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ORIGINAL RESEARCH

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# Impact of human immunodeficiency virus status on laryngeal cancer survival and locoregional control

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## Abstract

**Objectives:** To compare long-term outcomes of laryngeal cancer (LC) in people living with HIV (PLWH) versus uninfected individuals and determine how clinical and viral factors—such as demographics, cancer stage, HIV viral load, and CD4 nadir—contribute to these outcomes.

**Methods:** This was a retrospective case–control study of 749 patients seen for LC at a single tertiary care center between 2003 and 2017. Of these, 22 had HIV at the time of LC diagnosis, and they were matched in a 1:4 ratio to uninfected controls based on sex, presence of smoking history, and age at cancer diagnosis. Kaplan–Meier survival curves and Cox proportional hazards models were constructed to identify overall and disease-free survival differences based on HIV status, as well as other clinical and viral factors.

**Results:** Compared to all uninfected individuals, PLWH were diagnosed with LC approximately 6 years younger ($p = .013$). 1-, 2-, and 5-year overall survival for PLWH were 86.4% (63.4%–95.4%), 77.3% (53.7%–89.9%), and 65.8% (40.8%–82.2%), respectively following LC diagnosis, and HIV was not significantly associated with overall (HR = 3.34 [0.59–18.79]) or disease-free survival (HR = 2.12 [0.71–6.36]). The incidence rate of locoregional recurrence among PLWH was 541 compared to 371 per 10,000 person-years in controls, which were not significantly different ($p = .420$). Furthermore, among PLWH, peak viral load and CD4 nadir were not associated with overall or disease-free survival.

**Conclusion:** While previous work has shown that HIV is associated with elevated risk of LC, survival did not differ significantly between PLWH and uninfected individuals in this study.

**Level of evidence:** 3.

KEYWORDS
laryngeal cancer/vocal fold dysplasia, laryngology, larynx, neoplasia/malignancy, outcomes

## 1 | INTRODUCTION

With the advent of combined antiretroviral therapy (cART), the expected lifespan of a people living with HIV (PLWH) has dramatically increased. In 1996, the life expectancy for a 20 year old with HIV was 19.1 years, increasing to 47.1 years in 2008 and 53.1 years by 2011—only 8 years less than in uninfected individuals.[1] So, while the incidence of AIDS-defining cancers has dwindled with improved viral control, PLWH now have more opportunity to develop non-HIV-related cancers. As lifespan has increased among PLWH, so has the incidence of non-HIV-related cancers, including head and neck squamous cell carcinoma (HNSCC) and laryngeal squamous cell carcinoma (LSCC) specifically.[2] In fact, the rate of LSCC in PLWH has significantly exceeded, by between 1.4 and 11 times, that of uninfected individuals.[3–8]

PLWH have multiple unique risk factors—for example, immunosuppression, inflammation, oncogenic virus infection, cART toxicity, and HIV itself—that could potentially modify risk, clinical course, and outcomes of their laryngeal cancer (LC) compared to the general population.[9] So, as the incidence of LSCC increases among PLWH, it becomes increasingly important to fully characterize disease outcomes and compare them to HIV$^-$ LSCC in order to assist in prognostication and clinical decision-making.

Because people with HIV have traditionally been excluded from clinical trials and other studies in head and neck cancer, there is very limited evidence regarding outcomes of LC in PLWH, and only two studies thus far have directly compared them to HIV-negative controls.[3] One study by Haase et al., including four HIV+ LSCC cases and 27 controls, and another by Walline et al., with six patients in each group, both found no difference in overall survival between PLWH and controls.[3,10] For HNSCC overall, comparisons between those with and without HIV have yielded more inconsistent results, mostly reporting no differences in survival, but with one finding significantly lower overall and disease-free survival among PLWH compared to age-matched controls.[3,4,10,11] Given inconsistencies and small sample sizes in the exiting literature, there is a clear continued need to study the outcomes of LC in PLWH. Thus, we have performed a case–control study including 22 PLWH and 88 matched HIV-negative controls with LC to identify differences in overall and disease-free survival, as well as factors that may be associated with these outcomes among PLWH.

## 2 | METHODS

This retrospective case–control study was approved by the Johns Hopkins Medicine Institutional Review Board, which waived the requirement of informed consent. All patients seen for LC at The Johns Hopkins Hospital between 2003 and 2017—including those whose initial LC diagnosis was prior to this study period—were identified from billing data. Of these, 22 had HIV infection at the time of LC diagnosis. No exclusion criteria were applied, and follow-up was recorded through 2020. Power analysis using Schoenfeld's method with one-sided $\alpha = 0.05$ indicated that a total sample size of at least 110 was required to achieve 80% power to detect a hazard ratio of 1.8 or greater by the log-rank test. As such, 1:4 matching was performed with the HIV-negative patients based, in order of priority, on sex, presence of smoking history, and age at cancer diagnosis. In the case that a control with the same age at cancer diagnosis could not be identified, this criterion was extended to ±1 year.

For all patients, age at cancer diagnosis, ethnicity (white, Afroamerican, or other), sex, and smoking history (yes or no) were recorded. For all PLWH and selected controls, site of LC (supraglottic, glottic, or subglottic) and tumor (*T*) and nodal (*N*) status were noted according to American Joint Committee on Cancer 8th Edition Guidelines.[12] Date of death or last follow-up and pack-years of smoking history were also noted, as well as date of locoregional cancer recurrence and cause of death when applicable. For PLWH, the date of HIV diagnosis, CD4 nadir, highest measured viral load, and CD4 and viral load at the time of LC diagnosis were recorded.

All patients included in the study, following the National Cancer Institute guidelines, had access to the same surgical and oncological treatment strategies of HIV negative patients. In all patients diagnosed with LC, we follow the American Society of Anesthesiologists (ASA) physical status classification system to evaluate patients' preoperative general conditions. During ASA assessment, the CDC stage of HIV infection and presence of opportunistic infections is usually considered, and it may result in a higher ASA score. While high ASA score may in turn result in changing the choice of surgical procedure or therapy to be initiated, HIV was not in and of itself a consideration for treatment strategy.

All statistical analysis was done in Stata Statistical Software: Release 16 (StataCorp LLC). Cases and controls were compared with *t*-tests for continuous and Pearson $\chi^2$ tests for categorical variables. The primary outcome was overall survival, however we also looked at disease-free survival, defined as the time to death or locoregional cancer recurrence. 1-, 2-, and 5-year survival were estimated by Kaplan–Meier survival analysis. For each of these cutoffs, all patients still at risk were censored at that time point and a log-rank test performed to compare overall survival to that point between PLWH and controls. Log-rank tests were similarly used to compare the entire survival curves. After verifying the proportional hazards assumption via complementary log–log plots, Cox regression models were constructed to test the association of each variable of interest in isolation with survival. To test for effect modification by HIV of any of the covariates, Cox models were constructed including HIV, one additional covariate, and an interaction term between the two. The above analyses were repeated using multivariable models adjusting for HIV, *T* status, *N* status, pack-years of smoking, age at diagnosis, sex, ethnicity, site of tumor, and the relevant interaction term. Furthermore, univariable Cox regression was performed to test the effect of CD4 nadir (both as a continuous variable and dichotomized as CD4 ≤200 vs. CD4 >200), peak viral load, and time between HIV and LC diagnosis on survival

among PLWH. The Breslow method for ties was used in all Cox models, and the significance level was set at $p < .05$.

## 3 | RESULTS

Of 749 patients with LC, 22 were infected with HIV at the time of LC diagnosis. Compared to those without HIV (unmatched), PLWH were significantly more likely to be Afroamerican and female, whereas *T* and *N* status, site, and proportion with a positive smoking history were not different between the two groups. The mean age at LC diagnosis was about 6 years younger in PLWH ($p = .013$) and occurred, on average, 11.23 (7.04) years after the initial diagnosis of HIV. After 1:4 matching was performed on sex, and presence of smoking history, and age at diagnosis, there was no statistically significant difference in these parameters between the 22 cases and 88 controls. However, cases were still more likely to be Afroamerican than controls and had fewer pack-years of smoking history at the time of LC diagnosis. Mean follow-up time was 5.3 years in PLWH and 7.7 years in matched controls ($p = .022$; Table 1).

**TABLE 1** Patient baseline characteristics compared to unmatched and matched controls

| | PLWH ($n = 22$) Mean (stdev) or % | Unmatched patients ($n = 727$) | | Matched controls ($n = 88$) | |
|---|---|---|---|---|---|
| | | Mean (stdev) or % | *p* | Mean (stdev) or % | *p* |
| Years of follow-up | 5.32 (3.50) | — | — | 7.70 (6.50) | .022* |
| Age at LC diagnosis | 56.09 (5.53) | 61.96 (11.00) | .013* | 56.00 (5.46) | .945 |
| Sex | | | | | |
| Male | 59.1 | 78.0 | .036* | 59.1 | 1.000 |
| Female | 40.9 | 22.0 | | 40.9 | |
| Ethnicity | | | | | |
| White | 9.1 | 74.3 | <.001* | 73.3 | |
| Afroamerican | 77.3 | 21.1 | | 23.3 | <.001* |
| Other | 13.6 | 4.6 | | 3.5 | |
| Smoking history | | | | | |
| Yes | 100.0 | 90.8 | .136 | 100.0 | 1.000 |
| No | 0.0 | 9.2 | | 0.0 | |
| Pack-years of smoking history | 30.19 (14.52) | — | — | 46.67 (25.69) | .006* |
| *T* status | | | | | |
| 1 | 36.4 | 36.0 | | 34.1 | |
| 2 | 27.3 | 26.0 | .952 | 30.7 | .597 |
| 3 | 18.2 | 22.8 | | 26.1 | |
| 4 | 18.2 | 15.2 | | 9.1 | |
| *N* status | | | | | |
| 0 | 54.5 | 70.9 | | 69.3 | |
| 1 | 13.6 | 8.0 | .257 | 11.4 | .481 |
| 2 | 31.8 | 18.8 | | 18.2 | |
| 3 | 0.0 | 2.3 | | 1.1 | |
| Stage | | | | | |
| I | 31.8 | 33.7 | | 31.8 | |
| II | 13.6 | 17.9 | .874 | 21.6 | .481 |
| III | 18.2 | 19.7 | | 25.0 | |
| IV | 36.4 | 28.7 | | 21.6 | |
| Site | | | | | |
| Supraglottic | 45.5 | 48.4 | .739 | 51.1 | .533 |
| Glottic | 50.0 | 49.5 | | 47.7 | |
| Subglottic | 4.5 | 2.1 | | 1.1 | |

*Significant with $p < .05$.

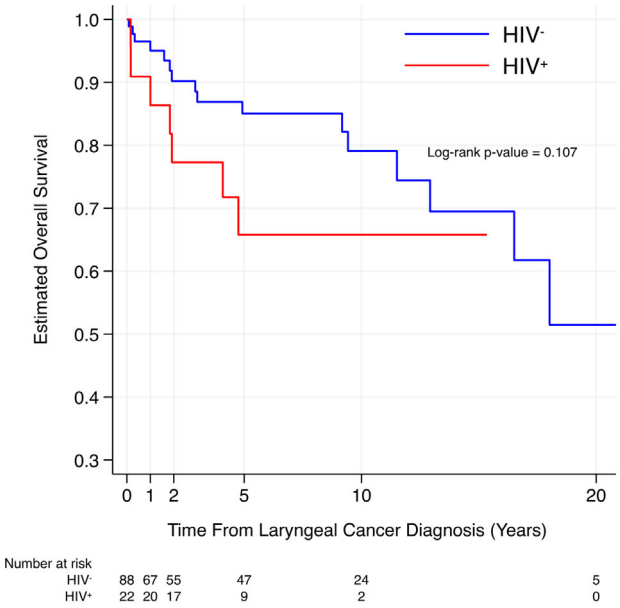


**FIGURE 1** Kaplan–Meier estimates of overall survival. Graph truncated at 20 years for visualization, as hazard was constant past this point

## 3.1 | Overall survival

Following LC diagnosis, the 1-, 2-, and 5-year overall survival for PLWH was 86.4% (63.4%–95.4%), 77.3% (53.7%–89.9%), and 65.8% (40.8%–82.2%), respectively. By comparison, for matched controls, 1-, 2-, and 5-year overall survival was 95.0% (87.3%–98.1%), 90.2% (80.4%–95.3%), and 85.1% (73.8%–91.8%), respectively (Figure 1). Survival to 1, 2, and 5 years was not significantly reduced among PLWH compared to controls ($p = .433$, .110, and .057, respectively). Overall, comparing these two groups, the hazard of death was not significantly different in either the univariable model or the multivariable Cox regression model adjusted for age at diagnosis, sex, ethnicity, site, *T* and *N* status, and pack-years of smoking history (HR = 2.10 [0.84, 5.29], aHR = 3.34 [0.59, 18.80]), though age at diagnosis and T3 or T4 disease were associated with poorer overall survival in both models (Table 2). The survival curves for PLWH and controls were not significantly different by the log-rank test ($p = .107$).

The incidence rate of death among PLWH was 600 per 10,000 person-years, compared to 263 per 10,000 person-years in controls, though this difference was not significant ($p = .087$). Only 2/7 deaths (171 per 10,000 person-years) among PLWH and 3/23 (33 per

**TABLE 2** Overall survival

| | Unadjusted | | Adjusted | |
|---|---|---|---|---|
| | HR | 95% CI | HR | 95% CI |
| HIV status | | | | |
| HIV− | Ref | — | Ref | — |
| HIV+ | 2.10 | 0.83–5.29 | 3.34 | 0.59–18.79 |
| Age at LC diagnosis | 1.07* | 1.00–1.15 | 1.15* | 1.06–1.25 |
| Sex | | | | |
| Male | Ref | — | Ref | — |
| Female | 1.41 | 0.62–3.19 | 1.57 | 0.50–5.00 |
| Ethnicity | | | | |
| White | Ref | — | Ref | — |
| Afroamerican | 1.22 | 0.50–2.96 | 0.42 | 0.09–2.03 |
| Other | 1.01 | 0.13–7.94 | 0.44 | 0.04–5.10 |
| Pack-years of smoking history | 1.00 | 0.98–1.02 | 1.00 | 0.97–1.02 |
| *T* status | | | | |
| 1 | Ref | — | Ref | — |
| 2 | 2.56 | 0.71–9.18 | 4.49 | 0.92–21.87 |
| 3 | 6.42* | 1.89–21.79 | 14.28* | 2.82–72.24 |
| 4 | 5.65* | 1.40–22.72 | 12.35* | 1.27–119.75 |
| *N* status | | | | |
| 0 | Ref | — | Ref | — |
| 1 | 0.34 | 0.04–2.56 | 0.20 | 0.02–2.15 |
| 2 | 2.62* | 1.03–6.67 | 1.74 | 0.44–6.86 |
| 3 | — | — | — | — |
| Site | | | | |
| Supraglottic | Ref | — | Ref | Ref |
| Glottic | 0.56 | 0.23–1.32 | 1.54 | 0.48–4.91 |
| Subglottic | 3.96 | 0.41–30.77 | 5.06 | 0.20–128.94 |

*Significant with $p < .05$.

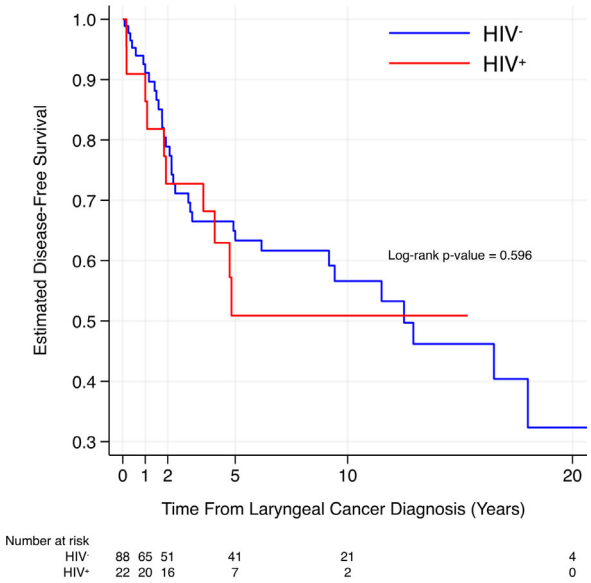


**FIGURE 2** Kaplan–Meier estimates of disease-free survival. Graph truncated at 20 years for visualization, as hazard was constant past this point

10,000 person-years) among controls were directly caused by LC ($p = .139$).

Among PLWH, CD4 nadir, peak viral load, time between HIV and LC diagnosis, and CD4 count and viral load at LC diagnosis were not associated with changes in overall survival (Table S1). In an unadjusted model, the hazard ratio associated with the interaction term between Afroamerican ethnicity and HIV was 2.25 (1.05, 4.81), indicating that Afroamerican ethnicity may be less protective for PLWH compared to controls; however, no deaths occurred among non-Afroamerican PLWH and the interaction term was not significant after adjustment for the other covariates (aHR = 1.06 [0.17, 6.64]), so interpretation of this result is limited. All other interaction terms were nonsignificant in both models (Table S2).

## 3.2 | Disease-free survival

Following LC diagnosis, the 1-, 2-, and 5-year disease-free survival for PLWH was 86.4% (63.4%–95.4%), 72.7% (49.1%–86.7%), and 50.9% (27.3%–70.3%), respectively. By comparison, for matched controls, 1-,

**TABLE 3** Disease-free survival

| | Unadjusted | | Adjusted | |
|---|---|---|---|---|
| | HR | 95% CI | HR | 95% CI |
| HIV status | | | | |
| HIV− | Ref | — | Ref | — |
| HIV+ | 1.21 | 0.59–2.49 | 2.12 | 0.71–6.36 |
| Age at LC diagnosis | 1.01 | 0.95–1.06 | 1.04 | 0.98–1.10 |
| Sex | | | | |
| Male | Ref | — | Ref | — |
| Female | 0.87 | 0.47–1.61 | 1.12 | 0.54–2.35 |
| Ethnicity | | | | |
| White | Ref | — | Ref | — |
| Afroamerican | 0.57 | 0.29–1.11 | 0.35* | 0.13–0.93 |
| Other | 0.68 | 0.16–2.90 | 0.48 | 0.09–2.50 |
| Pack-years of smoking history | 1.01 | 0.99–1.02 | 1.01 | 0.99–1.03 |
| *T* status | | | | |
| 1 | Ref | — | Ref | — |
| 2 | 0.85 | 0.38–1.88 | 1.06 | 0.42–2.67 |
| 3 | 1.85 | 0.87–3.91 | 1.92 | 0.73–5.05 |
| 4 | 1.30 | 0.43–3.90 | 1.77 | 0.37–8.51 |
| *N* status | | | | |
| 0 | Ref | — | Ref | — |
| 1 | 0.33 | 0.08–1.39 | 0.38 | 0.08–1.79 |
| 2 | 1.72 | 0.85–3.48 | 1.59 | 0.58–4.39 |
| 3 | — | — | — | — |
| Site | | | | |
| Supraglottic | Ref | — | Ref | — |
| Glottic | 1.01 | 0.55–1.86 | 1.51 | 0.67–3.43 |
| Subglottic | 2.32 | 0.31–17.39 | 2.68 | 0.19–38.85 |

*Significant with $p < .05$.

2-, and 5-year overall survival was 91.1% (82.2%–95.7%), 77.3% (65.5%–85.5%), and 63.3% (50.6%–73.6%), respectively (Figure 2). Disease-free survival was not significantly different between PLWH and controls in the univariable or multivariable models (HR = 1.214 [0.591, 2.494], aHR = 1.898 [0.655, 5.498]). Afroamerican ethnicity was significantly associated with a lower hazard of death in the multivariable model, while the hazard ratios associated with all other covariates were nonsignificant (Table 3). A log-rank test for equivalence of the survivor functions was nonsignificant ($p = .596$).

The incidence rate of locoregional recurrence among PLWH was 541 per 10,000 person-years, compared to 371 per 10,000 person-years in controls, though this difference is not significant ($p = .420$).

## 4 | DISCUSSION

In summary, we found that neither overall nor disease-free survival is significantly reduced among LC patients living with HIV compared to age, smoking history, and sex-matched controls. Age at diagnosis and tumor (*T*) stage were independently associated with worse overall survival, while sex, ethnicity, pack-years of smoking, nodal (*N*) status, and tumor site all had no impact. The only variable significantly associated with disease-free survival was Afroamerican ethnicity, which was protective. We have no explanation as to why Afroamerican ethnicity has a protective effect on survival in PLWH. Epidemiological studies indicate that ethnicity can be a determining factor in cancer susceptibility and survival. However, more research is needed to elucidate the mechanism behind this association.

No impact of HIV status on LC survival and locoregional control may be explained by the efficacy and widespread availability of cART. Thanks to early detection and treatment, HIV infection has now become a chronic, manageable condition with low or any impact on survival and health condition in affected individuals. Based on the results of our study, the HIV infection does not reduce the survival and worsen the outcomes in patients with LC.

This study is the largest to date comparing LC in HIV+ and HIV− individuals, with 22 and 88 cases respectively.[3,10] A number of other papers have included between 1 and 27 HIV+ LC patients, but without an HIV− control group. Previous studies have reported a mean duration of HIV infection prior to LSCC diagnosis of 10.5–18 years, which is in line with 11.2 years in this study.[3,13] On the other hand, it should be noted that PLWH in our cohort were healthier at the time of LC diagnosis compared to those in previous studies, with 55% presenting with advanced disease (stage III or IV) and only 5% having CD4 <200. By comparison, others have reported advanced disease in 66%–83% and CD4 <200 in 36%.[3,13]

On a population level, there is a clear association between HIV and head and neck cancer. It is estimated, for example, that the risk of HNSCC is between 1.4 and 4 times greater in PLWH, with the risk of laryngeal SCC being between 2- and 11-fold higher.[3–8] PLWH are also diagnosed at a younger age, by about 7–10 years for all HNSCC and 15–20 years for LSCC specifically.[3,5,7,14] Here, we found only a 6-year difference in age of LC diagnosis between PLWH and controls, though among PLWH, the median age of 56 was about 15 years older than in other reports.[13] Previous studies have also reported more advanced stage at diagnosis in PLWH compared to controls, though we did not find this to be the case.[5,13]

There is conflicting evidence regarding whether HIV+ HNSCC represents an etiologically distinct disease process from HNSCC in the general population.[3,15] In favor of such a distinction, HIV+ HNSCC has been found to have a unique mutation pattern in the TP53 tumor suppressor gene.[16] This specific mutation in HIV+ HNSCC suggests that HIV infection may play a direct role in pathogenesis of the cancer. Furthermore, the HIV proteins Nef and Tat both inhibit p53-dependent apoptosis and have been found in the cytoplasm of HIV+ HNSCC samples, possibly also contributing to tumorigenesis and progression.[16,17] In addition to unique biomolecular features, HIV+ HNSCC is also histologically distinct, being almost four times more likely to contain multinucleated giant cells compared to HIV− HNSCC.[8] There is also evidence to suggest that chronic exposure to HIV viral antigens results in PD1-regulated *T*-cell exhaustion, contributing to disease progression.[2,3,15,17]

However, there is also some evidence against a causal role of HIV in the development of HNSCC. There has been a progressive increase in the incidence of non-HIV related cancers among PLWH despite cART, and compared to PLWH on cART, untreated individuals have not been found to have an increased risk of HNSCC.[13,18] With the exception of one study, CD4 count has also not been identified as being significantly related to risk of non-HIV related cancers, and in the present study, neither CD4 nadir nor peak viral load was associated with overall survival.[4] So, while HNSCC is clearly more common in PLWH, it does not seem to be related to the amount of virus or severity of disease. As such, smoking has been proposed as a confounding mechanism underlying the difference in HNSCC incidence between people with and without HIV.[13] On a population level, smoking is, in fact, about twice as common in PLWH (33.6% vs. 16.8%), and among PLWH diagnosed with HNSCC, the smoking rate is around 76%.[3,19] The risk of HNSCC is about 10 times greater for smokers than never-smokers, so it follows logically that smoking is at least partially responsible for the apparent risk in PLWH.[20] Furthermore, overall survival for HNSCC is almost 10 years lower in those with a history of smoking than those without.[21]

To eliminate this likely confounder in our study, we matched PLWH with controls who had the same smoking history (positive or negative). Because all PLWH—and thus all of the matched controls—in this study had a positive smoking history, there was no basis to determine whether presence of a smoking history affects outcomes. However, we did not find a significant relationship between pack-years of smoking and overall or disease-free survival in either group, despite previous work suggesting a strong dose–response relationship.[22] This discrepancy may due to the unreliability of pack-year reporting in medical records.[23]

HPV is another potential confounder of the relationship between HIV and LSCC incidence and survival, though the relationship is unclear. On the one hand, PLWH are 2–3 times more likely than uninfected individuals to carry oral HPV, and HPV-associated neoplasms are more common among PLWH; yet, HPV is detected in comparable

proportions of HIV+ (0%–20%) and HIV− (4.3%–24%) LSCCs.[4,7,10,13,14,24,25] HPV is associated with improved HNSCC survival, both among those with and those without HIV.[4,10,11,25,26] There is some evidence to suggest that HIV may potentiate HPV-related head and neck cancers, but whether these mechanisms are at play in LC specifically is not yet known.[3,13]

While this work represents the largest direct comparison to date of $HIV^+$ LSCC patients to $HIV^-$ controls, it is still limited by a relatively small sample size and early censoring, particularly in the HIV+ group. The analysis had 87% power to detect the observed difference in overall survival, so this null result is unlikely to be related to sample size, though we cannot completely rule out the possibility of a smaller difference in overall survival. On the other hand, due to the limited number of PLWH, this study was inadequately powered to detect the observed difference in disease-free survival. This is also a single-institution study at a large tertiary care center, so the generalizability of the results is uncertain. Furthermore, patients frequently received their HIV primary care in the community, and because these medical records were mostly not accessible in the EMR, much of the HIV-related data such as peak viral loads, CD4 nadirs, and date of HIV diagnosis were based on patient self-report. Results related to these parameters should thus not be over-interpreted. Finally, while care was taken to perform appropriate matching and model construction, unexamined covariates such as tumor HPV status or treatment selection may confound or modify the effect of HIV on LSCC outcomes.

In summary, since the advent of cART, the life expectancy of PLWH is approaching that of uninfected individuals. As these patients live longer, the incidence of non-HIV related cancers, including LC, has substantially increased in this group, not only meeting, but actually exceeding that of the general population. As such, significant work has gone into characterizing the potential role of HIV in the development of head and neck cancers, whether through direct causality, indirect mediation, or behavioral associations. Etiology notwithstanding, few have actually studied the outcomes of LC in PLWH compared to uninfected individuals. Thus, we report a retrospective case–control study including 22 $HIV^+$ patients with LC and 88 age-, sex-, and smoking-matched $HIV^-$ controls—the largest such study to date. We found that, while PLWH were diagnosed about 6 years younger than controls, overall and disease-free survival were not significantly different between the two groups, even after adjusting for age, sex, ethnicity, pack-years of smoking, age at LC diagnosis, *T* status, *N* status, and tumor site. Furthermore, peak viral load and CD4 nadir were not found to be related to survival in PLWH, though the fidelity of this data was limited and these results should be confirmed.

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## CONFLICT OF INTEREST

The authors have no conflict of interest.

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