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Impact of human papillomavirus status on survival in patients with oral cancer

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Abstract

Objectives: To examine the association between the human papillomavirus (HPV) infection and overall survival rate in patients with oral cancer.

Methods: This retrospective cohort study examined HPV status in 454 patients who were diagnosed with oral squamous cell carcinoma (OSCC) using the records of patients who underwent an initial treatment for OSCC between 2012 and 2021 at our institution as retrieved from the Cancer Registry database. The survival rates of the HPV-positive and HPV-negative groups were assessed and compared, and independent factors associated with survival were analyzed using multivariate Cox regression models.

Results: Of the 454 patients with OSCC included in this study, 73 were excluded for invalid HPV tests. Of the remaining patients, 39 and 342 patients were categorized into HPV-positive and HPV-negative groups, respectively. The prevalence of HPV-positive in the patients with OSCC was 10.2% (95% confidence interval 7.2%–13.2%). The 3-year overall survival rates were 56.2% and 53.9% in the HPV-positive and HPV-negative groups, respectively. The 3-year disease-specific survival rates in the HPV-positive and HPV-negative groups were 60.2% and 56.9%, respectively. The survival differences were not statistically significant. HPV-positive status was not a significant predictor of overall survival in the multivariable Cox regression analyses ($p = 0.728$).

Conclusion: The prevalence of HPV-positivity among patients with OSCC in the study was 10.2%. No association was found between HPV-positive status and 3-year overall survival in patients with oral cancer.

Level of evidence: Level 3.

KEYWORDS
human papillomavirus, oral cancer, prevalence, survival rate

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1 | INTRODUCTION

Approximately 90% of all oral cancers are squamous cell carcinoma.[1] It is the sixth most common type of cancer worldwide,[2] and the leading cause of head and neck malignancies in the Thai population.[3] In addition, oral cancer accounts for the highest number of outpatient visits and admissions among all head and neck cancers in Thailand.[4] In southern Thailand, patients with oral cancer have a 5-year survival rate of only 33%,[5] whereas the US Surveillance, Epidemiology, and End Results database reported a rate of 68.5%.[6] Despite improvements in universal healthcare and early diagnosis in Thailand, survival rates have not improved,[7] underlining the need for more intensive research on the risk factors and maximization of treatment efficacy.

Proven risk factors for oral cancer include tobacco smoking, betel nut chewing, and excessive alcohol consumption (>60 g/day or >4–7 drinks per week).[8] New data obtained in the past decade provide strong evidence for a correlation between human papillomavirus (HPV) and oropharyngeal cancer, leading to an evolving perspective on the attribution of oral cancers to this virus. HPV is a double-stranded deoxyribonucleic acid (DNA) virus that affects stratified squamous epithelial cells, particularly those in the skin and mucosa.[9] The mucosal cells in the oral cavity are, thus, susceptible to HPV infection. HPV DNA integration; E5, E6, and E7 gene expression; and p53/pRb host protein repression promote cell proliferation, which contributes to the carcinogenesis induced by this virus.[10] HPV is classified into high-risk (HPV 16, 18, 31, 33–35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 70, 73, 82) and low-risk (HPV 6, 11, 42–44) subgroups. High-risk HPV is generally considered oncogenic, while low-risk HPV is associated with benign epithelial lesions.[11,12] The predominant genotype in head and neck malignancies is HPV 16, followed by HPV 18,[13,14] which is thought to have a higher but under-reported prevalence in non-oropharyngeal head and neck cancers.[11]

The established correlation between HPV infection and favorable survival rates of oropharyngeal cancer has influenced changes in the staging system,[15] and has created momentum for clinical trials implementing treatment de-escalation.[16] A recent study found a marked prevalence of HPV in oral cancer,[17] suggesting a possible causative relationship. However, the role of HPV infection in oral cancer and its impact on patient prognosis remains unclear. Some studies have found a favorable prognostic impact of HPV positivity on overall survival in patients with oral cavity cancer.[18–21] Conversely, other studies reported unfavorable survival outcomes,[22–24] while other studies found no significant association between HPV status and survival outcomes.[25–31] Several study limitations could have contributed to these conflicting data, including a variety of HPV test sensitivities, resulting in marked differences in the prevalences of HPV in oral cancer ranging from 3.9% to 19.0%[22,24,30,32–34]; the influence of confounding factors, including proven causative factors such as tobacco and betel nut chewing[14]; and marked heterogeneities of the research populations. These differences complicate attempts to identify significant correlations between HPV and oral cancer prognosis, thereby highlighting the requirement for large, standardized investigations.

To date, no clear evidence has demonstrated a simple correlation between HPV infection and overall survival in patients with oral cancer, and information on the HPV genotypes in oral cancer is limited. Moreover, few studies with large sample sizes have been conducted to confirm the HPV status using HPV DNA polymerase chain reactions (PCR). Therefore, we aimed to investigate the association between HPV infection in oral cancer and overall survival, in a large, standardized study of a homogeneous population, to aid in the development of more optimal staging and treatment regimens for HPV-positive oral cancer patients in the future.

2 | MATERIALS AND METHODS

2.1 | Patient selection

In this retrospective cohort study, the data of patients diagnosed with oral cavity cancer between January 2012 and December 2021 were extracted from the Cancer Registry Database of the Head and Neck Surgery Division of the Department of Otolaryngology, Prince of Songkla University, the major tertiary care center in Southern Thailand. The inclusion criteria were squamous cell carcinoma of the oral cavity (ICD-10 topology code: C00-C06) and treatment with curative intent. Patients who had been previously treated with surgery, radiotherapy, or chemotherapy were excluded.

Ethical approval for the study was granted by the relevant institutional review board, and all data were anonymized in a secure database. The need for informed consent was waived owing to the retrospective nature of the study.

2.2 | Data collection

All patients were pathologically confirmed to have squamous cell carcinoma. The cancers were staged according to the American Joint Commission on Cancer Staging Manual at the time of the patient's diagnosis. We collected information on demographic characteristics, Eastern Cooperative Oncology Group (ECOG) performance status score, underlying diseases, risk factors, tumor subsites, pretreatment TNM stages, modality of treatment, resection margin, date of diagnosis, date and status of last contact, and HPV status. Treatment modalities were classified as surgery, radiotherapy for early-stage cancer, surgery with postoperative radiotherapy, surgery with postoperative chemoradiotherapy, concurrent chemoradiotherapy, and sequential treatment by induction chemotherapy followed by surgery with postoperative radiotherapy for advanced-stage cancer.

HPV detection and genotyping of oral cancer tissues were performed using Anyplex II HPV28 (Seegene, Seoul, South Korea), an assay that employed multiplex real-time PCR for 28 HPV genotypes, including both high- (16, 18, 26, 31, 33, 35, 39, 45, 51–53, 56, 58, 59, 66, 68, 69, 73, 82) and low-risk (6, 11, 40, 42–44, 54, 61, 70) types.[34] The sensitivity and specificity for cervical malignancies were 98.9% and 93.6%, respectively.[35,36]

The tissue samples obtained from the oral tumors were transferred to a test kit plate and placed in an automated real-time PCR detection system. The data were analyzed using the Seegene Viewer program (https://www.seegene.com/software/seegene_viewer).

2.3 | Statistical analysis

Descriptive statistics were used to describe frequency and percentage or median and interquartile range, as appropriate. The chi-squared and Fisher's exact tests were used to compare differences in disease characteristics between the HPV-positive and HPV-negative groups. The log-rank test was used to compare the survival probabilities between the HPV-positive and HPV-negative groups. Exploratory analyses were conducted on all potential variables associated with overall survival using a univariable Cox proportional hazards model. Independent variables related to overall survival that were significant at a level of <0.2 and/or had clinical relevance in the univariable Cox proportional hazards model were included in the multivariable Cox proportional hazards model. A proportional hazards test was performed to ensure that the essential assumptions of the Cox regression models were not violated. A p value of <0.05 was considered statistically significant. All statistical analyses were performed using R software (https://www.r-project.org/).

3 | RESULTS

Of the 454 patients with oral cancer eligible for inclusion in this study, 73 were excluded because of invalid HPV tests. Of the remainder, 342 (89.8%) patients were HPV-negative and 39 (10.2%) were HPV-positive. Of the HPV-positive patients, 32 (82.1%) had HPV type 16, three (7.7%) had HPV type 18, three (7.7%) had HPV type 33, and one was co-infected with HPV types 16 and 33. The ages of the patients ranged from 21 to 80 years, with a median age of 60. Table 1 summarizes the demographic characteristics of the patients.

No significant differences in baseline characteristics, including sex, weight, height, and underlying diseases (hypertension, type

TABLE 1 Baseline characteristics of study patient.

	HPV status		
	Positive ($n = 39$)	**Negative ($n = 342$)**	***p* value**
Age			0.986[†]
< 60 years (%)	20 (51.3)	170 (49.7)	
≥ 60 years (%)	19 (48.7)	172 (50.3)	
Sex			0.999[†]
Male (%)	24 (61.5)	208 (60.8)	
Female (%)	15 (38.5)	134 (39.2)	
Weight, median (IQR)	54.5 (48.0, 64.5)	56.8 (49.7,64.0)	0.797[‡]
Height, mean (SD)	159.5 (9.0)	160.7 (8.5)	0.410[§]
ECOG score			0.592[¶]
0 (%)	12 (30.8)	83 (24.3)	
1 (%)	27 (69.2)	250 (73.1)	
2 (%)	0 (0.0)	8 (2.3)	
3 (%)	0 (0.0)	1 (0.3)	
4 (%)	0 (0.0)	0 (0.0)	
Underlying disease			
Hypertension (%)	12 (30.8)	92 (26.9)	0.746[†]
Type 2 diabetes mellitus (%)	5 (12.8)	32 (9.4)	0.565[¶]
Dyslipidemia (%)	5 (12.8)	39 (11.4)	0.791[¶]
Cardiovascular disease (%)	1 (2.6)	10 (2.9)	0.999[¶]
Pulmonary disease (%)	3 (7.7)	9 (2.6)	0.114[¶]
HIV (%)	0 (0.0)	4 (1.2)	0.999[¶]
Others (%)	10 (25.6)	37 (10.8)	**0.017**[¶]

Note: Values with p value <0.05 shown in **bold**.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; HIV, human immunodeficiency virus; HPV, human papillomavirus; IQR, interquartile range; SD, standard deviation.
[†]Chi-squared test.
[‡]Rank-sum test.
[§]t-test.
[¶]Fisher's exact test.

2 diabetes mellitus, dyslipidemia, cardiovascular disease, pulmonary disease, human immunodeficiency virus infection, and other diseases) were found between the HPV-positive and HPV-negative groups. Most patients had ECOG performance status scores of 0 or 1, while the remaining had ECOG performance status scores of 2 or 3. Considering the risk factors, tumor subsite, and staging, significant differences were observed between the groups in terms of betel nut chewing ($p = 0.040$) and tumor subsite ($p = 0.007$) (Table 2). Seven sites of oral squamous cell carcinoma (OSCC) were examined in this study: the floor of the mouth, gingiva, hard palate, buccal mucosa, lips, oral tongue, and retromolar trigone. The most common tumor site was the tongue (46.2% and 49.1% in the HPV-positive and HPV-negative groups, respectively). According to the American Joint Committee on Cancer (AJCC) staging, no statistically significant differences were found in tumor stage, nodal stage, or overall staging. However, T2 was most common in the HPV-positive group at 35.9%, while T4a was most commonly found in the HPV-negative group (33.9%). The highest numbers of patients in both the HPV-positive and HPV-negative groups were N0 (51.3% and 45.0%, respectively), and overall stage IVa (41.0% and 44.7%, respectively). We also evaluated the type of treatment administered to the patients and found that surgery was the most frequent form of treatment in both groups, with most cases having negative surgical margins, with no significant difference in the resection margins between the two groups ($p = 0.988$).

The median follow-up time was 28.7 (10.9–64.0) months. The 3-year overall survival rates were 56.2% and 53.9% in the HPV-positive and HPV-negative groups, respectively, which was not a significant difference ($p = 0.645$). The 3-year disease-specific survival rates in the HPV-positive and HPV-negative groups were 60.2% and 56.9%, respectively, and the difference was not statistically significant. Multivariate analysis using Cox proportional hazards model showed that ECOG performance status scores 2 and 3, overall stages IVa and IVb, and treatment with concurrent chemoradiation and sequential treatment were predictors of overall survival probability (Table 3), while HPV-positive status was not a significant predictor of survival in the Cox regression model ($p = 0.728$).

4 | DISCUSSION

In this study, we compared the survival outcomes of patients with HPV-positive and HPV-negative OSCC. The prevalence of HPV-positive oral cancer was 10.2% (95% CI 7.2–13.2%). The 3-year overall survival rates and the 3-year disease-specific survival rates were not statistically significantly different between the groups.

The patient demographics were similar to those reported in previously published studies. The prevalence of HPV-positive OSCC in our study was in the low range compared to earlier studies that had prevalences ranging from 3.9% to 19.0%[30,32–34]; these variations may be attributed to social factors such as differences in sexual behaviors and socioeconomic status.[35,36] We also found that HPV-positive OSCC was most common in patients younger than 60 years of age (50.3%) and in males (60.8%); these findings were consistent with those of previous studies that demonstrated that the highest HPV prevalence was commonly observed in younger age groups,[37] with a significantly higher prevalence of HPV-positive OSCC in men.[38] The oral tongue was the predominantly affected subsite in the HPV-positive group (46.2%), similar to that in the HPV-negative group (49.1%), which could be explained by the high incidence of oral cancer in the tongue subsite in the Thai population.[39] Another possible reason is that the oral tongue is covered with rough mucosa containing numerous taste buds that increase the surface area for virus exposure. Additionally, the epithelium covering the oral tongue is easily disrupted by HPV.[40] In terms of the AJCC staging, no significant differences in tumor stage, nodal stage, or overall staging were found between the HPV-positive and HPV-negative OSCC groups. The T1 and T2 tumor stages were higher in the HPV-positive group than in the HPV-negative group. However, in both groups, most patients were stage IVa, similar to the findings of a previous study conducted in Thailand.[41] Education and socioeconomic status could be the causes of late presentation to the hospital.[42]

In our assessment of survival outcomes in oral cancer, we identified several factors of interest. ECOG performance status scores of 2 and 3, along with the more advanced disease stages IVa and IVb, were negatively associated with patient survival. Treatment methods, specifically concurrent chemoradiation and sequential treatment—which are not the preferred options—were significantly associated with poorer survival rates. However, our analysis found that HPV-positive status was not a significant factor for predicting survival outcomes, even after adjusting for potential confounders in the multivariate analysis. This finding aligns with previous studies that found no significant association between HPV status and survival outcomes in oral cavity cancer. For instance, Nauta et al.[31] conducted a retrospective cohort study involving 940 patients with oral cancer and found no significant correlation between HPV positivity and survival. Similarly, Abreu et al.[43] and Schneider et al.[44] reported comparable findings in their studies. They also found no significant differences in survival between HPV-positive and HPV-negative patients with oral cancer. Contrary to these findings, Tian et al.[19] reported a favorable impact of HPV infection on survival outcomes in oral cancer. However, this finding was exclusively confined to cases of stage III–IVb oral cancer. Similarly, Sugiyama et al.[21] identified a higher survival rate among HPV-16 positive patients without nodal metastasis. However, the absence of adjustments for confounding factors such as smoking, alcohol consumption, or betel nut chewing may have introduced uncertainty into the observed outcomes. Several potential factors may account for the lack of an association between HPV status and survival outcomes in oral cavity cancer. First, oral cavity tumors originate from diverse anatomical sites and may exhibit heterogeneous molecular characteristics.[45] This heterogeneity may contribute to the variability in clinical outcomes observed among HPV-positive oral cancer cases. Second, the pathogenic mechanisms underlying HPV-associated oral carcinogenesis may differ from those in other anatomical sites. HPV-driven oropharyngeal cancers are frequently found to have mutations in tumor suppressor genes, which play pivotal roles in cell cycle regulation and apoptosis.[46,47] However, the prevalence and

TABLE 2 Clinicopathological characteristics and treatment modalities of study patients.

	HPV status		
	Positive ($n = 39$)	Negative ($n = 342$)	p value
Risk factors			
Smoking (%)	21 (53.8)	203 (59.4)	0.624[†]
Alcohol consumption (%)	17 (43.6)	142 (41.5)	0.939[†]
Betel nut chewing (%)	19 (48.7)	106 (31.0)	**0.040**[†]
Family history of head and neck cancer (%)	6 (15.4)	48 (14.0)	0.844[†]
Tumor subsite			**0.007**[‡]
Oral tongue (%)	18 (46.2)	168 (49.1)	
Buccal mucosa (%)	7 (17.9)	41 (12.0)	
Lips (%)	6 (15.4)	7 (2.0)	
Gingiva (%)	5 (12.8)	41 (12.0)	
Floor of mouth (%)	3 (7.7)	47 (13.8)	
Hard palate (%)	0 (0.0)	22 (6.4)	
Retromolar trigone (%)	0 (0.0)	16 (4.7)	
Tumor stage			0.858[†]
T1 (%)	6 (15.4)	56 (16.4)	
T2 (%)	14 (35.9)	95 (27.8)	
T3 (%)	7 (17.9)	62 (18.1)	
T4a (%)	11 (28.2)	116 (33.9)	
T4b (%)	1 (2.6)	13 (3.8)	
Nodal stage			0.575[‡]
N0 (%)	20 (51.3)	154 (45.0)	
N1 (%)	5 (12.8)	51 (14.9)	
N2a (%)	2 (5.1)	4 (1.2)	
N2b (%)	5 (12.8)	61 (17.8)	
N2c (%)	6 (15.4)	55 (16.1)	
N3a (%)	0 (0.0)	2 (0.6)	
N3b (%)	1 (2.6)	15 (4.4)	
Stage			0.914[†]
I (%)	6 (15.4)	47 (13.7)	
II (%)	7 (18.0)	54 (15.8)	
III (%)	8 (20.5)	59 (17.3)	
IVa (%)	16 (41.0)	153 (44.7)	
IVb (%)	2 (5.1)	29 (8.5)	
Treatment			0.953[‡]
Surgery (%)	12 (30.8)	89 (26.0)	
RT (%)	0 (0.0)	5 (1.5)	
Surgery + PORT (%)	16 (41.0)	134 (39.2)	
Surgery + POCCRT (%)	8 (20.5)	86 (25.1)	
CCRT (%)	3 (7.7)	26 (7.6)	
Sequential treatment (%)	0 (0.0)	2 (0.6)	
Resection margin			0.988[‡]
Negative margin (%)	27 (69.2)	233 (68.1)	
Positive margin (%)	9 (23.1)	80 (23.4)	
Treated by RT or CCRT (%)	3 (7.7)	29 (8.5)	

Note: Values with p value <0.05 shown in **bold**.
Abbreviations: CCRT, concurrent chemoradiotherapy; HPV, human papillomavirus; PORT, postoperative adjuvant radiotherapy; POCCRT, postoperative adjuvant chemoradiotherapy; RT, radiotherapy.
[†]Chi-squared test.
[‡]Fisher's exact test.

TABLE 3 Results of the univariate and multivariate analyses for overall survival in study patients.

	Univariate HR (95% CI)	*p* value	Multivariate HR (95% CI)	*p* value
Age				
< 60 years	1 (reference)			
≥ 60 years	1.09 (0.84, 1.40)	0.514		
ECOG score				
0	1 (reference)		1 (reference)	
1	1.63 (1.15, 2.31)	**0.007**	1.41 (0.98, 2.01)	0.061
2	2.56 (1.09, 6.04)	**0.032**	2.74 (1.14, 6.57)	**0.024**
3	80.12 (9.66, 664.38)	**<0.001**	42.11 (4.78, 371.32)	**<0.001**
Risk factors				
None	1 (reference)			
Smoking	1.31 (0.97, 1.75)	0.076		
Alcohol consumption	1.15 (0.90, 1.49)	0.268		
Betel nut chewing	0.92 (0.70, 1.20)	0.540		
Family history of head and neck cancer	1.02 (0.70, 1.47)	0.223		
Stage				
I	1 (reference)		1 (reference)	
II	1.53 (0.80, 2.91)	0.199	1.35 (0.69, 2.62)	0.380
III	2.13 (1.16, 3.92)	**0.014**	1.88 (0.94, 3.78)	0.075
IVa	2.87 (1.67, 4.95)	**<0.001**	2.17 (1.11, 4.24)	**0.024**
IVb	5.11 (2.64, 9.89)	**<0.001**	3.22 (1.45, 7.15)	**0.004**
Treatment				
Surgery	1 (reference)		1 (reference)	
RT	2.17 (0.67, 7.04)	0.196	1.75 (0.52, 5.90)	0.367
Surgery + PORT	1.38 (0.93, 2.04)	0.113	0.96 (0.59, 1.57)	0.876
Surgery + POCCRT	2.38 (1.57, 3.61)	**<0.001**	1.51 (0.88, 2.58)	0.134
CCRT	4.21 (2.50, 7.10)	**<0.001**	2.09 (1.08, 4.04)	**0.029**
Sequential treatment	9.43 (2.26, 39.45)	**0.002**	6.09 (1.38, 26.93)	**0.017**
HPV status				
Negative	1 (reference)		1 (reference)	
Positive	0.86 (0.54,1.37)	0.539	0.92 (0.57,1.48)	0.728

Note: Values with *p* value <0.05 shown in **bold**.

Abbreviations: CCRT, concurrent chemoradiotherapy; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; HPV, human papillomavirus; PORT, postoperative adjuvant radiotherapy; POCCRT, postoperative adjuvant chemoradiotherapy; RT, radiotherapy.

significance of these mutations in HPV-positive oral cancers remain uncertain. Third, the influence of co-factors such as tobacco, betel nut chewing, and alcohol consumption, which are prevalent risk factors for oral cavity cancers, may modify the biological behavior of HPV-infected oral tumors and impact patient outcomes.[48] Finally, the lack of an association between HPV status and survival outcomes in patients with oral cancers may also reflect differences in clinical management approaches. Although HPV-positive oropharyngeal cancers exhibit heightened sensitivity to chemoradiation therapy, the optimal treatment strategies for HPV-positive oral cavity tumors are primarily surgery-based. These variations in treatment modalities may influence patient outcomes and obscure the prognostic significance of HPV status in oral cancer. Therefore, our findings suggest that HPV status is not associated with overall survival in patients with OSCC.

This study conducted a comprehensive analysis involving a substantial sample size to document the survival rates of patients with HPV-related oral cancer. The robustness of our survival outcome analysis was strengthened by integrating staging and other prognostic variables into the multivariate analysis models. Furthermore, our investigation used PCR to ascertain HPV-positive status, delineating a distinct subset of oral cancer originating from HPV-related causes. However, a notable limitation of our study arose from the occurrence of invalid HPV-test results. The Anyplex II HPV28 assay is generally reliable for detecting HPV DNA in formalin-fixed paraffin-embedded (FFPE) specimens; however, we encountered instances of invalid test results. Typically, such occurrences are associated with prolonged storage of FFPE specimens, resulting in DNA degradation over time or the presence of DNA fragments too small to effectively bind the

test primer. Consequently, these invalid test results led to a reduction in the number of specimens available for review, potentially impacting the accuracy of our survival outcome estimations. To mitigate this problem in future studies, we recommend considering short-term storage of FFPE specimens to optimize the reliability and detection rate of HPV DNA. Our findings deviate from the association of HPV with oropharyngeal cancer as reported in previous studies, as HPV-positive status was not correlated with survival outcomes in OSCC patients in this study. Consequently, the necessity for pre-treatment evaluation of HPV in oral cancer cases remains uncertain, and further studies on HPV in oral cancer are required to provide additional insights into its clinical implications.

5 | CONCLUSION

Our study found a low prevalence of HPV infection among patients diagnosed with OSCC in Thailand, and no significant association was observed between HPV-positive status and 3-year overall survival rates in this patient population.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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