HHS Public Access

Author manuscript

J Cancer Res Clin Oncol. Author manuscript; available in PMC 2020 March 13.

Published in final edited form as:

J Cancer Res Clin Oncol. 2017 November ; 143(11): 2341–2350. doi:10.1007/s00432-017-2481-8.

Prognostic implications of human papillomavirus status for patients with non-oropharyngeal head and neck squamous cell carcinomas

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Abstract

Purpose—We examined overall survival in a large cohort of patients with human papillomavirus (HPV)-positive and HPV-negative non-oropharyngeal squamous cell carcinoma of the head and neck (non-OPSCC).

Methods—Patients diagnosed with non-OPSCC and known HPV status were identified in the National Cancer Database (NCDB). Multivariate logistic regression was applied to examine factors associated with HPV status. Multivariate analysis was utilized to determine factors correlated with overall survival. Propensity score-weighted Kaplan-Meier estimation was used to adjust for confounders in survival analyses. Multiple imputation method was used for sensitivity analysis.

Results—We identified 19,993 non-OPSCC patients with 5070 being positive for HPV in the NCDB. Median follow-up was 23.5 months. HPV-positive patients were more commonly male, white, with a lower comorbidity index score, presenting with T-stage <2, and N-stage ≥1. Unadjusted 3-year overall survival was 62% and 80% for HPV-negative and HPV-positive patients,

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Compliance with ethical standards

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Electronic supplementary material The online version of this article (doi:10.1007/s00432-017-2481-8) contains supplementary material, which is available to authorized users.

Conflict of interest The authors have no conflicts of interest.

respectively ($p < 0.0001$). On multivariate analysis, mortality was reduced for HPV-positive patients with early stage (HR = 0.68) and locally advanced disease (HR = 0.46). Adjusted 3-year overall survival was 65% for HPV-negative and 76% for HPV-positive patients ($p < 0.0001$). The survival advantage of HPV was maintained in all subsites and robust on sensitivity analysis.

Conclusions—Patients with HPV-positive non-OPSCC exhibit similar characteristics as HPV-positive OPSCC. Overall survival was significantly higher for patients with HPV-positive versus HPV-negative non-OPSCC. These data reveal that HPV-positive non-OPSCC represent a favorable cohort that warrants recognition in the design of future clinical trial investigation.

Keywords

Head and neck cancer; Survival outcomes; Human papillomavirus; Non-oropharyngeal; Squamous cell carcinoma

Introduction

Head and neck squamous cell carcinoma represents a spectrum of tumors arising from the oral cavity, pharynx, larynx, and sinuses. Established risk factors including tobacco and alcohol are associated with all subsites, while detection of human papillomavirus (HPV) is predominantly an attendant finding of oropharyngeal squamous cell carcinoma (OPSCC) (Maier et al. 1992; Gillison et al. 2008). The prevalence of HPV-positive OPSCC has increased over the past 3 decades and now approaches 70% (Chaturvedi et al. 2011). The salient clinical difference between HPV-positive and HPV-negative OPSCC is prognosis. Indeed, HPV-positivity confers a reduction in death by at least one-half (Licitra et al. 2006; Rischin et al. 2010; Gillison et al. 2012; Kumar et al. 2016). Clinically, the favorable prognosis has led to the development of numerous prospective clinical trials evaluating de-escalation of therapy (Mirghani et al. 2015). Conversely, cooperative oncology groups and institutional studies are evaluating the impact of treatment intensification for patients with HPV-negative tumors given their poor outcomes. Thus, identifying subsets of head and neck patients with either favorable or unfavorable prognosis has enabled prospective evaluation of risk-adapted therapies.

The prognostic implication of HPV infection and detection of its surrogate marker p16 in non-nasopharyngeal, non-OPSCC head and neck subsites is controversial. Concordance between HPV DNA and overexpression of p16 is not as robust in non-OPSCC subsites as in OPSCC, and has resulted in disparate reports on the incidence of HPV and p16 positivity in these subsites (Harris et al. 2011; Chung et al. 2014). Despite inconsistency, ranges of HPV/p16 detection approximate 10–30% with some variability across subsites (Clayman et al. 1994; Harris et al. 2011; Isayeva et al. 2012; Chung et al. 2014; Lassen et al. 2014; Shaughnessy et al. 2014). Cooperative group studies, single institution series, and epidemiologic analyses have reported both favorable (Harris et al. 2011; Chung et al. 2014; Shaughnessy et al. 2014) and unfavorable (Clayman et al. 1994; Lassen et al. 2014; D'Souza et al. 2016) prognostic implications of HPV/p16 detection in non-OPSCC. Reasons underlying these disparate outcomes are unclear. Here, we reviewed the National Cancer Database to examine much larger patient cohorts enabling statistical adjustments for

confounders in comparing overall survival of patients with HPV-positive and HPV-negative non-OPSCC.

Methods

Data source and patient selection

We performed a retrospective, observational, cohort study using the National Cancer Database (NCDB) for all patients with non-OPSCC between 2004 and 2012 (American College of Surgeons Commission on Cancer, American Cancer Society, National Cancer Data Base 2014). Overall survival is the only available outcome data. Patients who were designated as “HPV-positive” included those coded as non-16-non-18 high-risk HPV, HPV-16 only, HPV-18 only, and HPV-16 and −18 (CS_SITESPECIFIC_FACTOR_10 = 020, 030, 040, and 050). “HPV-negative” patients included those coded in the NCDB as CS_SITESPECIFIC_FAC-TOR_10 = 000. We excluded low-risk HPV-positive, high-risk HPV-positive not otherwise specified, HPV-positive not otherwise specified, and those that were not tested for HPV (CS_SITESPECIFIC_FACTOR_10 = 010, 060, 070, 998, 997, 998, and 999). Patients with oral cavity primary tumors managed with definitive radiotherapy approaches were excluded to reduce the possible contamination of patients with oropharyngeal cancers into the oral cavity cohorts.

Statistical analysis

The primary endpoint was overall survival (OS) defined as the date of diagnosis to date of death. All baseline demographics and patient characteristics were analyzed by Pearson chi-square tests except for age and tumor size, which were analyzed with Wilcoxon signed-rank test. Multivariate logistic regression with stepwise variable selection was applied to patient and tumor characteristics to examine factors associated with a positive HPV status.

Kaplan-Meier method was used to compare survival outcomes between HPV-positive and HPV-negative groups. Univariate survival analysis and multivariate analysis were performed with Cox proportional hazards models using OS as outcomes. Factors found to be significant in univariate analysis were included and selected by stepwise selection in multivariate analysis.

To account for confounding and covariate imbalances between HPV-positive and HPV-negative groups, we used propensity score-weighted Kaplan-Meier estimation with inverse probability of treatment-weighting (IPTW), where the probability of HPV-positive status (the propensity score) was estimated using multivariate logistic regression. Propensity score model used covariates found to be significant in multivariate survival analysis, including age, Charlson/Deyo comorbidity score, insurance, tumor size, treatments, head and neck subsites, overall stage, T-stage, and N-stage. Note that HPV is not an “intervention” in the conventional sense of causal inference, since it is not able to be manipulated. The propensity score here is a tool to balance the covariate distribution between groups for studies with either causal or non-causal purposes (Li et al. 2013). We evaluated the distribution of propensity scores for each HPV group and confirmed sufficient overlap in the distributions. We then grouped patients into quintiles according to their estimated propensity scores and

used the Cochrane-Mantele-Haenszel test to verify that covariates were balanced across all strata.

Above analyses were limited to patients with known HPV status, and additional sensitivity analyses were performed prior to removing patients with unknown HPV status. For unknown HPV status, we used the multiple imputation method based on missing at random (MAR) assumption (Rubin 1987). All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). All p values were two-sided, and a $p \leq 0.05$ was considered statistically significant.

Results

We identified 19,993 non-OPSCC patients with 5070 positive for HPV in the National Cancer Database (NCDB) treated definitively from 2004 to 2012. Baseline patient demographics and disease characteristics are listed in Table 1. Significant factors associated with HPV-positive non-OPSCC disease include male sex, white race, private insurance, income ≥$48,000, treatment at a high-volume center, lower comorbidity index score, oral cavity primary, tumor size, T-stage <2, and lymph node positive disease (Supplemental Table 1).

Outcomes analyses

Median follow-up for the entire cohort was 23.5 months. Three-year unadjusted survival rates for HPV-negative and HPV-positive non-OPSCC patients were 62 and 80%, respectively ($p < 0.0001$) (Table 3). IPTW-adjusted survival rates for the same cohorts were 65 and 76%, respectively (Table 3). Unadjusted and IPTW-adjusted Kaplan-Meier survival curves are shown in Fig. 1a, b.

Patients were analyzed by disease site and stage: early (I and II) and locally advanced (III-IVB). Median follow-up for early stage patients was 24.3 and 23.1 months for locally advanced. Unadjusted and adjusted 3-year overall survival for early stage and locally advanced disease by primary tumor site is shown in Table 2. As there were limited numbers of early stage hypopharynx patients, both early stage and locally advanced patients were grouped together. Unadjusted Kaplan-Meier survival curves for early stage and locally advanced non-OPSCC patients by subsite are shown in Fig. 2a–e.

Factors associated with overall survival

Univariate and multivariate analyses for overall survival of patients with HPV-negative and HPV-positive non-OPSCC were performed for both early stage and locally advanced disease. For early stage (HR = 0.68; 95% CI 0.51–0.92) and late stage (HR = 0.46; 95% CI 0.39–0.53) patients, only HPV-positive status was associated with improved overall survival. Factors associated with worse survival are shown in Tables 3 and 4.

Sensitivity analyses for overall survival for early stage and locally advanced patients were performed to assess the impact of unknown HPV status of patients identified in the original cohort. HPV-positive status maintained a significant association with improved survival for

early stage (HR = 0.71; 95% CI 0.55–0.92) and locally advanced patients (HR = 0.46; 95% CI 0.39–0.53) (Supplemental Tables 2 and 3).

Discussion

Here, we present the largest series evaluating HPV status in non-OPSCC. We evaluated 14,923 HPV-negative and 5070 HPV-positive non-OPSCC cases, and demonstrate improved overall survival for those with HPV association. These findings were consistent across oral cavity, hypopharynx, and larynx subsites. Improved outcomes were independent of clinical risk groupings, although the magnitude of difference was more pronounced in patients with locally advanced compared to early stage disease. Indeed, the reduction in death in the non-OPSCC associated with HPV was very similar to that ascribed to patients with HPV-positive OPSCC (Licitra et al. 2006; Rischin et al. 2010; Gillison et al. 2012; Kumar et al. 2016).

There are well-recognized epidemiologic differences between patients with HPV-positive and HPV-negative OPSCC. Notably, patients with HPV-positive OPSCC tend to be healthier, harbor more extensive adenopathy, and present with small primary tumors (Ang et al. 2010; Dahlstrom et al. 2013). We report comparable findings for HPV-positive non-OPSCC including an association with less patient comorbidities, lower T-stage, and higher nodal burden compared to HPV-negative patients. Taken together, these data demonstrate that the patient and disease characteristics of HPV-positive OPSCC and non-OPSCC are similar and suggest a related disease process.

Our data support an increasing body of evidence regarding the favorable prognostic implications of HPV status for non-OPSCC. A combined analysis of three cooperative oncology group trials reported that p16 expression was associated with improved progression-free survival and OS in this patient population (Chung et al. 2014). In a single institution study evaluating oral cavity SCC, p16 was shown to be a favorable prognostic factor correlating with improved relapse-free survival and OS (Harris et al. 2011). In a separate smaller study, patients with either HPV/p16 positive laryngeal or hypopharyngeal SCC treated with definitive therapy exhibited 2-year disease-free survival (DFS) and local recurrence-free survival (LRFS) of 100% in stark contrast to HPV/p16 negative patients who had 2-year DFS and LRFS rates of 68 and 72%, respectively (Shaughnessy et al. 2014). Another more recent series demonstrated that patients with HPV16 DNA-positive p16-overexpressing hypopharyngeal cancer exhibited better clinical outcome compared with those with HPV-negative cancer (Sivars et al. 2016).

The reason for the favorable prognosis identified for non-OPSCC HPV-positive patients in the current study is not entirely clear. Patients with HPV-positive disease had lower comorbidity index scores. Although we matched for comorbidity index scores, the range and granularity of comorbidity data in the NCDB is limited to a truncated Charlson/Deyo comorbidity index listing 0, 1, or 2. The extent of performance status as well as severity of illness unrelated to the cancer diagnosis is muted as a result. In a clinical context, this information would likely play a larger role in oncologic management.

Oral cavity primary tumors comprised 84.5% of patients in the HPV-positive group, whereas in the HPV-negative group, they accounted for only 57% of cases. One possibility is that patients underwent HPV analysis in an attempt to determine primary tumor origin given the proximity of the oral cavity to the oropharynx. It is possible that the improved survival in the oral cavity population that was HPV-positive may indicate that some were actually oropharyngeal primaries, which are known to exhibit favorable outcomes (Ang et al. 2010). In an attempt to control for this possible confounder, we evaluated only oral cavity primaries that underwent primary surgery with or without adjuvant treatment as this is standard of care for this patient cohort and excluded those that received a primary radiotherapy approach as this is a more standard approach for oropharyngeal tumors. In support of our clinical findings, however, Harris et al. reported a similar estimated 5-year OS rate of 80% for patients with p16 positive oral cavity primaries, while others have demonstrated an association with well-differentiated tumors that exhibit low recurrence rates (Elango et al. 2011; Harris et al. 2011). Furthermore, the 30% HPV-positive rate of oral cavity patients is well within the reported range (Sugiyama et al. 2003; Smith et al. 2004). Though attempts to control for oropharyngeal contamination in the oral cavity cohorts were made and published data exist in support of our reported outcomes, caution needs to be taken regarding our findings given the retrospective nature of the study and limited ability to confirm the primary tumor location.

Despite our data and others demonstrating improved outcomes for HPV-positive non-OPSCC, studies exist to the contrary. For example, investigators using the DAHANCA database compared clinical outcomes of patients with advanced p16 and non-p16 expressing laryngeal and hypopharyngeal tumors and were not able to identity an outcome advantage for patients with p16-positive disease (Lassen et al. 2011). Furthermore, attention needs to be focused on a recently published pooled analysis from two academic treatment centers, which confirmed the favorable prognosis of HPV status in oropharynx cancers and refuted any survival advantage for patients with larynx, oral cavity, or nasopharynx cancers (Fakhry et al. 2017). There were major differences in the demographics between the HPV-positive patient cohorts between this study and the aforementioned which may have contributed to the differences in outcomes that need to be considered. Specifically, median age, sex, race, inclusion of nasopharynx patients, and rate of HPV-positivity in the oral cavity cohorts were different between the different study cohorts.

Limitations of the current study are inherent to the data available in the NCDB. Routine HPV testing in non-OPSCC is not standard of care, as such; selection bias must exist in the data set. Therefore, factors driving the decision to test for HPV status may be contributing to the improved outcomes of the HPV-positive non-OPSCC cohort. Another limitation is the lack of additional outcomes data. It is known that HPV-positive OPSCC exhibit improved outcomes following development of progressive disease (Fakhry et al. 2014). Further investigation is, therefore, warranted in the HPV-positive non-OPSCC cohort to evaluate if similar trends may explain the current improvement of their outcomes. A significant limitation is the lack of tobacco use data. It is well established that smoking reduces the favorable prognosis associated with HPV status in OPSCC. Whether or not this holds true in non-OPSCC is unclear.

We identified improved survival outcomes for patients with HPV-positive versus HPV-negative disease that parallels the improved survival of patients with HPV-positive OPSCC. This finding provides further rationale for HPV testing of non-OPSCC head and neck cancer patients, and suggests the value of including HPV status as a stratifying variable in the design of clinical trials for head and neck cancer patients beyond OPSCC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding This work was funded in part by NIH/NCI P30 CA014520-UW Comprehensive Cancer Center Grant and NIH P50 DE026787-UW Head and Neck SPORE Grant.

References

Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tan PF, Westra WH, Chung CH, Jordan RC, Lu C, Kim H, Axelrod R, Silverman CC, Redmond KP, Gillison ML (2010) Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 363(1):24–35 [PubMed: 20530316]

Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, Jiang B, Goodman MT, Sibug-Saber M, Cozen W, Liu L, Lynch CF, Wentzensen N, Jordan RC, Altekruse S, Anderson WF, Rosenberg PS, Gillison ML (2011) Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol 29(32):4294–4301 [PubMed: 21969503]

Chung CH, Zhang Q, Kong CS, Harris J, Fertig EJ, Harari PM, Wang D, Redmond KP, Shenouda G, Trotti A, Raben D, Gillison ML, Jordan RC, Le QT (2014) p16 protein expression and human papillomavirus status as prognostic biomarkers of nonoropharyngeal head and neck squamous cell carcinoma. J Clin Oncol 32(35):3930–3938 [PubMed: 25267748]

Clayman GL, Stewart MG, Weber RS, el-Naggar AK, Grimm EA (1994) Human papillomavirus in laryngeal and hypopharyngeal carcinomas. Relationship to survival. Arch Otolaryngol Head Neck Surg 120(7):743–748 [PubMed: 8018327]

Dahlstrom KR, Calzada G, Hanby JD, Garden AS, Glisson BS, Li G, Roberts DB, Weber RS, Sturgis EM (2013) An evolution in demographics, treatment, and outcomes of oropharyngeal cancer at a major cancer center: a staging system in need of repair. Cancer 119(1):81–89 [PubMed: 22736261]

D'Souza G, Anantharaman D, Gheit T, Abedi-Ardekani B, Beachler DC, Conway DI, Olshan AF, Wunsch-Filho V, Toporcov TN, Ahrens W, Wisniewski K, Merletti F, Boccia S, Tajara EH, Zevallos JP, Levi JE, Weissler MC, Wright S, Scelo G, Mazul AL, Tommasino M, Brennan P, Cadoni G (2016) Effect of HPV on head and neck cancer patient survival, by region and tumor site: a comparison of 1362 cases across three continents. Oral Oncol 62:20–27 [PubMed: 27865368]

Elango KJ, Suresh A, Erode EM, Subhadradevi L, Ravindran HK, Iyer SK, Iyer SK, Kuriakose MA (2011) Role of human papilloma virus in oral tongue squamous cell carcinoma. Asian Pac J Cancer Prev 12(4):889–896 [PubMed: 21790221]

Fakhry C, Zhang Q, Nguyen-Tan PF, Rosenthal D, El-Naggar A, Garden AS, Soulieres D, Trotti A, Avizonis V, Ridge JA, Harris J, Le QT, Gillison M (2014) Human papillomavirus and overall survival after progression of oropharyngeal squamous cell carcinoma. J Clin Oncol 32(30):3365–3373 [PubMed: 24958820]

Fakhry C, Westra WH, Wang SJ, van Zante A, Zhang Y, Rettig E, Yin LX, Ryan WR, Ha PK, Wentz A, Koch W, Richmon JD, Eisele DW, D'Souza G (2017) The prognostic role of sex, race, and human papillomavirus in oropharyngeal and nonoropharyngeal head and neck squamous cell cancer. Cancer 123(9):1566–1575 [PubMed: 28241096]

Gillison ML, D'Souza G, Westra W, Sugar E, Xiao W, Begum S, Viscidi R (2008) Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. J Natl Cancer Inst 100(6):407–420 [PubMed: 18334711]

Gillison ML, Zhang Q, Jordan R, Xiao W, Westra WH, Trotti A, Spencer S, Harris J, Chung CH, Ang KK (2012) Tobacco smoking and increased risk of death and progression for patients with p16-positive and p16-negative oropharyngeal cancer. J Clin Oncol 30(17):2102–2111 [PubMed: 22565003]

Harris SL, Thorne LB, Seaman WT, Hayes DN, Couch ME, Kimple RJ (2011) Association of p16(INK4a) overexpression with improved outcomes in young patients with squamous cell cancers of the oral tongue. Head Neck 33(11):1622–1627 [PubMed: 21990227]

Isayeva T, Li Y, Maswahu D, Brandwein-Gensler M (2012) Human papillomavirus in non-oropharyngeal head and neck cancers: a systematic literature review. Head Neck Pathol 6(Suppl 1):S104–S120 [PubMed: 22782230]

Kumar B, Cipolla MJ, Old MO, Brown NV, Kang SY, Dziegielewski PT, Durmus K, Ozer E, Agrawal A, Carrau RL, Schuller DE, Leon ME, Pan Q, Kumar P, Wood V, Burgers J, Wakely PE Jr, Teknos TN (2016) Surgical management of oropharyngeal squamous cell carcinoma: survival and functional outcomes. Head Neck 38(Suppl 1):E1794–E1802 [PubMed: 26694981]

Lassen P, Eriksen JG, Krogdahl A, Therkildsen MH, Ulhoi BP, Overgaard M, Specht L, Andersen E, Johansen J, Andersen LJ, Grau C, Overgaard J, Danish H, Neck Cancer G (2011) The influence of HPV-associated p16-expression on accelerated fractionated radiotherapy in head and neck cancer: evaluation of the randomised DAHANCA 6&7 trial. Radiother Oncol 100(1):49–55 [PubMed: 21429609]

Lassen P, Primdahl H, Johansen J, Kristensen CA, Andersen E, Andersen LJ, Evensen JF, Eriksen JG, Overgaard J, Danish H, Neck Cancer G (2014) Impact of HPV-associated p16-expression on radiotherapy outcome in advanced oropharynx and non-oropharynx cancer. Radiother Oncol 113(3):310–316 [PubMed: 25544647]

Li F, Zaslavsky AM, Landrum MB (2013) Propensity score weighting with multilevel data. Stat Med 32(19):3373–3387 [PubMed: 23526267]

Licitra L, Perrone F, Bossi P, Suardi S, Mariani L, Artusi R, Oggionni M, Rossini C, Cantu G, Squadrelli M, Quattrone P, Locati LD, Bergamini C, Olmi P, Pierotti MA, Pilotti S (2006) High-risk human papillomavirus affects prognosis in patients with surgically treated oropharyngeal squamous cell carcinoma. J Clin Oncol 24(36):5630–5636 [PubMed: 17179101]

Maier H, Dietz A, Gewelke U, Heller WD, Weidauer H (1992) Tobacco and alcohol and the risk of head and neck cancer. Clin Investig 70(3–4):320–327

Mirghani H, Amen F, Blanchard P, Moreau F, Guigay J, Hartl DM, Lacau St Guily J (2015) Treatment de-escalation in HPV-positive oropharyngeal carcinoma: ongoing trials, critical issues and perspectives. Int J Cancer 136(7):1494–1503 [PubMed: 24622970]

Rischin D, Young RJ, Fisher R, Fox SB, Le QT, Peters LJ, Solomon B, Choi J, O'Sullivan B, Kenny LM, McArthur GA (2010) Prognostic significance of p16INK4A and human papillomavirus in patients with oropharyngeal cancer treated on TROG 02.02 phase III trial. J Clin Oncol 28(27):4142–4148 [PubMed: 20697079]

Rubin DB (1987) Multiple imputation for nonresponse in surveys. Wiley, New York

Shaughnessy JN, Farghaly H, Wilson L, Redman R, Potts K, Bump-ous J, Silverman C, Dunlap NE (2014) HPV: a factor in organ preservation for locally advanced larynx and hypopharynx cancer? Am J Otolaryngol 35(1):19–24 [PubMed: 24119488]

Sivars L, Bersani C, Grun N, Ramqvist T, Munck-Wikland E, Von Buchwald C, Dalianis T (2016) Human papillomavirus is a favourable prognostic factor in cancer of unknown primary in the head and neck region and in hypopharyngeal cancer. Mol Clin Oncol 5(6):671–674 [PubMed: 28105346]

Smith EM, Ritchie JM, Summersgill KF, Klussmann JP, Lee JH, Wang D, Haugen TH, Turek LP (2004) Age, sexual behavior and human papillomavirus infection in oral cavity and oropharyngeal cancers. Int J Cancer 108(5):766–772 [PubMed: 14696105]

Sugiyama M, Bhawal UK, Dohmen T, Ono S, Miyauchi M, Ishi-kawa T (2003) Detection of human papillomavirus-16 and HPV-18 DNA in normal, dysplastic, and malignant oral epithelium. Oral Surg Oral Med Oral Pathol Oral Radiol Endodontol 95(5):594–600

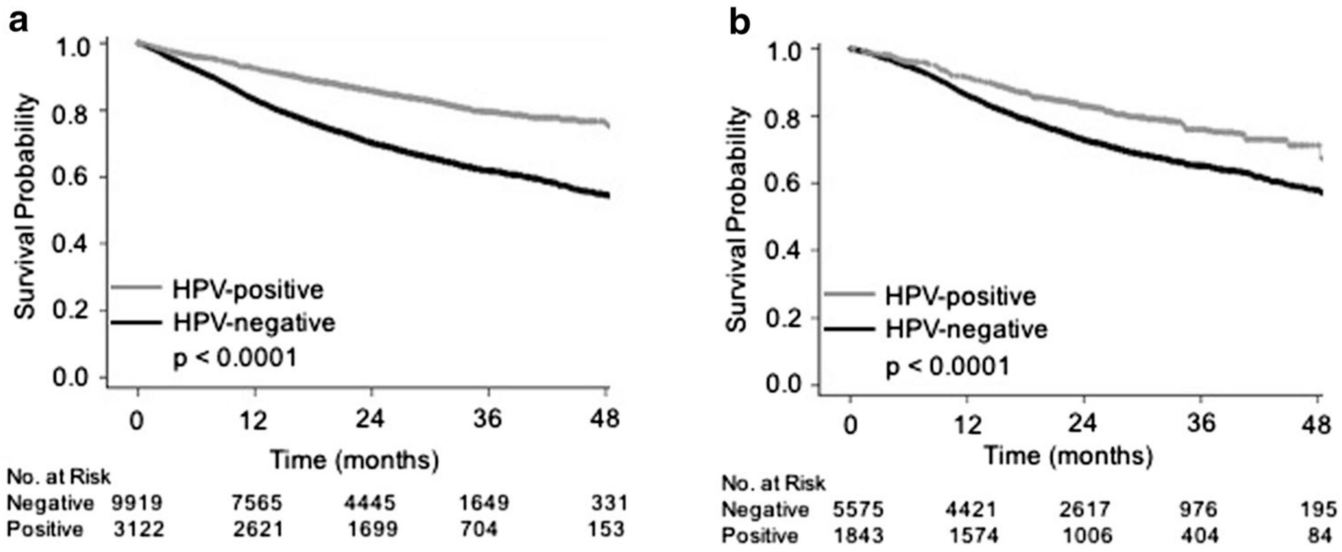

Fig. 1.

a Unadjusted and **b** IPTW-adjusted Kaplan–Meier overall survival curves for all HPV-negative and HPV-positive non-OPSCC

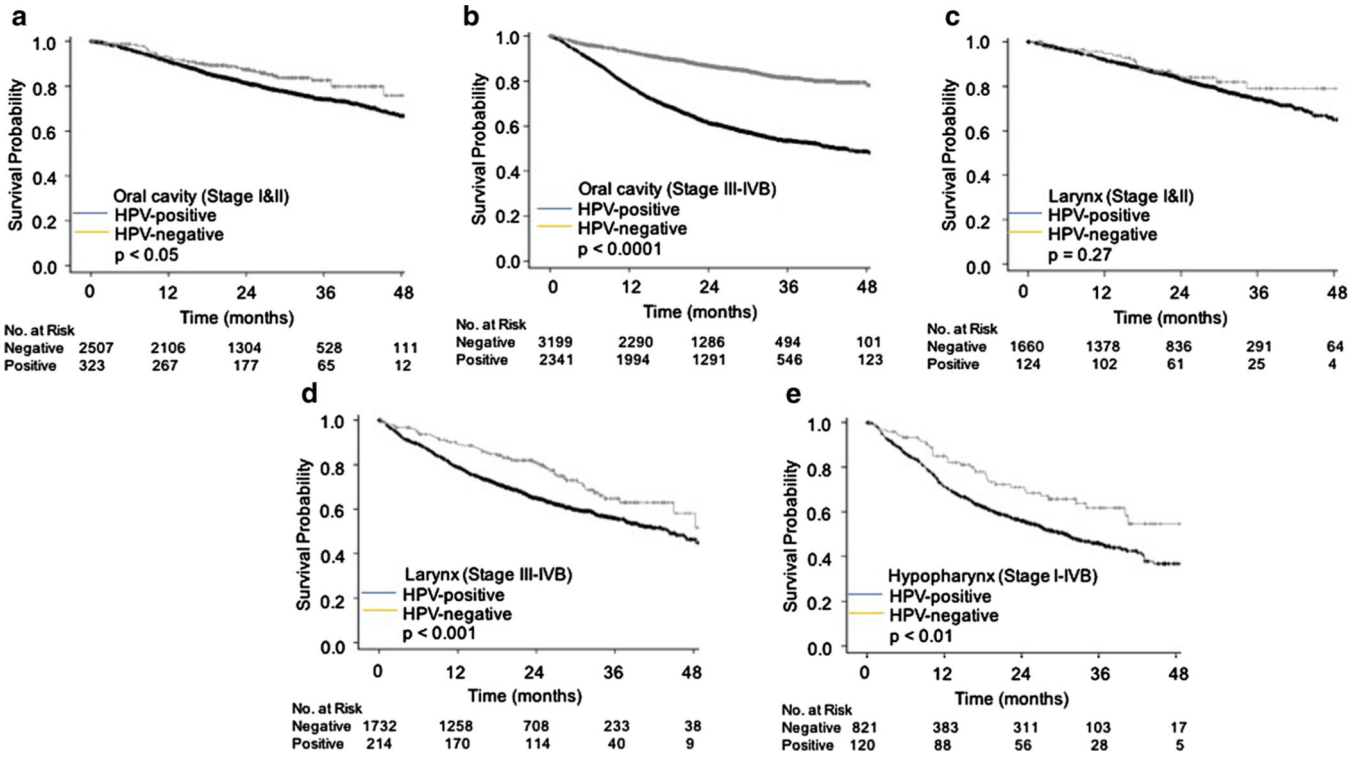

Fig. 2.

Unadjusted Kaplan-Meier overall survival curves for HPV-negative and HPV-positive early stage and locally advanced oral cavity (**a, b**), larynx (**c, d**), and combined early stage and locally advanced hypopharynx (**e**)

Table 1

Baseline demographics and patient characteristics

	HPV negative 14,923	HPV positive 5070	All 19,993	*p* value
Age, years				<0.001
Median (range)	63 (18–90)	60 (19–90)	62 (18–90)	
Mean (SD)	63.1 (12.2)	60.3 (10.2)	62.4 (11.8)	
Tumor size (mm)				<0.001
Median (range)	25 (0–100)	27 (0–100)	25 (0–100)	
Mean (SD)	28.2 (16.7)	28.4 (14.3)	28.3 (16.1)	
Age				<0.001
<65	8272 (55.4)	3391 (66.9)	11,663 (58.3)	
≥65	6651 (44.6)	1679 (32.1)	8330 (41.7)	
Sex				<0.001
Male	10,451 (70.0)	4213 (83.1)	14,664 (73.4)	
Female	4472 (30.0)	857 (16.9)	5329 (26.7)	
Race				<0.001
White	12,170 (81.6)	4581 (90.4)	16,751 (83.8)	
Black	1630 (10.9)	233 (4.6)	1863 (9.3)	
Hispanic	594 (4.0)	142 (2.8)	736 (3.7)	
Asian/Pacific islander	319 (2.1)	55 (1.08)	374 (1.9)	
Other	117 (0.8)	20 (0.4)	137 (0.7)	
Unknown	93 (0.6)	39 (0.8)	132 (0.7)	
Charlson/Deyo comorbidity score				<0.001
0	11,050 (74.1)	4110 (81.1)	15,160 (75.8)	
1	2922 (19.6)	768 (15.2)	3690 (18.5)	
≥2	951 (6.4)	192 (3.8)	1143 (5.7)	
Insurance type				<0.001
Private	5374 (36.0)	2758 (54.4)	8132 (40.7)	
Medicare	6605 (44.3)	1676 (33.1)	8281 (41.4)	
Medicaid	1631 (10.9)	279 (5.5)	1910 (9.6)	
Other gov.	246 (1.7)	103 (2.0)	349 (1.8)	

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	HPV negative 14,923	HPV positive 5070	All 19,993	*p* value
No insurance	831 (5.6)	208 (4.1)	1039 (5.2)	
Unknown	236 (1.6)	46 (0.9)	282 (1.4)	
Income				<0.001
<$48,000	6603 (44.3)	1723 (34.0)	8326 (41.6)	
≥$48,000	8255 (55.3)	3329 (65.7)	11,584 (57.9)	
Unknown	65 (0.4)	18 (0.4)	83 (0.4)	
Location				0.44
Urban	10,898 (73.0)	3748 (73.9)	14,646 (73.3)	
Non-urban	3631 (24.3)	1196 (23.6)	4827 (24.1)	
Unknown	394 (2.6)	126 (2.5)	520 (2.6)	
Facility				<0.001
Academic	7311 (49.0)	2727 (53.8)	10,038 (50.2)	
Community	7612 (51.0)	2343 (46.2)	9955 (49.8)	
Facility volume				<0.001
High volume	3431 (23.0)	1508 (29.7)	4939 (24.7)	
Low volume	11,492 (77.0)	3562 (70.3)	15,054 (75.3)	
Head and neck subsites				<0.001
Oral cavity	8507 (57.0)	4282 (84.5)	12,789 (64.0)	
Hypopharynx	1218 (8.2)	212 (4.2)	1430 (7.2)	
Larynx	5198 (34.8)	576 (11.4)	5774 (28.9)	
RT dose				<0.001
None	5203 (34.9)	874 (17.2)	6077 (30.4)	
Low (50–65 Gy)	2444 (16.4)	683 (13.5)	3127 (15.6)	
High (65–80 Gy)	5541 (37.1)	2964 (58.5)	8505 (42.5)	
Unknown	1735 (11.6)	549 (10.8)	2284 (11.4)	
Sequence of chemotherapy and radiotherapy				<0.001
Chemoradiotherapy	4068 (27.3)	2529 (49.9)	6597 (33.0)	
Chemotherapy ≫ radiotherapy	1157 (7.8)	584 (11.5)	1741 (8.7)	
Radiotherapy ≫ chemotherapy	360 (2.4)	126 (2.5)	486 (2.4)	
Unknown	9338 (62.6)	1831 (36.1)	11,169 (55.9)	
Primary treatment				<0.001

	HPV negative 14,923	HPV positive 5070	All 19,993	*p* value
No treatment	763 (5.1)	149 (2.9)	912 (4.6)	
Surgery	3888 (26.1)	590 (11.6)	4478 (22.4)	
Radiotherapy	1789 (12.0)	411 (8.1)	2200 (11.0)	
Surgery ≫ radiotherapy	1778 (11.9)	405 (8.0)	2183 (10.9)	
Chemotherapy	298 (2.0)	80 (1.6)	378 (1.9)	
Chemoradiotherapy	3988 (26.7)	2647 (52.2)	6635 (33.2)	
Surgery ≫ chemoradiotherapy	1813 (12.2)	660 (13.0)	2473 (12.4)	
Unknown	606 (4.1)	128 (2.5)	734 (3.7)	
T-stage				<0.001
T1	4710 (31.6)	1483 (29.3)	6193 (31.0)	
T2	4488 (30.1)	1820 (35.9)	6308 (31.6)	
T3	2776 (18.6)	862 (17.0)	3638 (18.2)	
T4	2775 (18.6)	707 (13.9)	3482 (17.4)	
Unknown	174 (1.2)	198 (3.9)	372 (1.9)	
N-stage				<0.001
0	8786 (58.9)	1191 (23.5)	9977 (49.9)	
1	1847 (12.4)	824 (16.2)	2671 (13.4)	
2	4050 (27.1)	3020 (59.6)	7070 (35.4)	
3	176 (1.2)	26 (0.5)	202 (1.0)	
Unknown	64 (0.4)	9 (0.2)	73 (0.4)	

Table 2

Unadjusted and adjusted 3-year survival probabilities (95% CIs) for HPV ± non-OPSCC using IPTW method

	Unadjusted 3-year survival rate		Adjusted 3-year survival rate	
	HPV-negative	**HPV-positive**	**HPV-negative**	**HPV-positive**
All	62% (61–63%)	80% (78–81%)	65% (64–67%)	76% (70–80%)
Early stage	74% (72–75%)	81% (76–85%)	74% (72–76%)	79% (67–87%)
Late stage	53% (51–55%)	79% (77–81%)	60% (57–62%)	74% (68–79%)
Oral cavity early	74% (72–76%)	83% (77–87%)	75% (72–77%)	79% (70–86%)
Oral cavity late	54% (51–56%)	81% (79–83%)	61% (58–64%)	75% (72–78%)
Larynx early	74% (71–77%)	79% (67–87%)	73% (67–78%)	81% (47–95%)
Larynx late	56% (53%−59%)	65% (56–72%)	60% (56–64%)	79% (60–90%)
Hypopharynx	46% (42–50%)	62% (50–71%)	50% (44–56%)	52% (28–72%)

J Cancer Res Clin Oncol. Author manuscript; available in PMC 2020 March 13.

Table 3

Univariate and multivariate analyses for overall survival of early stage (I&II) patients using Cox proportional hazards model

	Univariate			Multivariate		
	HR	**(95% CI)**	***p* value**	**HR**	**(95% CI)**	***p* value**
Age						
<65	1.00			1.00		
≥65	2.19	1.92–2.50	<0.001	1.82	1.50–2.20	<0.001
Sex						
Male	1.00		0.37			
Female	0.94	0.82–1.07				
Race						
White	1.00					
Non-white	1.01	0.85–1.21	0.88			
Charlson/Deyo comorbidity score						
0	1.00			1.00		
1	1.42	1.22–1.65	<0.001	1.09	0.88–1.34	0.43
≥2	2.10	1.68–2.63	<0.001	1.60	1.22–2.10	<0.001
Insurance type						
Private	1.00			1.00		
Non-private/unknown	2.21	1.91–2.55	<0.001	1.49	1.21–1.84	<0.001
Income						
<$48,000	1.00					
≥$48,000	0.82	0.72–0.93	<0.01			
Location						
Urban	1.00			1.00		
Non-urban	1.29	1.12–1.49	<0.001	1.21	1.02–1.44	<0.05
Facility						
Community	1.00					
Academic	0.90	0.80–1.03	0.12			
Facility volume						
Low	1.00					

	Univariate			Multivariate		
	HR	**(95% CI)**	***p* value**	**HR**	**(95% CI)**	***p* value**
High	0.90	0.77–1.04	0.15			
Head and neck subsites						
Oral cavity	1.00					
Hypopharynx	1.94	1.49–2.51	<0.001			
Larynx	0.98	0.85–1.12	0.72			
Dose						
None	1.00					
Low (50–65 Gy)	0.89	0.74–1.08	0.23			
High (65–80 Gy)	1.03	0.88–1.20	0.69			
Tumor size (cm)	1.37	1.30–1.44	<0.001	1.25	1.17–1.34	<0.001
Primary treatment						
No treatment	1.00			1.00		
Surgery	0.27	0.21–0.34	<0.001	0.23	0.17–0.33	<0.001
Radiotherapy	0.32	0.25–0.42	<0.001	0.29	0.20–0.43	<0.001
Surgery ≫ radiotherapy	0.23	0.17–0.31	<0.001	0.18	0.12–0.26	<0.001
Chemotherapy	1.85	1.14–3.00	<0.05	0.96	0.49–1.88	0.90
Chemoradiotherapy	0.53	0.39–0.71	<0.001	0.33	0.22–0.51	<0.001
Surgery ≫ chemoradiotherapy	0.43	0.31–0.59	<0.001	0.33	0.22–0.50	<0.001
T-stage						
1	1.00			1.00		
2	1.86	1.64–2.11	<0.001	1.44	1.19–1.73	<0.001
HPV						
Negative	1.00			1.00		
Positive	0.71	0.55–0.90	<0.01	0.68	0.51–0.92	<0.05

Table 4

Univariate and multivariate analyses for overall survival of locally advanced (III-IVB) patients using Cox proportional hazards model

	Univariate			Multivariate		
	HR	**(95% CI)**	***p* value**	**HR**	**(95% CI)**	***p* value**
Age						
<65	1.00		<0.001	1.00		<0.001
≥65	1.64	1.52–1.77		1.30	1.16–1.46	
Sex						
Male	1.00					
Female	1.17	1.07–1.27	<0.001			
Race						
White	1.00					
Non-white	1.35	1.23–1.48	<0.001			
Charlson/Deyo comorbidity score						
0	1.00			1.00		
1	1.33	1.21–1.46	<0.001	1.09	0.96–1.25	0.18
≥2	2.03	1.76–2.34	<0.001	1.81	1.48–2.22	<0.001
Insurance type						
Private	1.00			1.00		
Non-private/unknown	2.16	1.98–2.34	<0.001	1.38	1.22–1.57	<0.001
Income						
<$48,000	1.00					
≥$48,000	0.71	0.66–0.77	<0.001			
Location						
Urban	1.00					
Non-urban	1.09	1.00–1.19	<0.05			
Facility						
Community	1.00					
Academic	0.92	0.86–1.00	<0.05			
Facility volume						
Low	1.00					

	Univariate			Multivariate		
	HR	(95% CI)	*p* value	HR	(95% CI)	*p* value
High	0.82	0.75–0.89	<0.001			
Head and neck subsites						
Oral cavity	1.00			1.00		
Hypopharynx	1.90	1.69–2.13	<0.001	1.37	1.16–1.61	<0.001
Larynx	1.32	1.21–1.45	<0.001	0.93	0.80–1.07	0.28
Dose						
None	1.00					
Low (50–65 Gy)	0.42	0.37–0.48	<0.001			
High (65–80 Gy)	0.38	0.35–0.42	<0.001			
Tumor size (cm)	1.30	1.27–1.33	<0.001	1.19	1.15–1.24	<0.001
Primary treatment						
No treatment	1.00			1.00		
Surgery	0.28	0.24–0.33	<0.001	0.26	0.21–0.33	<0.001
Radiotherapy	0.41	0.34–0.49	<0.001	0.32	0.23–0.44	<0.001
Surgery ≫ radiotherapy	0.19	0.16–0.22	<0.001	0.17	0.14–0.22	<0.001
Chemotherapy	0.67	0.54–0.82	<0.001	0.63	0.47–0.85	<0.01
Chemoradiotherapy	0.16	0.14–0.19	<0.001	0.17	0.14–0.21	<0.001
Surgery ≫ chemoradiotherapy	0.19	0.16–0.22	<0.001	0.18	0.14–0.23	<0.001
T-stage						
1	1.00			1.00		
2	1.84	1.56–2.18	<0.001	1.33	1.06–1.67	<0.05
3	2.96	2.52–3.48	<0.001	1.59	1.24–2.03	<0.001
4	4.13	3.52–4.85	<0.001	1.96	1.54–2.51	<0.001
N-stage						
0	1.00			1.00		
1	0.72	0.65–0.81	<0.001	1.37	1.16–1.63	<0.001
2 and 3	0.76	0.69–0.83	<0.001	1.38	1.19–1.61	<0.001
HPV						
Negative	1.00			1.00		
Positive	0.34	0.31–0.38	<0.001	0.46	0.39–0.53	<0.001