different anatomical subsites in the oropharynx and investigate the differences in survival between HPV-positive OPSCC in TRAs versus nTRAs using a large national cancer database.

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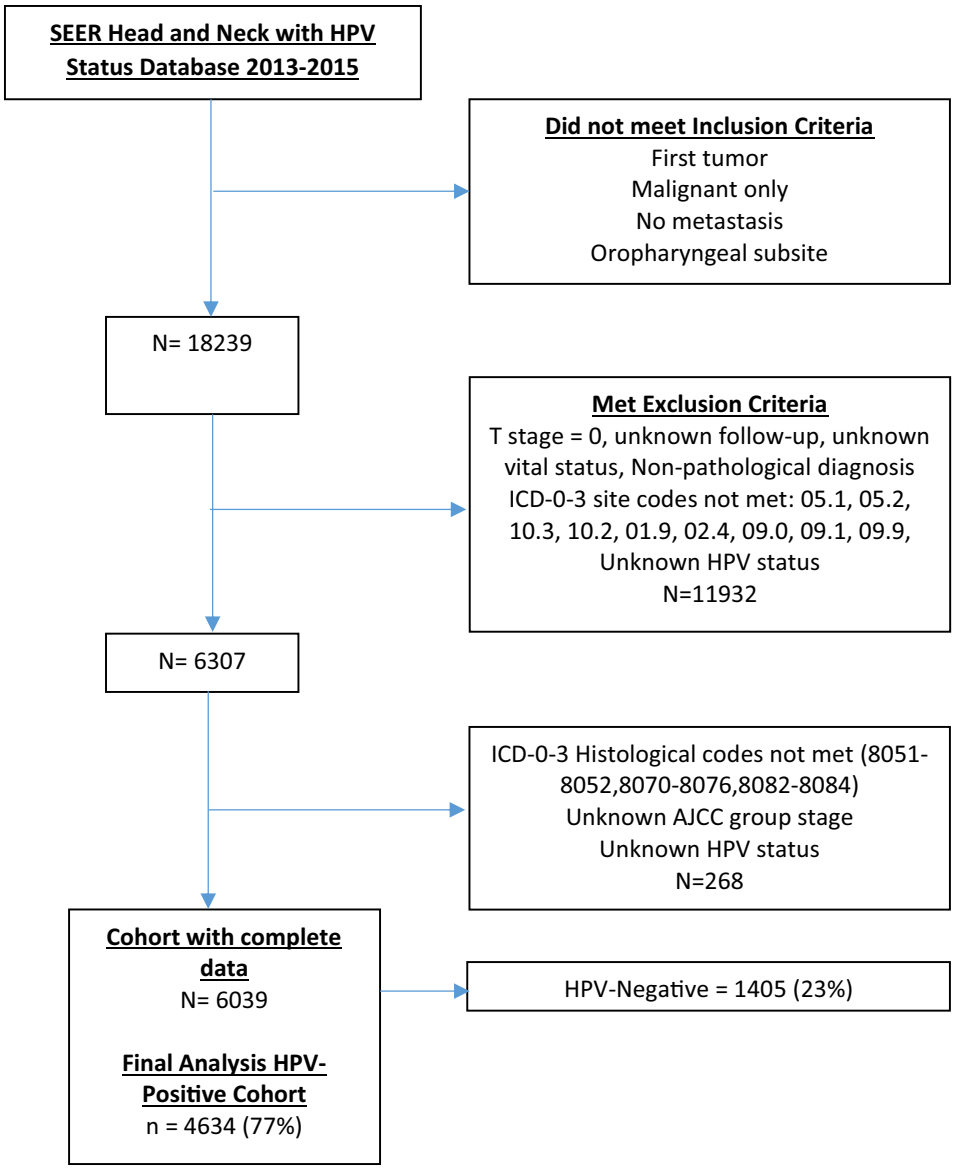

Fig. 1. Flow diagram for cohort selection.

2. Methods

2.1. Data source

The Surveillance, Epidemiology, and End Results (SEER) Database was used to perform a retrospective population-based cohort analysis. The SEER Program of the National Cancer Institute (NCI) is an authoritative source of information on cancer incidence and survival in the United States. The SEER database currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 34.6% of the U.S. population [9]. The '*Head and Neck with HPV Status Database*,' a specialized subset of the SEER database that records the HPV status of patients with head and neck cancer diagnosed between January 1st, 2013 and December 31st 2015, was used. This study was exempt from Institutional Review Board (IRB) review in our institution.

2.2. Patient and variable selection

Patients diagnosed with oropharyngeal cancers were identified using the International Classification of Disease for Oncology, 3rd Edition (ICD−O−3) topography code for the site of origin and histology. Patients were stratified into two primary groups according to ICD−O−3 site codes: (a) tonsillar-related area (TRA), which included ICD-0-3 codes 01.9 Base of Tongue, 02.4 Lingual Tonsil, 09.0 Tonsillar Fossa, 09.1 Tonsillar Pillar, and 09.9 Tonsil not otherwise specified; (b) non-tonsillar-related area (nTRA), which included ICD−O−3 codes 05.1 Soft Palate, 05.2 Uvula, 10.3 Posterior oropharyngeal wall, 10.2 Lateral pharyngeal wall. Other ICD-0-3 codes, such as 10.8 Overlapping lesion of oropharynx, or 10.9 Oropharynx not otherwise specified, were considered to be equivocal for TRA/nTRA, and they were not included in the analysis. Cases were also selected on histology based on ICD-0-3 codes, which included all variant types of OPSCC (8051-8052, 8070-8076, 8082-8084). Patients with a single primary cancer in their lifetime (sequence number = '0'), malignant tumors, non-metastatic disease, and pathologically confirmed diagnoses were included in the study. Exclusion criteria were patients with T0 stage as well as those with unknown stage, variables, vital status, follow-up, and HPV status.

The following variables were included in this study: age, sex, race, AJCC stage (7th Edition), HPV status, subsite (TRA/nTRA), radiation treatment, surgery treatment, income (county median income), and percentage of smokers/county. The SEER database records receipt of

chemotherapy treatment as only 'yes' or 'no/unknown', therefore this variable was not included in the analysis. Of note, HPV subtype and method of HPV detection were unavailable in the SEER database.

2.3. Statistical methods

The primary endpoint was cause-specific survival (CSS), defined as the date of diagnosis to the date of death from cancer. Patients who did not fulfill that criteria at the time of last follow-up were considered censored. The appropriate parametric tests were used to compare clinicopathologic characteristics of patients according to HPV status and to their anatomical subgroup (TRA versus nTRA). The Kaplan-Meier (KM) product limit method was utilized to estimate survival probability. The log-rank test was used to compare survival across each of these grouping variables in the KM analysis. Univariable and multivariable Cox Proportional Hazards (CPH) regression was used to analyze the CSS as a function of the clinical and patients variables listed above. A backwards approach was utilized in the multivariable analysis to select variables for the final model, with a model threshold of $p = 0.05$. Results were considered statistically significant if $p < 0.05$. All statistical analyses were performed in SPSS (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp).

3. Results

3.1. Cohort characteristics

After application of the inclusion and exclusion criteria, there were 6039 patients with OPSCC and known HPV-status (Fig. 1). Among these patients, 4634 (77%) were HPV-positive and 1405 (23%) were HPV negative (Table 1). A total of 5821 (96%) patients had SCC in a TRA and 218 (4%) patients had SCC in an nTRA (Table 1). There was a significant difference in HPV-prevalence between the TRA group (4566/5821, 73%) and the nTRA group (68/218, 31.2%) ($p < 0.001$, Table 1).

HPV-positive patients from both groups (4634) were used for the final survival analysis cohort. Within this cohort, 4064 (87.7%) were males and 570 (12.3%) were female. Mean age was 59.8 years. Most patients were Caucasian (90.9%) and had stage IV disease (75.3%), according to 7th Edition AJCC staging. Regarding treatment, 88.8% of the cohort had radiation therapy and 62.2% underwent surgery. When stratified by oropharyngeal subsite, (Table 2), TRA subsites had a higher proportion of radiation therapy ($p < 0.001$), higher AJCC-7 stage ($p < 0.001$), and more males ($p = 0.005$).

3.2. Survival analysis (CSS)

Survival analysis was performed in all HPV-positive patients. Survival analysis was performed with univariable and multivariable Cox proportional hazards regression. In the univariable model, the following variables were found to be significantly associated with CSS: higher age (HR = 1.06, 95% CI 1.05–1.07, $p < 0.001$), receiving radiation therapy (HR = 0.25, 95% CI 0.20–0.31, $p < 0.001$), receipt of surgical therapy (HR = 0.34, 95% CI 0.27–0.44, $p < 0.001$), stage IV versus I (HR = 3.13, 95% CI 1.17–8.41, $p = 0.02$), other versus black race (HR = 0.49, 95% CI 0.27–0.89, $p = 0.02$), white versus black race (HR = 0.49, 95% CI 0.34–0.89, $p \leq 0.001$), higher income with better CSS (HR = 0.99, 95% CI 0.98–0.99, $p = 0.001$), and nTRa versus TRA (HR = 2.17, 95% CI 1,22–3.86, $p = 0.008$) (Table 3).

In the multivariable model, the following variables were found to be significantly associated with CSS: advanced age at diagnosis (HR = 1.05, 95% CI 1.04–1.06, $p \leq 0.001$), treatment with radiation therapy (HR = 0.19, 95% CI 0.15–0.24, $p \leq 0.001$), treatment with

Table 2
Clinical features and characteristics of the HPV-positive study population stratified by subsite.

Variable	Total[b] (n = 4634)	HPV-positive tonsil related area (TRA)[b] (n = 4566)	HPV-positive non-tonsil-related area (nTRA)[b] (n = 68)	*p*-Value
Age	59.80 (9.29)	59.77 (9.27)	61.85 (10.55)	0.067
Radiation treatment				< 0.001*
No	517 (11.2%)	500 (11.0%)	17 (25.0%)	
Yes	4117 (88.8%)	4066 (89.0%)	51 (75.0%)	
Surgery				0.499
No	2884 (62.2%)	2839 (62.2%)	45 (66.2%)	
Yes	1750 (37.8%)	1727 (37.8%)	23 (33.8%)	
AJCC-7 stage				< 0.001*
I	120 (2.6%)	107 (2.3%)	13 (19.1%)	
II	225 (4.9%)	217 (4.8%)	8 (11.8%)	
III	800 (17.3%)	788 (17.3%)	12 (17.6%)	
IV	3489 (75.3%)	3454 (75.6%)	35 (51.5%)	
% of smokers in county	39.62 (7.17)	39.62 (7.16)	39.74 (7.45)	0.886
Race				0.68
Black	232 (5.0%)	228 (5.0%)	4 (5.9%)	
Other[a]	167 (3.6%)	163 (3.6%)	4 (5.9%)	
Unknown	24 (0.5%)	24 (0.5%)	0 (0.0%)	
White	4211 (90.9%)	4151 (90.9%)	60 (88.2%)	
County income ($10^3)[c]	63.39 (16.28)	63.43 (16.28)	60.82 (15.81)	0.188
Sex				0.005*
Female	570 (12.3%)	554 (12.1%)	16 (23.5%)	
Male	4064 (87.7%)	4012 (87.9%)	52 (76.5%)	

* p values < 0.05 were considered statistically significant.
[a] Other include American Indian, AK Native, Asian, Pacific Islander.
[b] Continuous values are presented as numbers or mean ± SD, categorical variables represented as integers.
[c] Median household income by county.

Table 1
HPV-status stratified by oropharyngeal subsite according to ICD-0-3 site codes.

	Total no.	HPV-positive (%)	HPV-negative (%)	*p*-Value*
Oropharyngeal subsite				< 0.001
Tonsillar Related Area (TRA)	5821	4566 (73%)	1255 (20.1%)	
Base of Tongue, NOS	2473	1883 (76.1%)	590 (23.9%)	
Lingual Tonsil	47	40 (85.1%)	7 (14.9%)	
Tonsillar Fossa	328	236 (72%)	92 (28%)	
Tonsillar Pillar	172	125 (72.7%)	47 (27.3%)	
Tonsil, NOS	2801	2282 (81.5%)	519 (18.5%)	
Non-Tonsillar Related Area (nTRA)	218	68 (31.2%)	150 (68.8%)	
Soft Palate, NOS	115	28 (24.3%)	87 (75.7%)	
Uvula	25	5 (20%)	20 (80%)	
Posterior Oropharyngeal Wall	42	11 (26.2%)	31 (73.8%)	
Lateral Oropharyngeal Wall	36	24 (66.7%)	12 (33.3%)	

* Chi-square test: Between tonsillar and non-tonsillar subsites ($p < 0.001$).

Table 3
Univariable cox regression for cause-specific survival (CSS).

Variable	HR (95% CI)	p-Value
Age at diagnosis	1.06 (1.05–1.07)	< 0.001*
Radiation treatment		
No	1(−)	Reference
Yes	0.25 (0.20–0.31)	< 0.001*
Surgery		
No	1(−)	Reference
Yes	0.34 (0.27–0.44)	< 0.001*
AJCC-7 stage		
I	1(−)	Reference
II	1.27 (0.39–4.11)	0.693
III	2.00 (0.72–5.54)	0.181
IV	3.13 (1.17–8.41)	0.023*
% of smokers/county	1.00 (0.99–1.02)	0.391
Race		
Black	1(−)	Reference
Other[a]	0.49 (0.27–0.89)	0.020*
Unknown	0.29 (0.04–2.12)	0.223
White	0.49 (0.34–0.89)	< 0.001*
County income (10^3)[b]	0.99 (0.98–0.99)	< 0.001*
Sex		
Female	1(−)	Reference
Male	0.83 (0.63–1.10)	0.202
Subsite		
TRA	1(−)	Reference
nTRA	2.17 (1.22–3.86)	0.008*

Abbreviations: HR = hazard ratio; 95% CI = 95% confidence interval.

* p values < 0.05 were considered as candidate variables for multivariable analysis.

[a] Other include American Indian, AK Native, Asian, Pacific Islander, TRA = tonsillar related area, nTRA = non-tonsillar related area.

[b] Median household income by county.

Table 4
Multivariable cox regression for cause-specific survival (CSS).

Variable	HR (95% CI)	p-Value
Age at diagnosis	1.05 (1.04–1.06)	< 0.001*
Radiation treatment		
No	1(−)	Reference
Yes	0.19 (0.15–0.24)	< 0.001*
Surgery		
No	1(−)	Reference
Yes	0.34 (0.26–0.44)	< 0.001*
AJCC-7 stage		
I	1(−)	Reference
II	ns	ns
III	2.10 (1.13–3.91)	0.019*
IV	3.29 (1.85–5.85)	< 0.001*
Race		
Black	1(−)	Reference
Other	ns	ns
Unknown	ns	ns
White	0.64 (0.48–0.86)	0.003*
County income (10^3)[a]	0.99 (0.98–0.99)	< 0.001*
Subsite		
TRA	1(−)	Reference
nTRA	2.16 (1.20–3.86)	0.010*

Abbreviations: HR = hazard ratio; 95% CI = 95% confidence interval.

* p values < 0.05 were considered statistically significant AJCC-7 stage II, other race, and unknown race were not included in the final model, TRA = tonsillar related area, nTRA = non-tonsillar related area; ns = non-significant, $p > 0.05$ in the multivariable model.

[a] Median household income by county.

surgical therapy (HR = 0.34, 95% CI 0.26–0.44, $p \leq 0.001$), stage III versus I (HR = 2.10, 95% CI 1.13–3.91, $p = 0.02$), stage IV versus I (HR = 3.29, 95% CI 1.85–5.85-0.89, $p \leq 0.001$), white race (HR = 0.64, 95% CI 0.48–0.86, $p = 0.003$), lower income (HR = 0.99, 95% CI 0.98–0.99, $p \leq 0.001$), and nTRA compared to TRA (HR = 2.16, 95% CI 1.20–3.86, $p = 0.01$) (Table 4). Finally, the Kaplan–Meier curve demonstrated a significant difference in CSS between the nTRA and TRA subgroups ($p = 0.007$, Fig. 2).

4. Discussion

4.1. Etiologic role of HPV within the oropharynx

HPV has been shown to play an important etiologic and prognostic role in the oropharynx. Within the oropharynx, HPV-positive disease is most common in the base of tongue and palatine tonsils. Similarly, we identified a significant difference in HPV-positive disease between tonsil-related and non-tonsil related areas (73.0% versus 31.2%, respectively, $p < 0.001$). Two recent meta-analyses also support these findings. In analyzing 56 cohorts, Haeggblom et al. concluded that HPV prevalence was significantly higher in the tonsil and base of tongue compared to other pharyngeal subsites wall regardless of HPV detection method [5]. Additionally, Ndiaye et al. found that the global prevalence of HPV in the tonsil and base of tongue was the highest (53.9% and 47.8%, respectively) while the global prevalence of HPV in the soft palate was low at 11.7% [10]. The authors noted that their results could be limited by small numbers as well as the possibility of misclassifying soft palate as palate non-specified, a group that had the third largest prevalence of HPV.

The difference in HPV prevalence among oropharyngeal subsites is likely secondary to the fundamental histologic differences between these regions; the presence of crypts and lymphoid tissue in the palatine and lingual tonsils is postulated to predispose this region to HPV infection and tumorigenesis, whereas other parts of the oropharynx are lined by uninterrupted stratified squamous cell epithelium [11]. Crypts are specialized areas of invaginated epithelium that have 'pockets' of disrupted basement membrane and a porous epithelial-subepithelial interface [11]. This disrupted membrane and increased porosity is one mechanism that enables HPV infection in these sites. The ability of HPV to invade (or infiltrate) sites with specific microanatomic features is also observed in HPV infections of the squamocolumnar junctions (transformation zones) of cervical and anorectal carcinoma [12].

Another mechanism of HPV predilection for this region is hypothesized to be the exploitation of specific immunologic checkpoints. Previous studies have shown a high expression of PD-L1:PD-1 expression in the reticulated tonsillar epithelium, which would serve to diminish cytotoxic T-cell responses to HPV infection, thus conferring an 'immune privileged' advantage to any viral infection [13]. Several studies have also highlighted the potential role of cytokeratin 7 (CK7), a squamocolumnar junctional marker found in the tonsillar crypts, but not in the surface squamous epithelium, and its interaction with HPV oncoprotein E7 [14,15].

In a study by Gelwan investigating OPSCC in nTRAs, most of the tumors were found to be keratinizing (50%), and most of them were found to be negative for p16 (94%) or mRNA ISH (97%). [6] They also observed that the histopathological characteristics of SCCs arising from nTRAs were more similar to SCCs of the oral cavity (OC). The nTRA SCCs in their cohort were often keratinizing, similar to the phenotype exhibited by smoking related SCCs of the OC. In contrast, HPV-positive SCC TRAs were often basaloid in appearance, and mostly non-keratinizing. Further, they also found that the risk factor profile of nTRAs were similar to SCCs of the OC in that the patients had significant alcohol and tobacco history. Due to the small numbers of patients with HPV-positive SCC in nTRA, a survival analysis was not possible with the cohort studied by Gelwan et al. In our study, we were unable to analyze the alcohol and smoking history of patients at the individual-level due to limitations in the database.

Current guidelines for the management and staging of SCCs of the OC make no distinction between HPV-positive OC SCC and HPV-negative OC SCC. This is largely based on data that the prognostic outcomes between those groups are similar [3]. Since preliminary data by

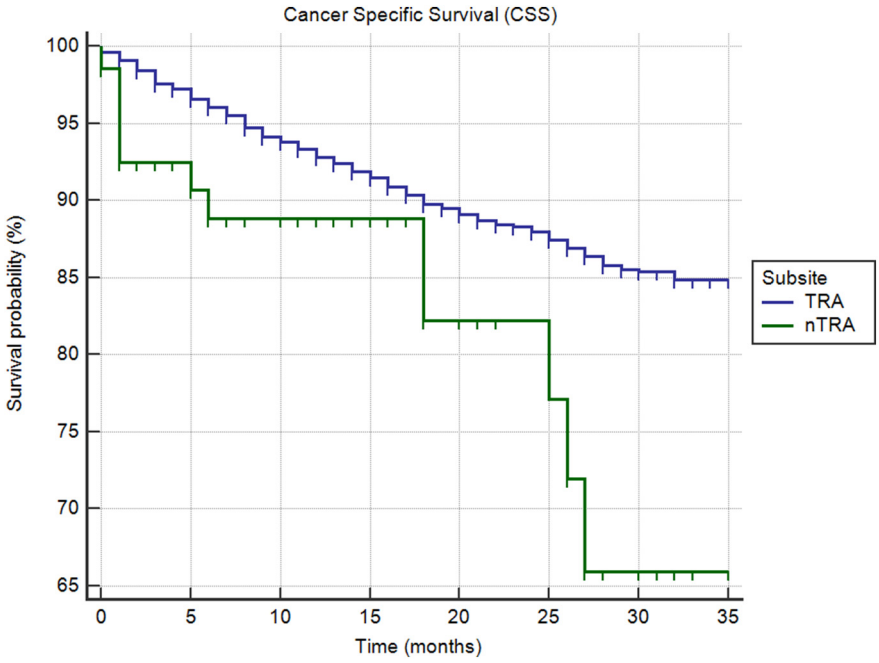

Fig. 2. Kaplan-Meier curve of cause-specific survival (CSS) stratified by anatomic subsite. The difference in survival between groups was significant ($p = 0.007$); tonsil-related area (TRA) (blue line) was associated with better CSS compared to non-tonsil related areas (nTRA) (green line). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

others has shown the similarity in histopathological characteristics between the OP SCCs in nTRA and the OC SCC, it is plausible that their prognostic and clinical behavior may be similar as well. If HPV-positive nTRA OP SCC is eventually shown to be distinct from HPV-positive TRA OP SCC and more similar instead to HPV-positive OC SCC, current treatment and staging guidelines may need to be reconsidered. Currently, in HPV-positive OC SCC, it has been observed that the prognostic impact of HPV is diminished [16]. This might be attributable to several factors such as inactive (non-transcriptionally active) 'passenger' HPV detected in highly sensitive assays (PCR-based), or in false-positive findings where p16 is found to be positive but through HPV-independent carcinogenesis [11]. In contrast to OC SCC, HPV-positive OPSCC has been shown to have a better prognosis than HPV-negative OPSCC, which may be secondary to a more homogenous tumor biology of HPV-related disease compared to the diverse array of mutations induced by traditional carcinogens [17].

While controlling for age at diagnosis, treatment modality, AJCC-7 stage, race, and income, this study found that patients with HPV-positive disease in tonsil-related areas had better survival than individuals with HPV-positive disease in non-tonsil related areas (HR = 2.16, 95% CI 1.20–3.86, $p = 0.01$). The results in this study confirm the preliminary findings previously published in a smaller cohort. In their study on prognostic factors in surgically-treated patients with OPSCC, Gopalaskrishnan et al. found that within a p16-positive subcohort, patients with soft palate cancers were 4.8 ($p = 0.016$) times more likely to die compared to individuals with cancers of the tonsil and base of tongue [18]. The primary limitation of their analysis was the small number of HPV-positive cases (106 patients), with only 8 nTRAs in their cohort.

There are two important considerations regarding the findings of this current analysis. Firstly, this study was not designed to evaluate the difference in survival between patients with HPV-positive and HPV-negative neoplasms in nTRA of the oropharynx. Two recent retrospective studies suggest that HPV does not have an impact on survival in subsites other than the tonsil and base of tongue [19,20]. One of these studies included 61 patients and used p16 immunohistochemistry (IHC) and HPV DNA polymerase chain reaction (PCR) [19], while the other study had 226 patients and used HPV DNA PCR [20].

Secondly, this current study grouped all histologic sites of the tonsil as tonsil-related area in the analysis. However, it has been shown that even within the tonsil, there are differences in HPV prevalence and prognostic value [7,21,22]. In their retrospective study from Sweden with 139 patients, Haeggblom et al. found that HPV-positive disease was more prevalent and had a better disease-specific and overall survival in tonsillar areas with crypts and lymphoid tissue with germinal centers compared to HPV-positive disease in areas of the tonsil with an epithelium similar to the oral cavity. Using a Danish cohort and a similar classification system, Garnaes found that HPV prevalence was higher in tonsillar areas with crypts and lymphoid tissue than tonsillar tissue without these features (77% versus 32%, $p < 0.0001$) [21,22]. Moreover, though both p16 and HPV DNA were associated with improved overall survival in both tonsil histological groups, the authors observed a lower 5-year overall survival for double positive HPV DNA+/p16+ and p16+ tumors with crypts and lymphoid tissue (5-year OS at 61% and 42%) versus those without crypts and lymphoid tissue (5-year OS at 78% and 63%). Given the current classification scheme in our current study, based on anatomic site rather than histologic characteristics, it is possible that the current design underestimated the difference in survival between the anatomic sites of the oropharynx that differ in histologic properties.

Nevertheless, the results in this study indicate that HPV confers better survival in the base of tongue and tonsil relative to the soft palate and pharyngeal walls, the four subsites specified in the AJCC 8th edition. The underlying rationale for this prognostic difference is unclear. The presence of lymphoid tissue in the palatine and lingual tonsil confers distinct immunological function, which may result in a unique interaction between the HPV virus and the immune system. It is also possible that treatment and management practices differ and may contribute to a survival disadvantage to nTRAs, however we detected survival differences after controlling for radiation and surgery in multivariate analyses.

4.2. Strengths and limitations

There are several important limitations in this study. Aside from bias implicit in the retrospective design, the number of patients with HPV-positive disease in non-tonsil-related areas was small. The smaller size of this cohort was due to a large number of overlapping tonsillar lesions which were excluded from the analysis. The dataset this study used is also limited to the 7th edition staging, as the 8th edition was not

available in SEER at time of this writing. Another limitation is the fact that the SEER database does not report information on HPV detection method. In their study on HPV prevalence, Haeggblom et al. found a high degree of statistical heterogeneity between studies that only used one detection method, but found little with combined methods, highlighting the importance of dual-modality testing [5]. Moreover, the correlation between p16 and HPV DNA was shown to be suboptimal in oropharyngeal subsites outside the palatine and lingual tonsils, suggesting that p16 is a poor surrogate marker in non-tonsil-related areas [19]. Given these two findings, it would very helpful to know the HPV detection method in future studies. Lastly, chemotherapy is a mainstay of treatment for advanced stage OPSCC, however, since the SEER database does not distinguish between "no" and "unknown," receipt of chemotherapy was not included in this analysis.

4.3. Clinical implications and future directions

The discipline of head and neck oncology is rapidly changing due to the rising epidemic of HPV-positive OPSCC in the form of a new staging system, expanded vaccination indications, and numerous clinical trials investigating de-intensified treatments for this population. In both the clinical and research setting, HPV-positive OPSCC is considered a single disease entity and is not stratified by anatomic or histologic subsite. Recent studies support a more nuanced paradigm where HPV-positive OPSCC is classified not according to current anatomical boundaries, which are location-based, but according to histopathological partitions along the interface between the crypt epithelium in the tonsils and the surrounding squamous epithelium [5–7].

In summary, this is the largest study to report the survival data between different subsites of HPV-positive OPSCC. Using a large national database, our study confirms preliminary evidence published by others [18], that HPV-positive OPSCC in non-tonsillar areas have poorer survival outcomes compared to tonsillar areas.

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Declaration of Competing Interest

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