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Primary surgery for human papillomavirus-associated oropharyngeal cancer: Survival outcomes with or without adjuvant treatment

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Abstract

Objectives—Human papillomavirus-associated (HPV +) oropharyngeal squamous cell carcinoma (OPSCC) is a unique form of head and neck cancer with improved prognosis. We assessed survival for stage I patients with low- or intermediate-risk pathologic features with surgery alone compared with surgery with adjuvant radiation (RT) or chemoradiation (CRT).

Materials and methods—We identified patients with stage I HPV+ OPSCC (after restaging with 8th edition staging system) treated with surgery alone, adjuvant RT or CRT in the National Cancer Data Base from 2010 to 2013. We compared survival for low-risk patients (1 metastatic lymph nodes with no adverse features) and intermediate-risk patients (2–4 metastatic lymph nodes, microscopic extranodal extension (ENE) or lymphovascular invasion).

Results—We examined 1677 patients with median follow-up of 43.9 months. In the intermediate-risk group, 4-year overall survival was 94.0% with surgery alone, 91.5% with adjuvant RT and 92.0% with adjuvant CRT (p = 0.72). There were similar rates of overall survival in the low-risk group. In multivariable models accounting for clinicopathologic differences the dose of adjuvant RT was not associated with mortality. On Cox proportional hazard modeling,

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Appendix A. Supplementary material

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adjuvant RT (HR 0.94; CI 0.43–2.08) or CRT (HR 0.96; CI 0.45–2.11) did not significantly improved survival compared with surgery alone in the intermediate-risk group (reference). Similar results were seen in the low-risk group. The composite number of pathologic risk features significantly improved risk stratification.

Conclusion—We provide observational evidence that adjuvant RT or CRT does not provide a survival benefit for stage I HPV+ OPSCC with low- or intermediate-risk pathologic features.

Keywords

Oropharyngeal cancer; Squamous cell carcinoma; Human papillomavirus; HPV; Surgery; Transoral robotic surgery; TORS; Adjuvant radiation; Adjuvant chemoradiation; Pathologic risk factors

Introduction

Human papillomavirus-associated (HPV +) oropharyngeal squamous cell carcinoma (OPSCC) is an emerging epidemic that accounts for over 70% of all OPSCC in the US [1]. HPV+ OPSCC differs sharply in etiology, pathophysiology and response to treatment from tobacco- and alcohol-associated OPSCC [2,3]. HPV+ OPSCC carries a significantly improved prognosis. However, the prognosis for HPV + OPSCC is poorly predicted using conventional staging of OPSCC [4], or using many conventional adverse pathologic features [5]. In response the American Joint Committee on Cancer (AJCC) created a separate staging system for HPV+ OPSCC, downstaging 92% of cases such that 64% of patients are restaged as stage I [6].

Treatment with either surgery with adjuvant therapy [7] or definitive chemoradiotherapy (CRT) achieves high rates of cure for HPV + OPSCC [2]. However, as patients are likely to live longer and experience the associated long-term toxicity of definitive CRT [8] there has been an interest in deintensification of CRT for those patients with an excellent prognosis. Both surgical and non-surgical deintensification strategies are actively being pursued in numerous clinical trials [9]. Transoral surgical techniques are one potential means of deintensifying therapy and can improve the safety, efficacy and tolerability of surgery. These surgical techniques are being investigated followed by deintensified adjuvant therapy [10]. Retrospective studied of transoral surgery compared with definitive CRT find improved functional results in patients undergoing surgery with decreased gastrostomy tube dependency [10–12]. Large, prospective multi-institutional surgical trials in this population include the Eastern Cooperative Oncology Group trial 3311 (E3311) and Post-operative Adjuvant Treatment for HPV-positive Tumors (PAHTOS). These trials risk stratify patients pathologically into low-, intermediate- or high-risk groups and correspondingly assign adjuvant therapy. While the results of these cooperative trials are pending, recent phase II single institutional data hint that these cooperative group surgical deintensification trials are likely to be successful and potentially could be extended significantly further [13].

In this environment, exploratory data from patients treated with surgery alone would be useful to understand the types of patients to target for future deintensification studies. Avoiding adjuvant therapy after primary surgery is associated with improvements in saliva

and taste-related quality of life [14], making it an appealing option for investigation. We studied patients that underwent surgery alone for stage I HPV+ OPSCC with low- and intermediate-risk pathologic features. The objectives of this study were as follows: (1) examine whether deintensification to surgery alone in patients with low- or intermittent- risk features was associated with any decrease in overall survival (OS); and (2) examine risk factors for death in patients treated with surgery alone.

Materials and methods

Data source and variables

We used the National Cancer Database (NCDB) to identify adults with HPV+ OPSCC diagnosed between January 1st, 2010, and December 31st, 2013. The NCDB is a nationwide oncology registry that collects information from Commission on Cancer Hospitals across the US. The NCDB is estimated to capture approximately 70% of all newly diagnosed cancers in the US. The NCDB shares data, coding and accuracy methods with state and national cancer registries and collects information on patient demographics, staging, treatment, and survival. The University of Pittsburgh Institutional Review Board approved a waiver for this study.

Patients with HPV+ OPSCC were identified based on the 3rd edition International Classification of Diseases for Oncology (ICD-O-3). Patients were then grouped by subsite within the oropharynx as shown in Supplemental Table 1. The NCDB collects information on the HPV subtype and those with low-risk HPV were excluded. We included patients that underwent definitive primary surgery and adequate neck dissection (Fig. 1). All patients were restaged using AJCC 8th edition guidelines [15]. Our study only included patients with stage I disease (pT1–2 pN1 M0). Patients with multiple primary cancers, incomplete information on treatment, incomplete information on follow up or start of adjuvant therapy > 180 days after diagnosis were excluded. To eliminate atypical treatment regimens, we excluded patients that underwent surgery and chemotherapy only. We excluded patients that had high-risk disease with either positive margins or macroscopic extranodal extension (ENE). Finally we excluded patients that did not undergo an adequate neck dissection. An adequate neck dissection was defined based on lymph node yield ≥ 15 LN using the same criteria as the Eastern Cooperative Oncology group trial 3311. This study defined removal of 15–20 LN yield as a minor protocol violation and LN removal < 15 as a major protocol violation. We grouped patients into low- and intermediate- disease using similar criteria to that used by E3311 based on the available information in the NCDB. We grouped treatment type as surgery alone, surgery with adjuvant RT or surgery with adjuvant CRT.

Statistical analysis

We calculated one-, two-, three- and four-year OS rates based on the date of diagnosis to date of death or last follow-up. We estimated univariate OS rates using the Kaplan-Meier method and then compared them using the log-rank test. We constructed multivariate Cox proportional hazard models were constructed to predict the hazard ratio (HR) of mortality as a function of treatment type (surgery alone, surgery with adjuvant RT, or surgery with adjuvant CRT) after adjustment for patient, tumor, pathology, and treatment variables. We

constructed additional Cox proportional hazard models to examine if the dose of RT delivered adjuvantly (< 50 Gy, 50–59.9 Gy, 60–60.9 Gy or > 70 Gy) was associated with survival after adjusting for patient, tumor, pathology, and treatment variables. We graphically confirmed the proportional hazard assumptions. We performed sensitivity analyses were performed in several subgroups to test the robustness of results. All p-values were two-sided. We considered comparisons statistically significant at $P < 0.05$ or associated 95% CIs did not include 1. We performed statistical analyses were performed with SPSS, version 24 (IBM, Armonk, NY).

Results

Study cohort and patient characteristics

We identified 1677 eligible patients with stage I HPV+ OPSCC that underwent primary surgical resection and neck dissection with low- or intermediate-risk pathologic features. Patient and tumor characteristics for the study cohort are shown in Table 1. Our study demographics are consistent with those reported for HPV+ OPSCC in the US. In our cohort, 83.0% were male, 92.7% were white and the mean age was 57.0 years. Oncologically, 53.1% were T1 and 64.7% were from the tonsil. Supplemental Table 2 contains full patient characteristics based on treatment group.

The characteristics of adjuvant RT delivered and reasons for not delivering RT were examined. Among those who received radiation, the mean dose of radiation delivered was 58.9 Gray in the low-risk group, and 59.7 Gray in the intermediate-risk group. In those that underwent surgery alone, the reason for no RT was examined. In the low-risk group, RT was not recommended for 92.1%, RT was recommended but refused for 7.5% and contraindicated for 0.3%. In the intermediate-risk group, RT was not recommend as the first course of treatment for 62.7%, recommended but refused for 35.2%, contraindicated for 0.7%, and recommended but not administered without reason noted for 1.4%.

Low and intermediate-risk groups

Median follow-up was 43.9 months (range 0.6–80.8). Four year OS in the intermediate-risk group was not significantly different than the low-risk group (Fig. 2). Four year OS in the low-risk group was 94.0% with surgery alone versus 97.5% with adjuvant RT and 96.0% with adjuvant CRT ($p = 0.17$). Four year OS in the intermediate-risk group was 94.3% with surgery alone versus 91.5% with adjuvant RT and 92.0% with adjuvant CRT ($p = 0.72$). After analysis was adjusted for differences in clinicopathologic characteristics and treatment type, there remained no significant difference in OS in the intermediate-risk group with surgery alone (reference) versus adjuvant RT (hazard ratio (HR), 0.94; CI 0.43–2.08) or adjuvant CRT (HR 0.96; CI 0.45–2.11, Table 2, Fig. 3). This was also true in the low-risk group. On multivariable analysis the only pathologic features associated independently with survival were T2 stage and 2–4 metastatic LN (Fig. 3).

When the composite number of pathologic adverse risk features was calculated, a population with clinically worse survival and true intermediate behavior could be identified. We calculated the composite number of adverse features with one point given for LVI,

microscopic ENE or pT2. Two points were given for 2–4 metastatic LN as the HR was nearly double that of the other adverse features. In patients with 1–2 adverse points OS at 4-years was 95.9% versus 88.2% for patients with >3 adverse points (HR 1.55; CI 1.28–1.89). In patients with 1–2 adverse points 4-year OS was 94.3% with surgery alone, 96.5% with adjuvant RT and 97.0% with adjuvant CRT ($p = 0.61$). In patients with 3+ adverse points 4-year OS was 85.0% with surgery alone, 86.3% with adjuvant RT and 88.6% with adjuvant CRT ($p = 0.61$). After adjusting for clinicopathologic characteristics there was no significant difference in survival based on the type of treatment in the 1–2 or 3+ adverse risk point groups (Supplemental Table 3).

Subgroup analysis: extranodal extension

As adjuvant therapy for patients with ENE is controversial, we performed subgroup analysis of intermediate-risk patients with microscopic ENE ($n = 588$) and without microscopic ENE ($n = 1229$). Similar to our findings for the overall intermediate-risk group, after adjusting for clinicopathologic characteristics there was no significant difference in OS in the group with microscopic ENE with surgery alone (reference) versus adjuvant RT (HR 0.85; CI 0.23–3.12) or adjuvant CRT (HR 1.05; CI 0.36–3.10). The same findings were also observed in the subgroup without microscopic ENE.

Sensitivity analysis: dose of adjuvant radiation

To examine whether dose reduction of RT is associated with adverse outcomes, we performed a sensitivity analysis based on the dose of adjuvant RT delivered in the intermediate-risk group (Fig. 4). After adjustment for clinicopathologic characteristics, increasing or decreasing the dose of adjuvant RT was not associated with mortality.

Discussion

In this study, we demonstrated that adjuvant RT or CRT dose not improve OS for stage I HPV+ OPSCC with low- or intermediate-risk pathologic features compared to surgery alone. Supporting this finding we show that deintensification of the dose of adjuvant RT is not associated with any decrease in survival. We found the composite number of adverse features improved risk-stratification suggesting potential refinement in our pathologic risk assessment. Overall these results suggest that many low- and intermediate-risk patients are suitable candidates for potential of deintensification.

Current National Comprehensive Cancer Network guidelines recommend adjuvant therapy guided by pathologic risk-assessment for surgically resected HPV+ OPSCC. These guidelines recommend no adjuvant treatment for low-risk pathologic features, adjuvant RT for intermediate-risk and adjuvant CRT for high-risk features [16,17]. However, this treatment paradigm is primarily based on multicenter trials studying the role of adjuvant RT versus CRT in a HPV- population, before the importance of HPV+ disease was recognized [17]. In these trials in primarily HPV- disease the 4-year OS in patients with intermediate-risk pathologic features with adjuvant RT was 55–70% [17]. Given the improved prognosis observed with HPV+ OPSCC it is reasonable to hypothesize that the pathologic risk-stratification derived from HPV- cohorts may overestimate the risk of death. Validating this

premise, we observed similar OS in both low- and intermediate-risk patients of 92–95% at 4-years with surgery alone. Further, some conventional intermediate-risk adverse features including LVI and microscopic ENE were not prognostic on multivariate modeling when assessed independently. Previous cohorts have similarly identified that conventional pathologic adverse features have a diminished impact compared with HPV-negative series [18,19]. We identified that when adverse risk features were considered as a composite variable, patients with 3+ adverse risk points were much more likely to die. This enabled splitting of the intermediate-risk group into those with a 96% 4-year OS (1–2 risk points) and those with an 88% 4-year OS (3+ risk points). This may permit identification of those intermediate-risk patients with a favorable prognosis that are best suited for deintensification.

Deintensification in the surgical paradigm is being investigated by several prospective, randomized controlled trials including E3311 and PATHOS. These trials are testing deintensification of adjuvant RT for intermediate-risk patients [20,21] or deintensification of chemotherapy for high-risk surgically resected HPV+ OPSCC [20]. Both studies use conventional pathologic adverse risk-stratification with some small differences including whether ENE ≥ 1 mm is considered intermediate-risk (E3311) or high-risk (PATHOS) and whether a single > 3 cm LN is an intermediate-risk feature (PATHOS). Using a risk-stratification system based on E3311, we examined whether deintensification in the dose of adjuvant RT or elimination in adjuvant therapy entirely decreased survival. We observed no significant difference in survival based on the dose of adjuvant RT compared to surgery alone. Our data suggest that ongoing surgical deintensification trials are likely to find equivalent survival with reduced dose radiation.

Our data indicates that neither adjuvant RT nor CRT provided an OS benefit for low- or intermediate-risk patients with HPV+ OPSCC. Previous studies assessing the risk of recurrence in HPV+ OPSCC patients treated with surgery alone have shown favorable outcomes for many intermediate-risk patients [22–24]. A recent retrospective multi-institutional study of 53 patients with HPV+ OPSCC supports our findings that there is a substantial group that are potential candidates for deintensification to surgery alone [23]. This study reported a 3-year recurrence free survival rate of 88% in intermediate-risk patients undergoing surgery alone [23]. The long-term morbidity from transoral surgery alone is minimal [25] and significantly better than when adjuvant RT or CRT is required [26], making this an attractive option to pursue for future deintensification efforts.

We would recommend caution before using our findings in routine clinical practice. Retrospective studies of treatment can be confounded, as there is no randomization. We attempted to minimize this risk by adjusting for measured confounders, however there is the potential for unmeasured confounders. We believe that further prospective study of surgery alone in low- and intermediate-risk stage I HPV+ OPSCC is needed before changing routine clinical practice. Importantly, the results of this study do provide clinical equipoise for random assignment to surgery alone for future deintensification trials in particular for patients with 1–2 adverse features. These adverse features should be further refined by verification in datasets that contain information about other potentially important adverse features in surgically treated patients including perineural invasion, close margins, tobacco

smoking history and molecular markers to help better identify low-, intermediate- and high-risk groups in HPV+ OPSCC.

As only surgery provides definitive pathology for staging and risk-stratification it was not possible to compare OS of low- and intermediate-risk patients in our cohort to those treated with definitive concurrent CRT. Cheraghlou et al. compared outcomes for stage I-III (8th edition) HPV+ OPSCC treated with surgery with or without adjuvant therapy or definitive concurrent CRT in the NCDB [27]. This study did not identify patients that underwent definitive surgery requiring treatment of both the local and regional disease, as neck dissection was performed in only 39–73% of the surgery alone group. Even with this limitation, they observed equivalent survival for stage I disease treated with definitive CRT, surgery alone, or with adjuvant therapy.

Several additional caveats to this analysis need to be considered. First, like all large oncologic registries the NCDB is subject to potential errors in coding. Second, there is an absence of recurrence or disease specific survival metrics. Thus, our results should be validated in independent data sets to determine if there is a difference in rates of local-regional or distant relapse. Third, there are several unmeasured variables including perineural invasion [28] and previous tobacco smoking history [2], which may be relevant to determining the risk of death in HPV+ OPSCC. Further, factors such as the chemotherapy regimen and quality of RT cannot be assessed. Despite these limitations, we believe this provides compelling evidence to help frame future deintensification trials.

In conclusion, in a retrospective cohort we observed that neither adjuvant RT nor CRT provides a survival benefit for stage I HPV + OPSCC with low- or intermediate-risk pathologic features. Our data further suggest that classic intermediate-risk pathologic features offer diminished prognostic value in HPV+ OPSCC. We found that the composite number of adverse risk features significantly improved identification of intermediate-risk patients with worse prognosis. This may help to identify intermediate-risk patients that are the best candidates for deintensification. Together this data supports efforts to deintensify adjuvant treatment for HPV+ OPSCC and provides equipoise for intermediate-risk patients to undergo random assignment to surgery alone.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclosure statement

The data used in the study are derived from a de-identified National Cancer Data Base (NCDB) file. 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 investigators.

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Fig. 1.
Flow diagram of cohort selection.

Fig. 2.

Kaplan meier overall survival based on risk level and type of treatment. (A) Low-risk versus to intermediate-risk group. (B) Stratified by composite number of adverse features with one point given for T2, microscopic ENE, LVI and two points for 2–4 metastatic LN. (C) Low-risk group by type of treatment. (D) Intermediaterisk group by type of treatment.

Fig. 3.

Cox proportional hazard model for low and intermediate groups based on treatment type. (A) Low-risk group. (B) Intermediate-risk group. (C) Subgroup with no microscopic ENE. (D) Subgroup with microscopic ENE. (E) Subgroup with 0–1 metastatic LN. (F) Subgroup with 2–4 metastatic LN. After adjusting for age, gender, race, comorbidities, oropharynx subsite, T-stage, number of metastatic lymph nodes, size of metastatic lymph nodes, extranodal extension and lymphovascular invasion.

Fig. 4.

Cox proportional hazard model based on the dose of radiation received in the intermittent group. After adjusting for age, gender, race, comorbidities, oropharynx subsite, T-stage, number of metastatic lymph nodes, size of metastatic lymph nodes, extranodal extension and lymphovascular invasion and chemotherapy received.

Table 1

Demographics and clinical characteristics of the study cohort.

Overall Cohort (n = 1677)	
Variable	N (%)
<i>Sex</i>	
Male	1392 (83.0)
Female	285 (17.0)
<i>Age</i>	
Mean, standard deviation	57.0 (9.1)
<i>Race</i>	
White	1554 (92.7)
African American	43 (2.6)
Hispanic	41 (2.4)
Other	39 (2.3)
<i>Charlson/Deyo comorbidity index</i>	
0	1414 (84.3)
1	263 (15.7)
<i>Pathologic T-stage</i>	
T1	891 (53.1)
T2	786 (46.9)
<i>Lymphovascular invasion</i>	
Absent	1391 (82.9)
Present	286 (17.1)
<i>Number of metastatic LNs</i>	
0	219 (13.1)
1	758 (45.2)
2–4	700 (41.7)
<i>Size of metastatic LNs</i>	
< 3cm	0 (0)
3–6cm	809 (48.2)
> 6cm	52 (3.1)
<i>Extranodal extension</i>	
None	1222 (72.9)
Microscopic ENE	455 (27.1)
<i>Surgical approach</i>	
Robotic	644 (38.4)
Endoscopic	163 (9.7)
Open	601 (35.8)
Unknown	269 (16.0)
<i>Insurance status</i>	
Private	1181 (70.4)
Medicaid/Uninsured	113 (6.7)

Overall Cohort (n = 1677)	
Variable	N (%)
Medicare/Other government	383 (22.8)
<i>Hospital type</i>	
Non-academic	528 (31.5)
Academic	1149 (68.5)

Table 2

Cox multivariable regression analysis of the hazard of mortality by adjuvant treatment. Adjusted hazard ratio < 1 indicates decreased hazard of mortality. Multivariate models were adjusted for confounding variables including age (< 55 years, 55–64 years, 65–74 years, and ≥ 75 years), sex, race (White, African American, and Other), comorbidities, oropharynx subsite, T-stage, size of metastatic lymph nodes for the low-risk group and for the same variables plus number of metastatic lymph nodes, extranodal extension and lymphovascular invasion. Abbreviations: RT = radiation therapy; CRT = chemoradiation therapy; HR = adjusted hazard ratio.

	<u>Low Risk Group</u>		<u>Intermediate Risk Group</u>	
	HR	CI	HR	CI
<i>Treatment</i>				
Surgery only	1.00	(Reference)	1.00	(Reference)
Surgery + RT	0.67	0.25–1.80	0.94	0.43–2.08
Surgery + CRT	1.44	0.51–4.09	0.96	0.45–2.11
<i>Age</i>				
< 55 years	1.00	(Reference)	1.00	(Reference)
55–64 years	1.01	0.43–2.38	1.74	0.92–3.29
65–74 years	1.40	0.37–5.30	7.42	3.17–17.37
≥ 75 years			12.23	3.86–38.75
<i>Sex</i>				
Male	1.00	(Reference)	1.00	(Reference)
Female	0.97	0.38–2.47	0.76	0.37–1.56
<i>Race</i>				
White	1.00	(Reference)	1.00	(Reference)
African American	0.56	0.06–4.84	1.22	0.28–5.23
Hispanic			2.56	0.75–8.67
Other			0.80	0.11–6.06
<i>Comorbidity</i>				
0	1.00	(Reference)	1.00	(Reference)
1	1.07	0.44–2.60	0.52	0.24–1.15
<i>T-stage</i>				
T1	1.00	(Reference)	1.00	(Reference)
T2	2.83	1.26–6.33	1.69	1.03–2.77
<i>Lymphovascular invasion</i>				
Absent			1.00	(Reference)
Present			1.53	0.89–2.66
<i>Number metastatic lymph nodes</i>				
0	1.25	0.53–2.92	1.50	0.18–12.49
1	1.00	(Reference)		
2–4			2.42	1.22–4.80
<i>Size of metastatic lymph nodes</i>				
< 3cm	1.00	(Reference)	1.00	(Reference)
3–6 cm	0.32	0.11–0.96	1.27	0.75–2.15

	<u>Low Risk Group</u>		<u>Intermediate Risk Group</u>	
	HR	CI	HR	CI
> 6cm			0.37	0.05–2.87
<i>Bilateral or contralateral LN</i>				
Absent			1.00	(Reference)
Present			0.53	0.07–4.03
<i>Extranodal extension</i>				
Absent			1.00	(Reference)
Microscopic			0.97	0.56–1.68
<i>Neck dissection lymph node yield</i>				
15–19 LN	1.00	(Reference)	1.00	(Reference)
20 LN	1.19	0.3504.06	1.09	0.48–2.45
<i>Insurance status</i>				
Private	1.00	(Reference)	1.00	(Reference)
Medicaid/Uninsured	5.30	1.76–15.95	1.04	0.392.74
Medicare/Other government	1.78	0.54–5.87	0.45	0.21–0.97
<i>Hospital type</i>				
Non-academic	1.00	(Reference)	1.00	(Reference)
Academic	0.66	0.30–1.42	0.71	0.42–1.20
<i>Year of diagnosis, continuous</i>				
2010	1.00	(Reference)	1.00	(Reference)
2011	0.88	0.29–2.70	0.92	0.44–1.90
2012	0.84	0.26–2.69	0.73	0.34–1.57
2013	1.34	0.41–4.34	0.89	0.39–2.01