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Original Article

Locally advanced hypopharyngeal and laryngeal cancer: Influence of HPV status

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ABSTRACT

Background: Larynx preservation with chemoradiotherapy (CRT) is used frequently in the treatment of locally advanced hypopharyngeal/laryngeal squamous cell carcinoma (LSCC). Multiple large retrospective analyses have shown that CRT is associated with worse overall survival (OS) compared to total laryngectomy (TL) in patients with T4a disease. Burgeoning evidence suggests HPV status may play a prognostic role in patients with LSCC. We aimed to determine if HPV status influences OS among patients with T4a LSCC, and, if so, if it may be useful in selecting patients for CRT.

Methods: Using the National Cancer Database (NCDB), we identified 810 patients with T4a N0-3 M0 squamous cell carcinoma of the larynx or hypopharynx with known HPV status who received either definitive CRT (to 66–81.6 Gy with any chemotherapy) or definitive TL (with the addition of 60–70 Gy of adjuvant RT). We evaluated differences in OS using the Kaplan–Meier method and Cox proportional hazards analyses.

Results: On multivariate analysis, HPV-negative status (HR = 1.42, $p = 0.02$) and receipt of CRT (HR = 1.34, $p = 0.01$) were associated with worse OS when compared to HPV-positive patients and patients receiving TL, respectively. Among patients receiving CRT, 5-year OS was lower among HPV-negative patients (33.4%) when compared to HPV-positive patients (50.6%).

Conclusions: These data suggest that HPV status may be a prognostic factor in patients with T4a LSCC. Further, it supports further investigation into the usefulness of HPV status as a selection factor for larynx preservation with CRT in these patients.

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The role of organ preservation with chemoradiotherapy (CRT) in cases of locally advanced laryngeal and hypopharyngeal squamous cell carcinoma (LSCC) has been well-established by multiple prospective randomized trials [1–4]. However, in the intervening decades since the initial publication of the VA Larynx trial, survival for LSCC has declined [5]. Several large retrospective analyses have suggested that, in broader clinical practice, larynx preservation is associated with worse overall survival (OS) when compared to total laryngectomy (TL), especially among patients with T4a disease [6–8]. Consequently, much effort has been placed on best identifying patients most likely to benefit (or most likely not to be harmed by) primary CRT for LSCC. Stratifying patients by tumor volume or response to neoadjuvant chemotherapy have both been promising at selecting patients most likely to be successful with a larynx-preservation strategy [9,10].

It has been well-established that, in patients with oropharyngeal squamous cell carcinoma, those with disease associated with human papillomavirus (HPV) experience substantially improved outcomes [11]. Burgeoning evidence exists that HPV status may have prognostic significance in squamous cell carcinoma of other sites of the head and neck, including in patients with LSCC [12–14]. A recent analysis of the National Cancer Database (NCDB) showed that patients with HPV-positive hypopharyngeal (HR = 0.59) and laryngeal (HR = 0.71) squamous cell carcinoma had significantly improved OS relative to patients with HPV-negative disease [13].

Using a large, hospital-based database, we aimed to evaluate if HPV status remained an independent predictor of OS in patients with T4a LSCC. Additionally, we queried if HPV status could be useful as an additional factor in selecting patients for larynx preservation with CRT.

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Materials and methods

We used the National Cancer Database (NCDB) to identify patients with T4a N0-3 M0 squamous cell carcinoma of the hypopharynx or larynx as defined by the 7th edition of the AJCC Cancer Staging Manual [15,16]. We included only patients receiving "definitive" therapies in our analysis: For patients receiving TL, we included only those receiving a TL and 60 to 70 Gy of adjuvant radiotherapy; for patients receiving CRT, we included only those receiving 66–81.6 Gy of radiotherapy, no definitive surgery, and any chemotherapy (including neoadjuvant and/or concurrent chemotherapy). Doses were determined from the most recent National Comprehensive Cancer Network (NCCN) guidelines [17]. HPV status was evaluated from "CS_SITESPECIFIC_FACTOR_10." We considered all patients marked as positive for HPV, regardless of high- or low-risk HPV status, as "HPV positive." Patients with unknown HPV status were excluded. The NCDB does not report the method for determining HPV status.

The Kaplan–Meier method and Cox proportional hazards analyses were used to evaluate OS differences by demographic, tumor-specific, and treatment-related variables. We used SAS software, version 9.4, to perform all statistical analyses (SAS Institute Inc., Cary, NC, USA).

Results

Within the NCDB, we identified a total of 810 patients treated between 2010 and 2014 with definitive treatment for T4a squamous cell carcinoma of the hypopharynx or larynx with known HPV status. Of these, 300 were treated with total laryngectomy (and adjuvant RT) and 510 were treated with chemoradiotherapy. The median follow-up for all patients was 25 months. As shown in Tables 1a and 1b, most patients were male, 65 years or older at diagnosis, had 0 or 1 medical comorbidity, and had a primary tumor in the larynx. Approximately 17% of patients had HPV-positive disease. On univariate analysis (Table 2a), we found that lower N stage, age under 65 years, laryngeal primary location, HPV-positive status, and treatment with TL were associated with improved OS. On multivariate analysis (Table 2b) which considered N classification, gender, age, the Charlson–Deyo score, primary site, HPV status, and treatment type, we found that HPV-negative status (hazard ratio [HR] = 1.42; 95% CI = 1.06–1.94; $p = 0.02$; 5-year OS, 40.0% vs 49.9%; Table 2; Fig. 1) was associated with worse OS. Receipt of chemoradiotherapy (HR = 1.34; 95% CI = 1.07–1.68; $p = 0.01$) was also associated with worse OS. The number of events (deaths) in each grouping is reported in Table S1.

When considering 5-year OS by both HPV status and treatment type, patients receiving TL (regardless or HPV status) and HPV-positive patients receiving CRT had a 5-yr OS rate ranging from 48.6% to 50.6%. However, patients with HPV-negative disease receiving CRT had a 5-year OS rate of 33.4% ($p = 0.002$; Table 3; Fig. 2).

Table 1a
Characteristics of patients with T4a laryngeal/hypopharyngeal squamous cell carcinoma.

Characteristic	Treatment type (*n*, %)	
	Total Laryngectomy (*n* = 300)	Chemoradiotherapy (*n* = 510)
N classification		
N0-1	162 (54.0%)	240 (47.1%)
N2-3	138 (46.0%)	270 (52.9%)
Gender		
Male	260 (86.7%)	422 (82.7%)
Female	40 (13.3%)	88 (17.3%)
Age		
≥65 years	222 (74.0%)	352 (69.0%)
<65 years	78 (26.0%)	158 (31.0%)
Charlson–Deyo's score		
0–1	281 (93.7%)	468 (91.8%)
>1	19 (6.3%)	42 (8.2%)
Site		
Hypopharynx	55 (18.3%)	143 (28.0%)
Larynx	245 (81.7%)	367 (72.0%)
HPV status		
Positive	49 (16.3%)	91 (17.8%)
Negative	251 (83.7%)	419 (82.2%)

Table 1b
Characteristics of Patients with T4a Laryngeal/Hypopharyngeal Squamous Cell Carcinoma.

Characteristic	HPV (*n*, %)	
	Negative (*n* = 670)	Positive (*n* = 140)
N classification		
N0-1	348 (86.6%)	54 (13.4%)
N2-3	322 (78.9%)	86 (21.1%)
Gender		
Male	567 (83.1%)	115 (16.9%)
Female	103 (80.5%)	25 (19.5%)
Age		
≥65 years	468 (81.5%)	106 (18.5%)
<65 years	202 (85.6%)	34 (14.4%)
Charlson–Deyo's score		
0–1	622 (83%)	127 (17%)
>1	48 (78.7%)	13 (21.3%)
Site		
Hypopharynx	166 (83.8%)	32 (16.2%)
Larynx	504 (82.4%)	108 (17.6%)
Treatment type		
Chemoradiotherapy	419 (82.2%)	91 (17.8%)
Total laryngectomy	251 (83.7%)	49 (16.3%)

Table 2a
Univariate analysis for overall survival of patients receiving definitive therapy for laryngeal/hypopharyngeal squamous cell carcinoma.

	Hazard ratio	95% confidence interval	*p* value
N classification			
N0-1	0.61	0.5–0.76	<0.0001
N2-3	–	–	–
Gender			
Male	1.28	0.95–1.74	0.1038
Female	–	–	–
Age			
≥65 years	–	–	–
<65 years	0.6	0.49–0.75	<0.0001
Charlson–Deyo's score			
0–1	0.93	0.64–1.42	0.7305
>1	–	–	–
Site			
Hypopharynx	–	–	–
Larynx	0.73	0.58–0.92	0.0093
HPV status			
Positive	–	–	–
Negative	1.36	1.02–1.85	0.0384
Treatment type			
Total laryngectomy	–	–	–
Chemoradiotherapy	1.39	1.11–1.74	0.0034

Table 2b
Multivariate analysis for overall survival of patients receiving definitive therapy for laryngeal/hypopharyngeal squamous cell carcinoma.

	Hazard Ratio	95% Confidence Interval	*p* value
N classification			
N0-1	0.61	0.49–0.76	<0.001
N2-3	–	–	–
Gender			
Male	1.25	0.93–1.72	0.13
Female	–	–	–
Age			
≥65 years	–	–	–
<65 years	0.61	0.49–0.76	<0.001
Charlson–Deyo's score			
0–1	0.92	0.63–1.42	0.71
>1	–	–	–
Site			
Hypopharynx	–	–	–
Larynx	0.87	0.69–1.11	0.25
HPV status			
Positive	–	–	–
Negative	1.42	1.06–1.94	0.02
Treatment type			
Total laryngectomy	–	–	–
Chemoradiotherapy	1.34	1.07–1.68	0.01

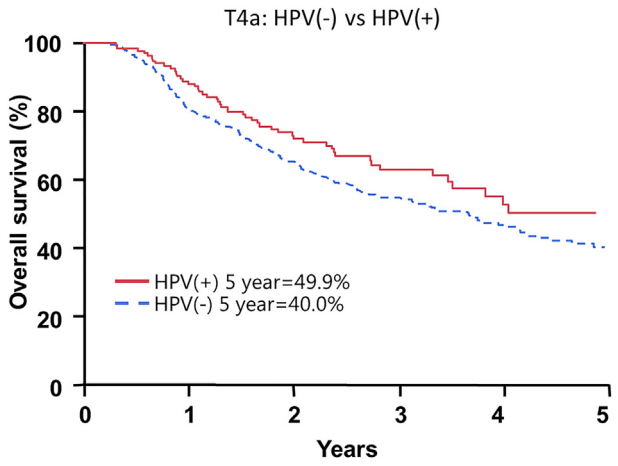

Fig. 1. Kaplan–Meier's plot of overall survival by HPV status for patients with T4a laryngeal/hypopharyngeal squamous cell carcinoma.

Table 3
Five-year overall survival in patients with T4a laryngeal/hypopharyngeal squamous cell carcinoma by treatment type and HPV Status.

	Total Laryngectomy	Chemoradiotherapy	*p* value
HPV Positive	48.6%	50.6%	0.002
HPV Negative	49.8%	33.4%	

Discussion

In agreement with prior analyses of the NCDB, we show that patients with HPV-positive T4a LSCC have improved OS relative to patients with HPV-negative disease. In a hypothesis-generating fashion, we also suggest that this difference is particularly pronounced in patients receiving CRT-based larynx preservation. Among patients receiving CRT, those with HPV-positive disease had a 5-year OS rate of 50.6% as compared to a 5-year OS of 33.4% for those with HPV-negative disease. These results are consistent with a prior single-institution retrospective review

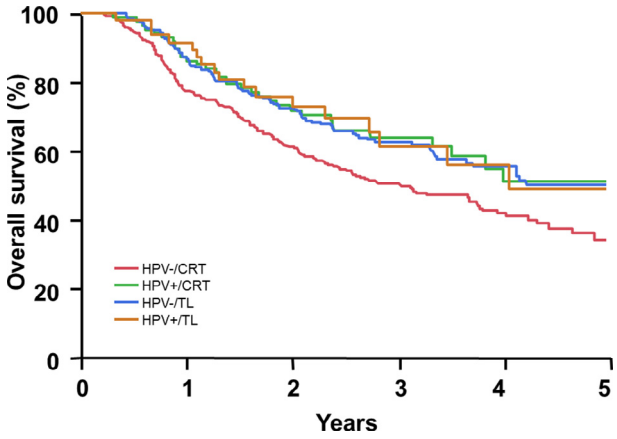

Fig. 2. Kaplan–Meier's plot of overall survival by HPV status and receipt of chemoradiotherapy (CRT) or total laryngectomy (TL) in patients with T4a laryngeal/hypopharyngeal squamous cell carcinoma.

showing improved disease-free survival in patients with HPV-positive LSCC treated with CRT as compared to those with HPV-negative tumors [14]. These findings suggest that HPV status may be an additional factor for the armamentarium of methods by which to consider patients with T4a disease for larynx preservation. Our institution has begun routinely reporting HPV status for all squamous cell carcinomas of the head and neck. However, we have not yet altered our treatment practices based on this information. Future study will be necessary to clarify the prognostic utility of HPV status in the treatment of laryngeal and hypopharyngeal squamous cell carcinoma.

There are several limitations in this analysis. As with any retrospective review, we cannot assess the rationale for treatment decisions for each individual patient. Additionally, HPV testing methods are not reported and may be inconsistent across hospitals. We additionally included patients coded as positive for low- or high-risk HPV as "HPV-positive" based on a prior analysis showing the inaccuracy of coding for specific HPV subtypes in a similar database [18]. We also cannot ascertain the rationale for HPV testing as it is not routinely performed for non-oropharyngeal squamous cell carcinoma of the head and neck.

We report that HPV status is prognostic among patients with T4a LSCC. We also provide evidence that HPV status may be useful in selecting patients for larynx preservation as patients with HPV-positive disease receiving CRT have significantly better OS than patients with HPV-negative disease receiving CRT; this difference is not seen among those receiving primary TL. Validation of this finding either prospectively or in other retrospective cohorts would be beneficial in ascertaining the therapeutic utility of HPV status in T4a LSCC.

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Declaration of Competing Interest

The authors have no conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.05.013.

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