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Trimodality therapy for HPV-positive oropharyngeal cancer: A population-based study
Trimodality therapy for HPV + OPC

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ABSTRACT

Background: Although HPV status is a well-established prognostic factor in oropharyngeal squamous cell carcinoma (OPSCC), approximately 20% of HPV-positive patients die from their disease. We therefore sought to ascertain whether there is a benefit to trimodality therapy with surgery among patients with locally advanced (LA) disease receiving chemoradiation.

Methods: The SEER Head and Neck with HPV Status Database identified adult patients with non-metastatic OPSCC between 2013 and 2014 with known HPV status who received chemoradiation as part of definitive treatment. The primary outcome was cancer-specific mortality (CSM) for locally-advanced (LA) (T3-T4, or N2-N3, per AJCC 7) versus early-stage (ES) (T1-T2 and N0-N1) disease, stratified by HPV status. The secondary outcome was overall survival (OS).

Results: Among 2974 patients who met study criteria, 671 patients (22.6%) received upfront surgery (trimodality therapy). In the LA setting, there was a significant reduction in CSM with trimodality therapy compared to chemoradiation alone in HPV-positive (Adjusted Hazard Ratio [AHR] 0.19, 95% Confidence Interval [CI] 0.04–0.80; P = 0.024), but not HPV-negative disease [$P_{interaction}$ = 0.04]. There was no benefit to trimodality therapy for ES disease, regardless of HPV status. There was also an improvement in OS with trimodality therapy for HPV-positive LA patients (AHR = 0.28, p = 0.006, 95% CI = 0.11–0.70). In contrast, trimodality therapy was not associated with improved OS for HPV-negative patients regardless of stage.

Conclusions: HPV status may predict for improved outcomes with surgery/trimodality therapy in LA OPSCC. Our findings support prospective investigations to optimize care for the subset of HPV-positive patients who are at greatest risk of cancer death, where trimodality therapy may be appropriate.

Introduction

Human papilloma virus (HPV) infection represents the primary cause of the increasing incidence of oropharyngeal squamous cell carcinoma (OPSCC) in developed countries [1]. HPV-positive OPSCC possesses epidemiological and clinical characteristics that are distinct from HPV-negative OPSCC. Specifically, HPV-positive OPSCC is typically seen in non-smokers who are younger and is prognostic for better overall survival when compared to HPV-negative OPSCC [2]. Therefore, those diagnosed with HPV-positive OPSCC have greater potential for experiencing treatment-related morbidity over long intervals, which has prompted development of de-escalation protocols with the goal of reducing toxicity while maintaining high cure rates [3–10].

Despite the relatively better prognosis for HPV-positive OPSCC, approximately 20% of these patients die from their disease, the majority of whom have locally advanced (LA) cancer [2].

To date, efforts to guide treatment of OPSCC based on HPV status have focused on treatment de-escalation for HPV-positive patients, regardless of disease burden. However, the appropriateness of widespread homogenous de-escalation for HPV-positive OPSCC in the clinical trial

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setting has been questioned [11]. Furthermore, it is hypothesized that there may be distinct genetic subtypes of HPV-positive OPSCC with variable response to therapy, for which different treatment paradigms may be appropriate. To date, there has been less research on whether intensification strategies such as trimodality therapy may be indicated for the subset of HPV-positive patients with poor outcomes and a high risk of death from their disease [12]. An alternative hypothesis to treatment de-escalation is that HPV-associated disease may be an overall highly curable entity, even when locally-advanced, that could benefit from an aggressive trimodality approach. We therefore sought to ascertain whether there is a benefit to intensified trimodality therapy in patients with LA HPV-positive OPSCC using a contemporary population-based cohort from a novel database.

Methods

Study cohort

In this study, we used the Head and Neck with HPV Status Database [13] to identify 2974 adult patients (age > 18) with primary M0 potentially resectable OPSCC with known HPV status who received chemoradiation as a part of initial definitive treatment, diagnosed from 2013 to 2014; Patients with T4b disease who are typically considered unresectable were not queried given the aims of this study. This data is not public and has not yet been reported on. We obtained access via a proposal to the SEER custom data group, where the analyses described were determined to be appropriate use of the data.

The study inclusion period of 2013–2014 represents the years in which HPV status has been collected and reviewed for quality assurance. The study cohort was composed of patients who received chemoradiation as a part of initial definitive treatment given our aim to determine the outcomes of trimodality therapy (surgery followed by chemoradiation) versus chemoradiation alone stratified by HPV status. The SEER database includes information on first treatment course, thus data on receipt of salvage surgery was not available and these patients were not included in the trimodality cohort. Patients were also stratified in pre-determined groups as either LA (T3-T4, or N2-N3, per AJCC 7, N = 2464) or early stage (ES) (T1-T2 and N0-N1, N = 510), based on current practice patterns and treatment guidelines [14], where definitive chemoradiation remains a standard of care in the locally advanced setting per AJCC 7, regardless of HPV status. Patients with multiple primaries or where diagnosis was made at autopsy or death certificate were not queried.

SEER cancer registries code primary cancer site and histology per the International Classification of Diseases for Oncology, third edition (ICD-O-3). Subsites of the oropharynx in this study were captured by the following ICD-O-3 site codes: C01.9, C02.4, C05.1, C05.2, C09.0, C09.1, C09.8, C09.9, C10.0, C10.2–10.4, and C10.8–10.9. SCC histology was identified by the following ICD-O-3 histologic type codes: 8050, 8051, 8054, 8070–8076, 8083, 8094. TNM staging was determined using the American Joint Committee on Cancer (AJCC) 7th edition, as provided by SEER (where 8th edition staging is not yet reported by the database). Race was classified as white versus non-white (SEER reported black, Asian/Pacific Islander, American Indian/Alaskan Native, or unknown). Ethnicity was classified by SEER as Non-Spanish-Hispanic-Latino versus Spanish-Hispanic-Latino. Small area estimates for percent ever smoker was linked to SEER via estimates developed from the Behavioral Risk Factor Surveillance System (BRFSS) and the National Health Interview Survey (NHIS). Surgery included any surgical procedure with the exception of local tumor destruction (photodynamic therapy, electrocautery, cryosurgery, laser, stripping) and local tumor excision (polypectomy, excisional biopsy).

Of note, though sensitivity of chemotherapy and radiation therapy data in SEER is moderate (~80%), the specificity of chemotherapy and radiation therapy information is quite high and therefore the SEER program states that "since we have a high confidence that an individual received radiation therapy or chemotherapy if the variable is listed as 'yes', analyses identifying a cohort of patients who received treatment would be supported by the data." [15]. Notably, SEER surgery data is both highly sensitive and specific. Thus, our study was designed to apply analyses that would be strongly and accurately supported by the available SEER data by selecting those who received chemoradiation as the principle cohort where the specificity of the data is high, and then varying receipt of surgery (trimodality therapy) as the primary independent variable of interest where both the sensitivity and specificity

Table 1
Distribution of baseline patient characteristics by HPV status among patients with potentially resectable M0 HNSCC of the oropharynx (N = 2974). P < 0.05 when comparing across treatment approach (chemoradiation alone versus surgery followed by chemoradiation) for all baseline characteristics.

Characteristic[a]		Received Chemoradiation alone (N = 2303)	Received Surgery followed by Chemoradiation (Trimodality) (N = 671)
HPV Status			
	HPV Positive Disease	1724 (74.9)	544 (81.1)
	HPV Negative Disease	579 (25.1)	127 (18.9)
Tumor Stage, N (%)			
	T1	418 (18.2)	247 (36.8)
	T2	827 (35.9)	268 (39.9)
	T3	516 (22.4)	66 (9.8)
	T4	304 (13.2)	44 (6.6)
	Unknown T	238 (10.3)	46 (6.9)
Nodal Stage, N (%)			
	N0	207 (9.0)	54 (8.1)
	N1	398 (17.3)	121 (18.0)
	N2a	34 (1.5)	3 (0.5)
	N2b	198 (8.6)	125 (18.6)
	N2c	876 (38.0)	285 (42.5)
	N2 NOS	455 (19.8)	46 (6.9)
	N3	123 (5.3)	36 (5.4)
	Unknown N	12 (0.5)	1 (0.15)
Age at Diagnosis, Median (IQR)		60 (54–66)	58 (52–63)
Race, N (%)			
	Non-White	258 (11.2)	63 (14.9)
	White	2045 (88.8)	608 (90.6)
Ethnicity, N (%)			
	Non-Spanish-Hispanic-Latino	2172 (94.3)	628 (93.6)
	Spanish-Hispanic-Latino	131 (5.7)	43 (6.4)
Sex, N (%)			
	Female	308 (13.4)	100 (14.9)
	Male	1995 (86.6)	571 (85.1)
Smoking Propensity,[b] Median (IQR)		40.0 (33.5–44.5)	40.7 (33.3–45.2)
Percent High School Education,[c] Median (IQR)		87.0 (83.1–90.5)	87.2 (83.2–90.4)
Household Income,[c] Median (IQR)		59,990 (50770–71380)	59,950 (51870–71380)

Abbreviations: HNSCC, Head and Neck Squamous Cell Carcinoma; HPV, Human Papillomavirus.
N/A, not applicable.
[a] Percent may not add up to 100 due to rounding (Percent for Initial Definitive Treatment does not add up to 100 due to receipt of multiple treatments).
[b] Percent ever smoker determined by small area estimates, linked to SEER via estimates developed from the Behavioral Risk Factor Surveillance System (BRFSS) and the National Health Interview Survey (NHIS).
[c] County attribute data, linked to SEER population data by state-county FIPS codes.

Table 2
Multivariable adjusted hazard ratios for cancer-specific mortality among patients with M0 locally advanced (AJCC 7th edition T3-4 or N2-N3) HNSCC of the oropharynx (N = 2464).

Characteristic	No. patients/No. Cancer-Deaths/No. Competing Deaths	Cancer-Specific Mortality	
		AHR (95% CI)	P
Surgery (Trimodality) * HPV status[a]	2464/95/44	0.18 (0.035–0.93)	0.04
HPV Positive Disease	1891/47/31		
No Receipt of Surgery (Chemoradiation only)	1387/45/28	1.0 (ref)	
Receipt of Surgery (Received Trimodality)	426/2/3	0.19 (0.04–0.80)	0.024
HPV Negative Disease	573/48 /13		
No Receipt of Surgery (Chemoradiation only)	475/42/13	1.0 (ref)	
Receipt of Surgery (Trimodality)	98/6/0	0.78 (0.33–1.87)	0.58
Age at Diagnosis (per year increase)	2464/95/44	1.04 (1.01–1.06)	0.002
Race			
Non-White	286/13/10	1.0 (ref)	
White	2178/82/34	0.94 (0.51–1.72)	0.84
Ethnicity			
Non-Spanish-Hispanic-Latino	2318/88/44	1.0 (ref)	
Spanish-Hispanic-Latino	139/7/0	1.24 (0.58–2.66)	0.58
Sex			
Female	320/15/4	1.0 (ref)	
Male	2144/80/40	0.98 (0.56–1.69)	0.93
Smoking Propensity (per 10% increase)[b]	2464/95/44	1.02 (0.97–1.07)	0.77
High School Education (per 10% increase)[c]	2464/95/44	1.00 (0.99–1.00)	0.29
Median Household Income (per 10 K increase)[c]	2464/95/44	0.99 (0.99–1.00)	0.50

Abbreviations: AHR, adjusted hazard ratio; CI, confidence interval; HNSCC, Head and Neck Squamous Cell Carcinoma; HPV, Human Papillomavirus. N/A, not applicable; No, number; Ref, reference.

[a] Interaction term: Surgery/Trimodality (Surgery followed by chemoradiation versus chemoradiation alone) * HPV status (HPV-positive versus HPV-negative).

[b] Percent ever smoker determined by small area estimates, linked to SEER via estimates developed from the Behavioral Risk Factor Surveillance System (BRFSS) and the National Health Interview Survey (NHIS).

[c] County attribute data, linked to SEER population data by state-county FIPS codes.

of the data is high.

Statistical analyses

Comparison of baseline patient characteristics by treatment approach

The Wilcoxon rank-sum and Fisher Exact tests were used to compare distributions of continuous and categorical covariates, respectively, stratified by treatment approach (chemoradiation alone versus surgery followed by chemoradiation (N = 2974).

CSM estimates by treatment approach and HPV status

The primary goal of this study was to ascertain whether there is a differential response to trimodality therapy (chemoradiation alone versus surgery followed by chemoradiation) by HPV status among patients with locally advanced disease (T3-4 or N2-3) receiving chemoradiation as a part of initial definitive therapy. Therefore, our primary endpoint was cancer-specific mortality (CSM), where we applied a multivariable Fine-Gray competing-risks regression model for CSM including a surgery/trimodality (surgery followed by chemoradiation versus chemoradiation alone) * HPV status (HPV-positive versus HPV-negative) interaction term.

In addition to the interaction term, the following variables were included in the models: age (continuous), race (non-white [referent] versus white), ethnicity (non-Spanish-Hispanic-Latino [referent] or Spanish-Hispanic-Latino), sex (female [referent] versus male), smoking propensity (determined as a continuous variable from SEER provided % ever smoker small area estimates), income (continuous county variable), and education (continuous county variable).

Of note, for the purposes of illustration and in order to ascertain whether there may be a potential differential impact by stage (locally advanced T3-4 or N2-3 versus not) or utilization of trimodality therapy by HPV status, a third model was employed including a dichotomized stage variable (locally advanced T3-4 or N2-3 versus not) in the following interaction term: HPV status * Stage * Treatment. Cumulative incidence plots for CSM were generated for the purposes of illustration.

In addition to assessing CSM for the entire cohort, subgroup analyses were performed for the following four groups: patients with T3-4 tumors, N2-3 nodal status, T3-4/N1 stage, and T3-4/N2-3 stage.

OS estimates by treatment approach and HPV status

We sought to ascertain whether there is a differential survival benefit associated with trimodality therapy by HPV status and stage of disease. Therefore, our secondary endpoint was overall survival (OS), where we applied a multivariable Cox regression model for OS also including HPV status (positive versus negative), initial treatment approach (trimodality versus chemoradiation alone), and the other demographic variables described above. Kaplan-Meier plots for OS were generated for the purposes of illustration.

In addition to assessing OS for the entire cohort, subgroup analyses were performed for the following four groups: patients with T3-4 tumors, N2-3 nodal status, T3-4/N1 stage, and T3-4/N2-3 stage.

Stata/SE 14.2 (StataCorp, College Station, TX, USA) was used for cause-specific survival analyses and overall survival analyses for all patients with at least 1 month of follow-up. Adjusted hazard ratios (AHRs) with associated 95% confidence intervals (CIs) and P-values were calculated for all covariables in the Fine-Gray competing-risks regression and Cox multivariable analyses. The Dana-Farber/Harvard Cancer Center IRB granted permission for the performance of this study.

Results

Baseline patient characteristics by treatment approach

Among patients treated with chemoradiation as a part of first course

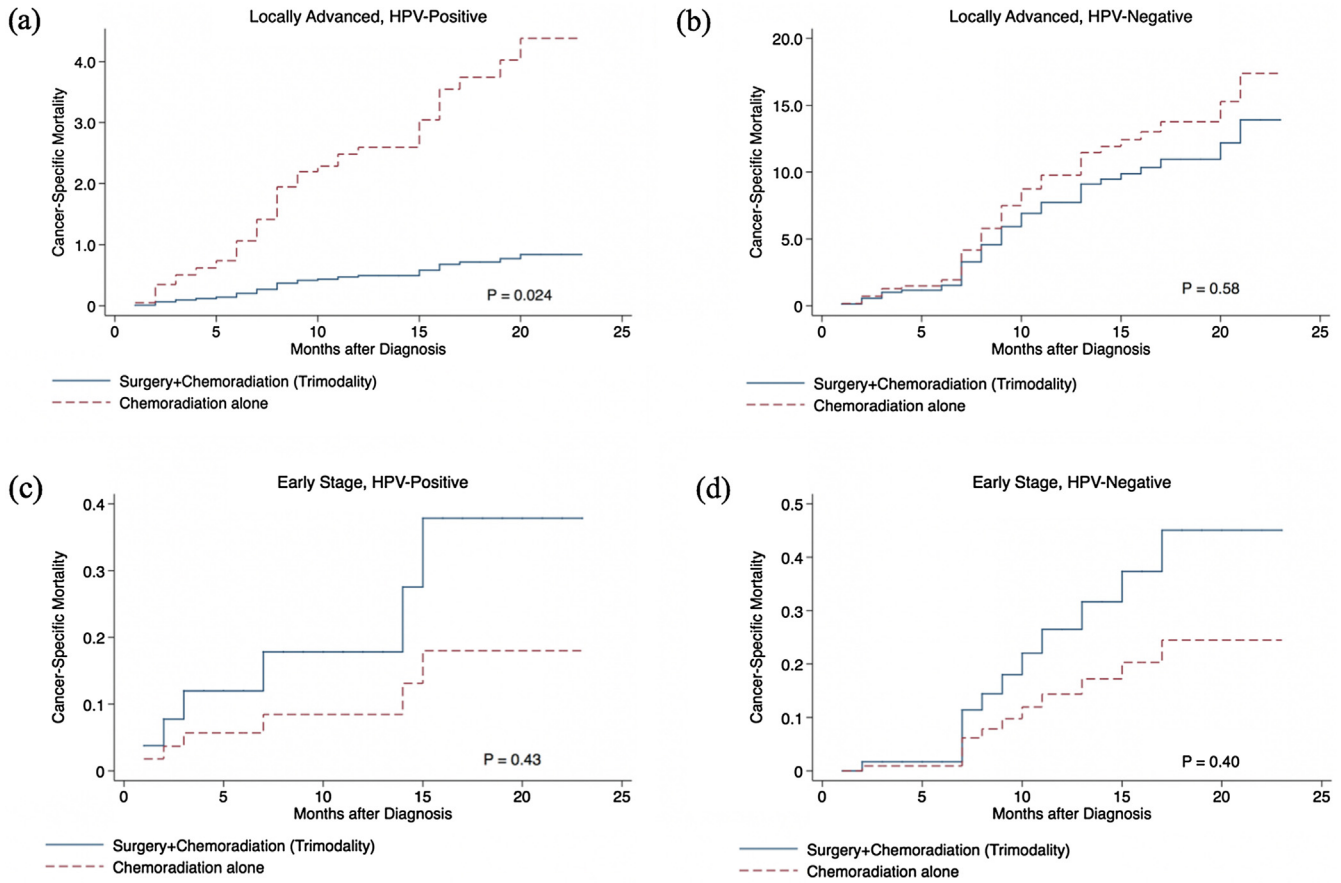

Fig. 1. Adjusted cumulative incidence plots of cancer-specific mortality among patients with (a) locally advanced (T3-4 or N2-N3), HPV-positive disease (N = 1813), (b) locally advanced (T3-4 or N2-N3), HPV-negative disease (N = 573), (c) early stage, HPV-positive disease (N = 377), and (d) early stage, HPV-negative disease (N = 133). Median follow-up was 10 months (IQR 5–16, max = 24). HPV status (positive versus negative) * Stage (locally advanced versus early stage) * Surgery (trimodality versus chemoradiation alone) interaction P-value = 0.035.

treatment, 671 out of 2974 patients (22.6%) received upfront surgery or trimodality therapy. There were 2464 patients (82.9%) with LA disease (T3-T4 or N2-3). The factors associated with receipt of trimodality therapy included white race, non-Hispanic ethnicity, male sex, earlier stage, HPV-positive disease, and smoking propensity (Table 1). Notably, 81.1% of patients who received trimodality therapy versus 74.9% of patients who received chemoradiation alone had HPV positive disease ($P < 0.001$).

CSM estimates by treatment approach and HPV status

Median follow-up for survival analyses was 10 months (IQR 5–16 months, max = 24 months). There was a significant interaction between treatment approach and HPV status ($P_{interaction} = 0.04$; Table 2) among patients with LA OPSCC, such that HPV status was predictive of CSM following trimodality therapy. Specifically, there was a significant reduction in CSM with receipt of trimodality therapy (surgery followed by chemoradiation) as compared to chemoradiation alone [referent] among patients with HPV-positive disease (AHR 0.19, 95% CI 0.04–0.80; P = 0.04, Fig. 1a), while there was no such survival benefit observed among patients with HPV-negative disease (AHR 0.78, 95% CI 0.33–1.87; P = 0.58, Fig. 1b). For patients with HPV-positive LA OPSCC, the 18-month CSM was 0.7% vs. 3.7% with and without surgery, respectively (N = 386 patients at risk at 18 months).

This differential response to trimodality therapy by HPV status appeared to be stage dependent. Specifically, patients with ES disease did not appear to have a benefit from trimodality therapy compared to chemoradiation alone [referent] for both patients with HPV-positive (AHR 2.10, 95% CI 0.33–13.43, P = 0.43, Fig. 1c) and HPV-negative disease (AHR 1.84, 95% CI 0.44–7.71, P = 0.40, Fig. 1d). This differential pattern of response to trimodality therapy by HPV status and stage was associated with a significant HPV status * Stage * Surgery interaction ($P_{interaction} = 0.035$).

On subgroup analysis, trimodality therapy did not confer a statistically significant improvement in CSM for any of the groups, with exception of those with HPV+, N2-N3 disease and any T-stage (AHR 0.23, 95% CI 0.05–0.98) (Table 3).

OS estimates by treatment approach and HPV status

There was a statistically significant improvement in OS with trimodality therapy for HPV-positive LA patients (AHR = 0.28, p = 0.006, 95% CI = 0.11–0.70, Fig. 2A). For patients with HPV-positive LA OPSCC, the 18-month OS was 98.0% vs. 91.8% with and without surgery, respectively (N = 386 patients at risk at 18 months). This benefit was not observed in HPV-negative LA patients (AHR = 0.59, p = 0.25, 95% CI = 0.25–1.39) or ES patients, regardless of HPV status (HPV-positive AHR = 0.86, p = 0.86, 95% CI = 0.17–4.49 m; HPV-negative AHR = 1.54, p = 0.54, 95% CI = 0.39–6.01) (Fig. 2B–D).

On subgroup analysis, trimodality therapy did not confer a statistically significant improvement in OS for any of the groups, with exception of those with HPV+ N2-N3 disease and any T-stage (AHR 0.32, 95% CI 0.13–0.0.79) (Table 3).

Table 3
Multivariable adjusted hazard ratios for cancer-specific mortality and overall survival among patients with M0 locally advanced (AJCC 7th edition T3-4 or N2-N3) HNSCC of the oropharynx (N = 2464), stratified by T and N stage groups, for patients receiving trimodality therapy versus chemoradiation alone.

Subgroup*	Cancer-Specific Mortality		Overall Survival	
	AHR (95% CI)	P	AHR (95% CI)	P
T3-T4, any N				
HPV positive (N = 670)	0.64 (0.15–2.65)	0.54	0.38 (0.09–1.55)	0.17
HPV negative (N = 305)	1.29 (0.49–3.38)	0.60	1.07 (0.41–2.79)	0.13
N2-3, any T				
HPV positive (N = 1,760)	0.23 (0.05–0.98)	0.05	0.32 (0.13–0.79)	0.01
HPV negative (N = 478)	0.60 (0.22–1.64)	0.32	0.43 (0.15–1.21)	0.11
T3-4, N1				
HPV positive (N = 106)	0.74 (0.18–3.11)	0.69	0.42 (0.10–1.75)	0.24
HPV negative (N = 55)	1.18 (0.43–3.22)	0.75	0.74 (0.41–1.38)	0.86
T3-4, N2-3				
HPV positive (N = 468)	0.69 (0.17–2.80)	0.60	0.36 (0.09–1.50)	0.16
HPV negative (N = 191)	0.97 (0.31–2.97)	0.95	0.75 (0.23–2.49)	0.64

Abbreviations: AHR, adjusted hazard ratio; CI, confidence interval; HNSCC, Head and Neck Squamous Cell Carcinoma; HPV, Human Papillomavirus. N/A, not applicable; No, number; Ref, reference.

* Other variables included in the models, not shown are: age (continuous), race (non-white [referent] versus white), ethnicity (non-Spanish-Hispanic-Latino [referent] or Spanish-Hispanic-Latino), sex (female [referent] versus male), smoking propensity (determined as a continuous variable from SEER provided % ever smoker small area estimates), income (continuous county variable), and education (continuous county variable).

Discussion

In this population-based study from a novel database, we found that HPV status predicts for improved outcomes with surgery combined with chemoradiation (trimodality therapy) in LA OPSCC. In uncovering improved oncologic outcomes with trimodality therapy for LA HPV-positive OPSCC, our findings suggest that this group of patients may benefit from surgery in addition to chemoradiation. We postulate that the unique disease burden and biological characteristics associated with LA HPV-positive OPSCC may benefit from multimodality therapy including surgery to maximize the chances of cancer cure. The lack of benefit with the addition of surgery in HPV-negative patients is likely due to adverse biologic factors that portend a poor prognosis, regardless of treatment intensity [16–18]. In contrast, the lack of benefit in HPV-positive patients with ES disease may be due to unnecessary treatment of low-burden favorable disease.

The results of this study suggest that there may be a biologic threshold in HPV-positive patients where uniform treatment de-escalation may not be appropriate for all and there may be a subset of patients that benefits from escalation of therapy, or a combination of trimodality therapy. The study findings are relevant in the current era of treatment de-escalation for HPV-positive OPSCC—via reduction in radiotherapy dose (Quarterback Trial [7], ECOG 1308 [6]), reduction in chemotherapy intensity or dose (De-ESCALaTE [4], RTOG 1016 [3]), or through the use of upfront transoral robotic surgery with de-intensification of adjuvant therapy [9]. Notably, all of these studies include patients with locally advanced disease, in whom our findings suggest a benefit to upfront surgery/trimodality therapy. However, it should be noted that while these patients may benefit from a trimodality approach, de-escalating other factors in treatment such as chemotherapy and/or radiotherapy intensity may still be appropriate. Our work adds to a growing body of observational studies comparing treatment modalities for oropharyngeal SCC with differing conclusions [19–21], further emphasizing the need to generate Level I evidence on this subject.

In an editorial by Orlandi et al, the authors advocated for genomically driven trials for head and neck cancer [11]. Our findings further support the creation of biomarker or risk-group driven trials in OPSCC, as is done in other disease sites [22,23]. These trials seek to identify biologic subtypes that may have differential responses to treatment or to match targeted therapies with expression of specific biomarkers. Given that it appears there is a differential response to trimodality therapy by stage within HPV-associated disease, our findings also suggest that further research is needed to identify genomic alterations in HPV-positive disease that are prognostic and/or predictive of treatment response. Recent research has identified oncogenic mutations in HPV-positive HNSCC, including mutations in PIK3CA, amplification of E2F1 and loss of TRAF3 [24]. Future efforts investigating whether such mutations are targetable or whether they influence the chemosensitivity and/or radiosensitivity of HPV-positive OPSCC may inform appropriate risk-based treatment de-escalation and intensification.

There are several limitations to this work. First, the median follow-up is this cohort was short with minimum follow-up of 1 month for some patients. Yet even with limited follow-up, a statistically significant difference in CSM and OS outcome was observed in the HPV-positive LA group. Second, patients undergoing surgery were surgically staged, while those treated with chemoradiation alone were staged clinically. However, patients receiving adjuvant chemoradiation, particularly chemotherapy, often have extracapsular extension and positive margins [25,26], characteristics not included in the SEER database. Furthermore, comparisons made across patients who received surgery show that surgery only benefited the group with LA-HPV-positive disease. At the same time, surgical upstaging from pathologic staging data could improve lead to observed improved outcomes in the surgical group. As with any retrospective study comparing treatment modalities, selection bias remains a concern and patients treated with trimodality therapy may have been more able to tolerate intensive treatment due to better underlying health status which may be driving their improved cancer specific and overall survival. Third, SEER lacks certain patient and treatment characteristics in particular patient-level smoking status along with comorbidity status, as well as specifics on radiotherapy dose and chemotherapy agent given. We attempted to control for smoking status by using county attributes, but acknowledge this is less accurate than patient-level data. Given that SEER does not include details such as radiotherapy dose and chemotherapy agent given, we also cannot conclude that even if surgery or trimodality therapy is beneficial, other de-escalation strategies are not. Fourth, SEER collects information on HPV positivity rather than p16 overexpression with studies showing an approximately 10% rate of discordancy between the two tests [2,27]. Fifth, the SEER database does not include specific systemic therapy agent given, thus it is possible that more of the non-surgical subgroup received cetuximab, which was recently shown to be associated with worse survival among HPV+ OPSCC [28,29]. Sixth, there is no information on whether patients completed all prescribed cycles of chemotherapy and radiotherapy. Seventh, patients receiving trimodality therapy were more likely to be early stage, thus this group may have been enriched in other characteristics such as positive margins and extranodal extension not captured by the SEER database. Our subgroup analyses suggest greater benefit in locally advanced HPV+ patients, however perhaps due to small numbers, statistical significance was achieved only in the largest subgroup. Eighth, our overall cohort size of 2.974 patients was modest thus subgroups may have been underpowered to observe a statistically significant difference, such as in the HPV negative groups. Ninth, patients undergoing any surgical procedure with the exception of local tumor destruction and local tumor excision were included as receiving surgery, thus some of the trimodality patients may have had tonsillectomy rather than intentional primary tumor treatment.

In conclusion, we found that patients with HPV-positive LA OPSCC

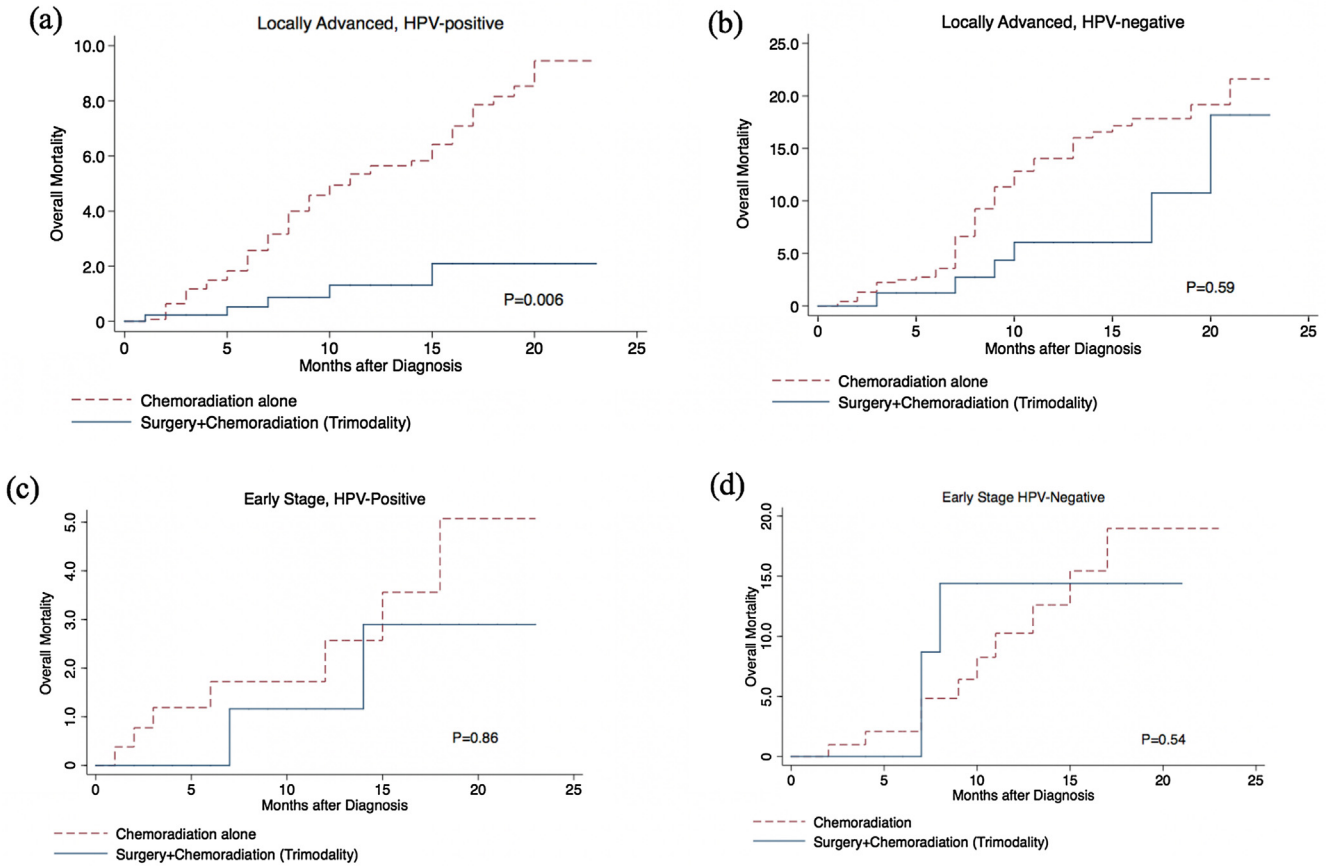

Fig. 2. Overall survival among patients with (a) locally advanced (T3-4 or N2-N3), HPV-positive disease (N = 1813), (b) locally advanced (T3-4 or N2-N3), HPV-negative disease (N = 573), (c) early stage, HPV-positive disease (N = 377), and (d) early stage, HPV-negative disease (N = 133). Median follow-up was 10 months (IQR 5–16, max = 24).

appear to benefit from the addition of surgery to chemoradiation, suggesting that in this cohort of patients with biologically favorable disease, outcomes may be improved with trimodality therapy. Further studies on biological differences between early stage and locally advanced HPV-positive OPSCC may further inform our clinical findings and identify novel therapeutic vulnerabilities. Ultimately, prospective investigations are needed to optimize care for the subset of HPV-positive patients who are at greatest risk of cancer death, where trimodality therapy may be appropriate.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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