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Clinicopathologic characteristics of HPV-associated head and neck squamous cell carcinoma in Southern China: long-term retrospective study of 400 cases

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Abstract

Background: Human papillomavirus (HPV)-associated head and neck squamous cell carcinoma (HNSCC) is an evolving and growing disease, especially in developing countries. However, the clinical characteristics of HPV-associated HNSCC in regard to HPV infection rates, patient features, and prognosis are under-reported in the Asian population.

Methods: In this study, we retrospectively enrolled a 400-case cohort of HNSCC with p16 immunochemistry and analyzed with long-term follow-up. We investigate the current HPV prevalence of HNSCC, unique HPV-associated patient clinical characteristics, and patient prognosis in the southern China population.

Results: HPV infection exhibited a 15% prevalence in all HNSCC cases, notably higher in oropharyngeal cases (30.7%), followed by oral cavity (11.8%), laryngeal (10.1%), and hypopharyngeal (2.5%). HPV status, gender, old age, and location of tumor were significantly associated with the patient's survival. Tonsil invasion was found more frequent in HPV-positive oropharyngeal HNSCC than in HPV-negative cases. HPV-associated HNSCC patients tend to possess stronger tobacco and alcohol habits, which were correlated to poor survival. HPV status's correlation with gender, age, and anatomical location is associated intricately with patient survival. The secondary primary tumor rate was found higher within the HPV-negative group, compared to the HPV-positive group (9.12% *versus* 1.67%).

Conclusion: Our study provided a current picture of HPV-associated HNSCC in the southern China population and elaborated the understanding of key factors that correlate to HNSCC prognosis. Our findings indicated a strong susceptibility of HPV-associated oropharyngeal HNSCC in the tonsil and the difference in secondary primary tumor rates associated with HPV status.

Plain language summary

HPV in head and neck cancer

In this study, we retrospectively enrolled a 400-case cohort of HNSCC with p16 immunochemistry and analyzed with long-term follow-up. We investigate the current HPV prevalence of HNSCC, unique HPV-associated patient characteristics, along with patient prognosis in southern China population. Our findings indicated a strong susceptibility of HPV-associated oropharyngeal HNSCC in tonsil and difference of secondary primary tumor associated with HPV status. Our study provided a current picture of HPV-associated HNSCC in southern China population and elaborated the understanding of key factors that correlate to HNSCC prognosis.

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Introduction

Head and neck squamous cell carcinoma (HNSCC) ranks as the seventh most prevalent cancer worldwide and can be categorized into human papillomavirus (HPV)-positive HNSCC and HPV-negative HNSCC based on HPV status.[1–3] Divergent treatment responses and survival outcomes linked to HPV statuses prompted HNSCC treatment guidelines to advocate for p16 as a crucial clinical test for HPV detection.[4] Although HPV plays a pivotal role in HNSCC pathogenesis, limited clinical data on HPV-associated HNSCC exist in regions like China. Furthermore, comprehensive studies on HPV-associated HNSCC are insufficient, with most focus on HPV-associated oropharyngeal cancer.

Notably, significant differences in HPV infection rates exist between countries due to diverse lifestyles encompassing sexual behavior, tobacco use, and alcohol consumption.[5,6] In addition, limited data are comparing clinical outcomes based on anatomical locations, gender, age, and secondary tumor risks concerning HPV presence or absence.[7,8] Crucially, the predilection for tonsil involvement in pathogenesis and diverse secondary tumor risks in HPV-associated HNSCC within the southern Chinese population remains inadequately studied.

This study retrospectively obtained 400 HNSCC tissue samples from 2008 to 2018 admissions in southern China and assessed p16 expression. The goal was to evaluate clinical-pathological data to analyze differential clinical outcomes concerning HPV status, gender, age, and anatomical location. Furthermore, the study aimed to provide evidence regarding HPV-associated tonsillar preference and variations in secondary tumor risks in HPV-associated HNSCC.

Materials and methods

Ethics approval and consent to participate

The study received ethical approval from Sun Yat-Sen University Cancer Center (SL-B2023-374-01). The requirement for informed consent to participate has been waived by the Ethics Committee since this is a retrospective observational study only, and it has been deemed that consent from most individuals would be impossible or impracticable to obtain. Sample collection commenced following approval, with subsequent preliminary analysis, tissue microarray construction, immunohistochemistry staining, and pathological scoring performed.

Patient cohort and sample information

There were 478 HNSCC cases, with complete records and tissue blocks, admitted to Sun Yat-Sen University Cancer Center between 2008 and 2018, among which 400 patients were confirmed eligible and included in the study for analysis. The criteria for inclusion and exclusion of cases were as follows.

The inclusion criteria are as follows:

(1) Clinical diagnosis and biopsy confirmed primary HNSCC located in the oral cavity, oropharynx, larynx, and hypopharynx.
(2) Patients with complete medical information, including age, sex, smoking/drinking, Tumour/Node/Metastasis stage (TNM stage), location of the tumor, follow-up (>5 years), treatment, time of admission, and discharge.
(3) No other primary cancers at the time of diagnosis.

The exclusion criteria are as follows:

(1) Patient with inadequate formalin-fixed paraffin-embedded (FFPE) tissue blocks or incomplete medical records;
(2) The HNSCC tumor was found to be a metastatic tumor from elsewhere.

Tissue microarray construction, immunohistochemistry, and pathological scoring

Tissue pairs of HNSCC tissue and adjacent tissue were arrayed onto slides. Immunohistochemistry

staining for p16 (Cell Signaling Technology, #68410, 1:50) was conducted with a 60% staining cutoff.[5] Scoring criteria ranged from 0 to 3 based on staining intensity, with scores assigned by random clinical pathologists in the Department of Pathology, Sun Yat-sen University Cancer Center.

Statistical analysis

SPSS 20.0 (IBM, Armonk, NY) and Prism 9 (Graphpad) software facilitated statistical analysis and figure generation. Kaplan–Meier survival analysis and log-rank tests compared survival outcomes. Fisher's exact test examined factors correlated with survival and HPV status. Statistical significance was considered under p value <0.05.

Reporting statement

The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology – Molecular Epidemiology (STROBE-ME): An extension of the STROBE statement,[33] which is available in the Supplemental Materials.

Results

Demographic and clinical characteristics

Baseline characteristics and survival data of the 400 patients, grouped by p16 staining and prognosis/gender, exhibited significant differences across multiple parameters (Table 1 and Table 2). HPV status correlated with gender, age, tumor location, TNM classification, tobacco/alcohol use, and primary treatment. Oropharyngeal HNSCC demonstrated the highest HPV prevalence with significant differences observed in the N and T stage. Poor prognosis was associated with male gender, hypopharyngeal HNSCC, older age, late T and N stage, and tobacco smoking/alcohol drinking habits.

HPV prevalence and single factor prognostic analysis

HPV-associated HNSCC exhibited a 15% prevalence [Table 1, Figure 1(a) and (b)], notably higher in oropharyngeal cases (30.7%), followed by oral cavity (11.8%), laryngeal (10.1%), and hypopharyngeal (2.5%). Survival analysis revealed significantly better outcomes in HPV-positive cases and among females [Figure 1(c)–(f), OS $p=0.0104$, $p=0.0004$; DFS $p=0.0051$, $p=0.0001$]. Old age, especially age >70 years, was found associated with poor prognosis [Figure 1(g), $p=0.0411$]. The location of the tumor was significantly associated with shortened patients' survival, as hypopharyngeal and laryngeal tumors showed the worst outcome [Figure 1(h) and (i), $p=0.0001$, $p=0.0001$]. Tonsil invasion was more frequent in HPV-positive oropharyngeal HNSCC [Figure 1(j), $p=0.0001$]. HPV-associated HNSCC patients tend to possess stronger tobacco and alcohol habits [Figure 1(m) and (n), $p=0.0472$ and $p=0.0382$], which were correlated to poor survival [Figure 1(k) and (l), $p=0.0106$ and $p=0.0285$].

Sub-stratification analysis

HPV status's correlation with gender, age, anatomical location, and survival remained intricate relationships. In this context, we sought to analyze in detail the divergent prognostic role of HPV status with considerations of gender, location of tumor, and specific groups. Our study found that HPV's impact on survival was more pronounced in male patients [Figure 2(a), $p=0.0375$ *versus* $p=0.3998$]. Gender-related survival showed a significant difference in the HPV^{neg} group [Figure 2(b), $p=0.0021$ *versus* $p=0.1925$]. Location-associated prognosis divergence was found significant in the HPV^{neg} group [Figure 2(c), $p=0.0001$ *versus* $p=0.2965$]. Old age (>70 years old) showed much worse overall survival in the HPV^{pos} group instead of in the HPV^{neg} group [Figure 2(e), $p=0.0045$ *versus* 0.0817]. Specifically, among all locations of the HNSCC tumor, the oropharyngeal tumor showed marked gender-related and HPV-related survival differences [Figure 2(d), $p=0.0181$ and $p=0.0215$]. HPV status showed prognostic value in the 50–59 years of age group [Figure 2(f), $p=0.0284$], while no significant difference was observed in other age groups (data not shown).

Secondary primary tumors

We evaluate the secondary primary tumors manifested in 11.52% (37 out of 400) of the HNSCC cases assessed. These secondary primary tumors exhibited a predilection for emerging in the esophagus, nasopharynx, and oral cavity [Figure 3(a)]. Notably, variations emerged in the incidence rates of secondary primary tumors based on the HPV status. Specifically, 9.12% of cases within the HPV-negative group were associated with secondary primary tumors, compared with

Table 1. Demographic and clinical characteristics of 400 enrolled HNSCC patients.

Parameters	Stratified by p16 immunohistochemistry (IHC) staining ($n=400$)		p	Stratified by prognosis ($n=400$)		p
	Positive (%)	Negative (%)		Alive (%)	Deceased (%)	
Gender						
Total	60 (15.0)	340 (85.0)	0.12	251 (62.8)	149 (37.2)	<0.01
Male	47 (13.8)	293 (86.2)		202 (59.4)	138 (40.6)	
Female	13 (21.7)	47 (78.3)		49 (81.7)	11 (18.3)	
Age diagnosis in years (SD)						
28–49	13 (15.5)	71 (84.5)	0.63	56 (66.7)	28 (33.3)	<0.01
50–59	23 (17.0)	112 (83.0)		88 (65.2)	47 (34.8)	
60–69	18 (15.0)	102 (85.0)		76 (63.3)	44 (36.7)	
>70	6 (9.8)	55 (90.2)		31 (50.8)	30 (49.2)	
Tumor location						
Oral cavity	15 (11.8)	112 (88.2)	<0.01	90 (70.9)	37 (29.1)	<0.01
Oropharyngeal	35 (30.7)	79 (69.3)		96 (84.2)	18 (15.8)	
Laryngeal	8 (10.1)	71 (89.9)		42 (53.2)	37 (46.8)	
Hypopharyngeal	2 (2.5)	78 (97.5)		23 (28.8)	57 (71.2)	
TNM						
Tumor category						
T1	10 (10.4)	86 (89.6)	0.10	64 (66.7)	32 (33.3)	<0.01
T2	30 (19.6)	123 (80.4)		120 (78.4)	33 (21.6)	
T3	8 (13.6)	51 (86.4)		36 (61.0)	23 (39.0)	
T4	8 (9.6)	75 (90.4)		24 (28.9)	59 (71.1)	
Tx	4 (44.4)	5 (55.6)		7 (77.8)	2 (22.2)	
Nodal category						
N0	26 (12.6)	180 (87.4)	0.05	152 (73.8)	54 (26.2)	<0.01
N1	19 (23.5)	62 (76.5)		54 (66.7)	27 (33.3)	
N2	10 (10.8)	83 (89.2)		39 (41.9)	54 (58.1)	
N3	1 (6.7)	14 (93.3)		2 (13.3)	13 (86.7)	
Nx	4 (80.0)	1 (20.0)		4 (80.0)	1 (20.0)	
Metastasis category						
M0	56 (14.2)	339 (85.8)	N/A	247 (62.5)	148 (37.5)	N/A

(Continued)

Table 1. (Continued)

Parameters	Stratified by p16 immunohistochemistry (IHC) staining ($n = 400$)		p	Stratified by prognosis ($n = 400$)		p
	Positive (%)	Negative (%)		Alive (%)	Deceased (%)	
M1	0	0		0	0	
Mx	4 (80.0)	1 (20.0)		4 (80.0)	1 (20.0)	
Tobacco use						
Yes	28 (10.2)	205 (89.8)	0.05	134 (57.5)	99 (42.5)	0.01
No	32 (2.0)	133 (98.0)		117 (70.9)	48 (29.1)	
Not recorded	0	2 (100)		0	2 (100)	
Alcohol use						
Yes	13 (9.6)	123 (90.4)	0.04	73 (56.2)	57 (43.8)	0.06
No	47 (17.8)	217 (82.2)		173 (65.8)	90 (34.2)	
Not recorded	0	0		5 (71.4)	2 (28.6)	
Primary treatment						
Surgery	30 (12.8)	204 (87.2)	0.27	160 (68.4)	74 (31.6)	0.01
Surgery + CT/RT	30 (18.3)	134 (81.7)		91 (55.5)	73 (44.5)	
CT/RT	0	2 (100)		0	2 (100)	

Table 2. Overall and disease-free survival of HNSCC patients stratified by p16 IHC and gender.

Parameters	Stratified by p16 IHC				Stratified by Gender			
	Positive	Negative	95% CI HR	p	Male	Female	95% CI HR	p
5-Year overall survival (%)	69.44	52.13	0.3753–0.9764	0.0405	50.37	77.55	0.3029–0.6968	0.0003
5-Year disease-free survival (%)	66.67	47.02	0.3786–0.9351	0.0241	44.49	75.51	0.3110–0.6843	0.0001

1.67% of cases in the HPV-positive group [$p = 0.0098$, as depicted in Figure 3(b)]. In addition, the HPV-negative HNSCC cases exhibited a marginally higher recurrence rate [$p = 0.1573$, as illustrated in Figure 3(c)].

Discussion

Scientific evidence has illuminated several factors in predicting the prognosis of HPV-associated HNSCC. Early studies unveiled significant distinctions within HPV-positive HNSCC cases, characterized by younger age, smaller primary tumor sizes, earlier N stage, and lifestyle including alcohol consumption.[9,10] Nonetheless, these investigations predominantly enrolled western populations, with only a limited representation of Asians. Consequently, a comprehensive understanding of the clinical features and epidemiology of HPV-associated HNSCC remained elusive. Limited research on the Chinese HNSCC population usually involved cohorts of fewer than 200 patients.[11]

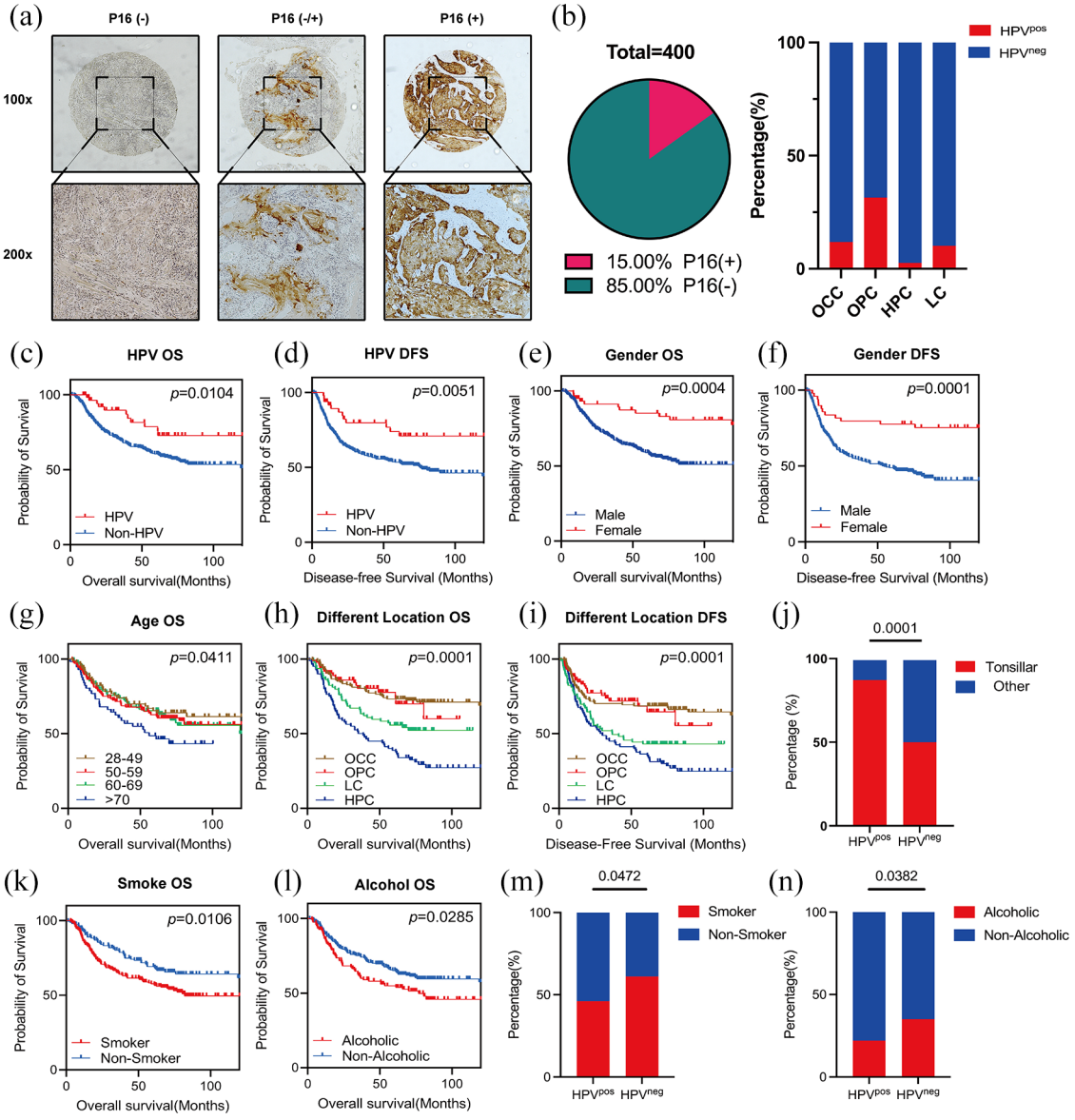

Figure 1. HPV infection rates and single factor prognostic analysis. (a) Representative p16 immunohistochemistry result of p16(−), p16(±), and p16(+) formalin-fixed paraffin-embedded HNSCC tissue; (b) HPV-positive rates in HNSCC and specific anatomic HNSCC groups; (c and d) result of overall survival (c) and disease-free survival (d) compared between HPV-positive and HPV-negative patients; (e and f) result of overall survival (e) and disease-free survival (f) compared between male and female patients; (g) result of overall survival compared among different age groups; (h and i) result of overall survival (h) and disease-free survival (i) compared among different anatomic groups; (j) percentage of tonsillar HNSCC frequency compared between HPV-positive and HPV-negative groups; (k and l) result of overall survival compared between smokers and non-smokers (k) and the alcoholic and non-alcoholic (l); and (m and n) percentage of smoking and alcohol addiction status in HPV-positive and HPV-negative groups.
HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus.

In our study, we conducted a comprehensive evaluation of the clinicopathologic characteristics of 400 HNSCC patients, shedding light on the comparative outcomes across different HPV statuses. Our findings corroborated earlier observations, confirming that HPV-positive HNSCC patients exhibited superior survival outcomes. A higher prevalence of HPV infection was observed in the oropharyngeal with lower tumor stages and a greater proportion of advanced N stage pathology.

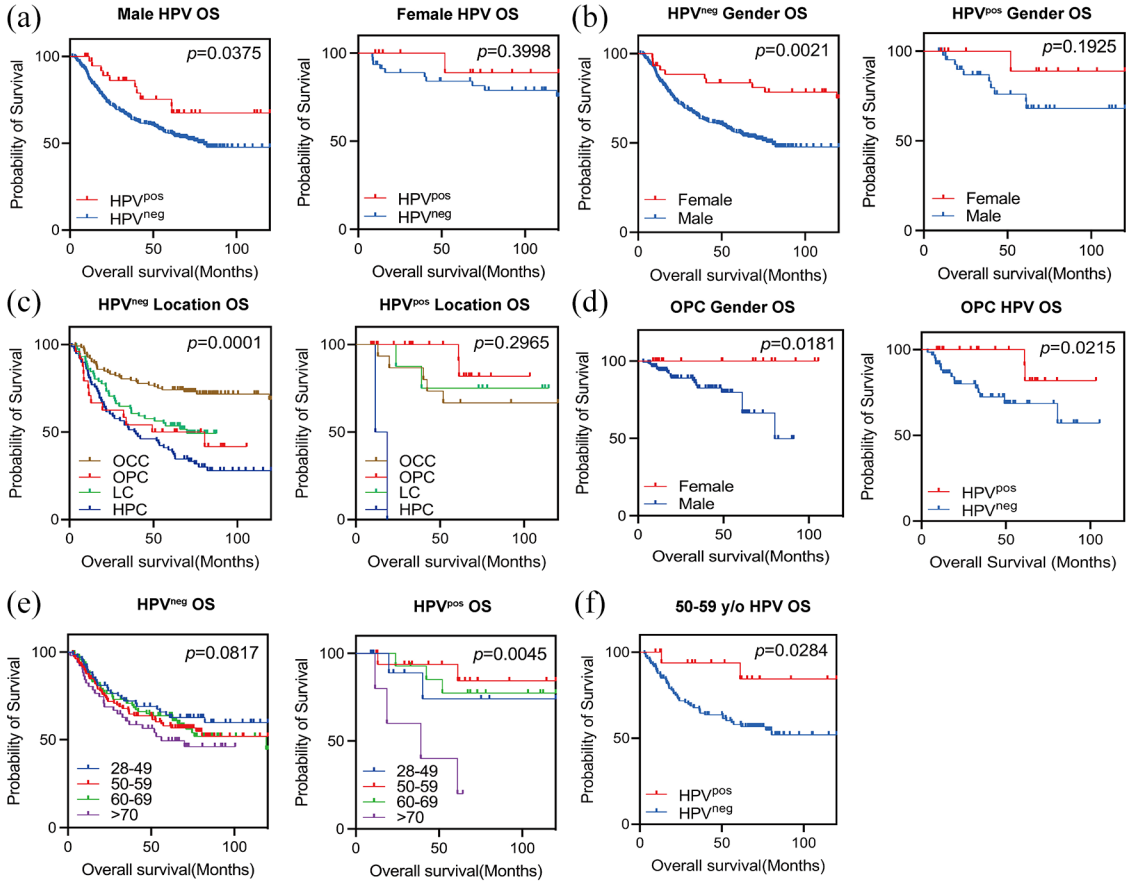

Figure 2. Sub-stratification analysis reveals intricate relationships between HNSCC survival and HPV status's correlation with gender, age, and anatomical location. (a) Result of overall survival compared between HPV-positive and HPV-negative groups in male (left) and female (right) HNSCC patients; (b) result of overall survival compared between male and female groups in HPV-negative (left) and HPV-positive (right) HNSCC patients; (c) result of overall survival compared among different anatomic groups in HPV-negative (left) and HPV-positive (right) HNSCC patients; (d) result of overall survival compared between male and female (left) and HPV-positive and HPV-negative groups (right) in oropharyngeal tumor patients; (e) result of overall survival compared among different age groups in HPV-negative (left) and HPV-positive (right) HNSCC patients; and (f) result of overall survival compared between HPV-positive and HPV-negative groups in 50 and 59 years old HNSCC patients.
HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus.

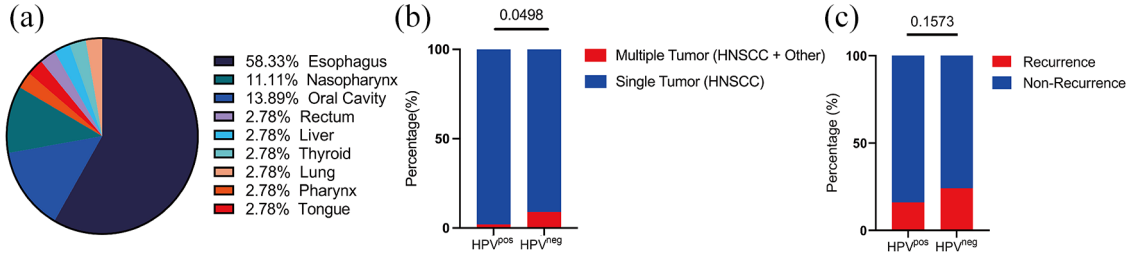

Figure 3. HPV-associated HNSCC showed less secondary primary tumor. (a) Percentage of anatomic locations of secondary primary tumors; (b) percentage of secondary primary tumor compared between HPV-positive and HPV-negative HNSCC patients; and (c) percentage of tumor recurrence compared between HPV-positive and HPV-negative HNSCC patients.
HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus.

Of importance, we presented evidence regarding HPV prevalence within the southern Chinese population, indicating rates of 15% in general HNSCC and a notably higher rate of 30.7% in oropharyngeal HNSCC. This percentage is significantly greater than previously reported Chinese population studies back in 2012, which found an HPV rate of less than 20%.[12,13] Moreover, our results underscored the prognostic significance of considering the interplay of HPV, gender, age, and anatomical location. In addition, our study identified a higher susceptibility to tonsil-associated HPV pathology among patients with oropharyngeal HNSCC. Notably, HPV-negative HNSCC patients exhibited a heightened predisposition to secondary primary tumors, a finding that has not been systematically explored in previous extensive retrospective studies in southern China. Of importance, HPV-negative HNSCC usually arises from genetic factors and carcinogen exposure, which might be a common mechanism underlying the development of secondary primary tumor; while HPV-positive HNSCC results mainly from viral infection, thus not contributing to tumorigenesis elsewhere.

Current guidelines underscore the importance of utilizing p16 as an indicator for diagnosing HPV-associated HNSCC.[4,14] This recognition is rooted in the understanding that HPV-associated HNSCC demands distinct treatment approaches due to its unique etiology and clinical attributes. However, a substantial divergence exists in reported HPV rates across studies conducted in different geographical locations. For instance, recent studies from Europe and America consistently report high HPV positivity rates of 50–80% in oropharyngeal HNSCC patients.[15,16] Conversely, investigations in Chinese HNSCC patients, often with smaller cohorts, have reported variable and often lower HPV rates ranging from 5% to 40%.[12,13,15–18] Several factors may underlie this discrepancy, including diverse cultural sexual behaviors, variations in HPV diagnostic methods, genetic diversity among ethnicities, and cohort size. Notably, lifestyle may contribute to a rise in HPV-positive HNSCC cases within the Chinese population, necessitating precise updates in HPV-related cancer statistics. Moreover, elucidating the distinct and intricate patterns of HPV-associated HNSCC cases is crucial for constructing de-escalation strategies, thereby enabling tailored treatment plans with reduced toxicity for HPV-negative HNSCC patients.

In contrast to other studies examining HPV-associated HNSCC within the Chinese population, our dataset offers several enhanced insights into the clinical and pathological features of this disease. Our findings notably underscore the significant role of HPV in oropharyngeal HNSCC, revealing a significantly higher HPV rate in this region compared to non-oropharyngeal sites (30.7% *versus* 9.6%). This distinction has not been thoroughly explored in previous studies, which often focused on HNSCC at single sites. In addition, within the oropharyngeal HNSCC patients, our data demonstrate that HPV-positive cases are more frequently associated with tonsil involvement compared to HPV-negative cases (87.5% *versus* 50.9%).

In addition, our study employed a sub-stratification approach, categorizing HNSCC cases based on HPV status, gender, age, and anatomical location. This aimed to pinpoint conditions under which HPV status and other parameters closely correlate with HNSCC survival. Several of our findings provide novel perspectives and predictive value for clinical practice. For instance, we observed that HPV status played a stronger predictive role in male HNSCC survival. Conversely, in the negative HPV group, female HNSCC patients demonstrated significantly better survival than males. Survival outcomes varied across HNSCC locations, particularly evident in the HPV-negative group. However, this trend could be attributed to the limited cases in the HPV-positive hypopharyngeal group, necessitating further investigation with a larger cohort. Our analysis particularly highlighted oropharyngeal HNSCC, as it displayed the most significant survival disparities when divided by gender and HPV status. Importantly, the adverse impact of older age (>70 years old) on HNSCC survival was more pronounced in the HPV-positive group, indicating that older age (>70 years old) had a predominantly disadvantageous effect on HPV-positive HNSCC cases.

Our clinical data demonstrated lower rates of secondary primary tumors in HPV-positive HNSCC cases. A recent retrospective study involving a cohort of 352 laryngeal cancer cases reported a high percentage of secondary primary tumors, most commonly in the lung.[19] However, these results did not compare HPV status with HNSCC in other anatomical locations. In terms of comparing secondary primary tumor rates between HPV-positive and HPV-negative HNSCC, a study of

oropharyngeal HNSCC found that the HPV-positive group tended to have lower rates of secondary primary tumors, although HNSCC in other anatomical locations remained unstudied.[20] By contrast, our study analyzed secondary tumors in a larger HNSCC cohort, considering HPV status and different anatomical locations, thereby offering a clearer perspective on this issue. In addition, our study revealed that esophageal tumors were correlated with HNSCC, which concurs with previous research.[21,22] Our findings indicate that esophageal tumors constituted 58% of all patients with secondary primary tumors, followed by the oral cavity (14%) and nasopharynx (11%).

In this study, we utilized p16 immunohistochemistry staining (60% staining cutoff)[5] as the diagnostic criteria for HPV status, which is a commonly used and recommended method by most current guidelines for its effective use as a surrogate marker and ease of clinical adoption.[4,14] The other method used by many is HPV polymerase chain reaction (PCR) assay, the golden standard for diagnosing HPV infection. Though discrepancy remains in the superiority comparison among p16 immunohistochemistry staining and PCR assay, recent studies have indicated that p16 immunohistochemistry was almost comparable to the golden standard HPV PCR in terms of sensitivity (96.4% *versus* 100%) and specificity (92.5% *versus* 92.5%), while combined p16 + DNA assay showed marginally higher specificity than single p16 staining or PCR testing but brought difficulties of detection workflow, sample requirements, and examination costs.[23] Some studies reported the discordance rate (5–10%) between p16 and HPV to prompt the awareness of potential detection error and suggest combined p16 + DNA assay.[24,25] Therefore, we admit the potential limitations in HPV detection variance by different methods, but by following guideline recommendations and standard detection pipelines, this is not likely to affect our conclusion. Still, we hold the view that the current undetermined detection strategy necessitates further exploration through real-world analysis, with considerations of accuracy, economics, and standardization difficulties, to provide valuable evidence to further the consistency of the HPV detection approach.

HPV-associated HNSCC, a dynamically evolving disease entity, predominantly affects younger individuals characterized by active sexual behavior and limited engagement in smoking and drinking habits. This variant of HNSCC is frequently localized in the oropharynx and is progressively garnering heightened attention in clinical circles. While some nations are grappling with the zenith of the 'HPV pandemic', witnessing a significant prevalence of HPV-associated conditions, developing regions are witnessing a gradual surge in such cases. Consequently, meticulous surveillance and consistent conceptual updates pertaining to HPV-associated HNSCC are imperative to ensure preparedness in this context.

Immunotherapy has evolved as one of the most promising treatments of choice for improving HNSCC prognosis.[26–28] Several leading immunotherapeutic HNSCC clinical trials, such as the KEYNOTE, HAWK, and CheckMate, have established the superiority of anti-PD-1 inhibitors in treating HNSCC as first-line treatment, with consideration of metastasis, recurrence, and PD-L1 scoring.[28–30] These studies also led to a discussion of the role of HPV status in tailoring HNSCC immunotherapy planning. It became a consensus recommendation in the immunotherapy field that HPV status should be included in HNSCC treatment planning, based on p16 overexpression.[26] Nevertheless, due to a lack of strong data supporting the difference of benefit in p16+ *versus* p16- patients, most experts and guidelines have not reached a point where alteration of HNSCC immunotherapy planning based on HPV status should be implemented. Also, the microenvironment is considered by many as a predictive biomarker for immunotherapy outcomes.[31] For instance, an RNA-based composite score consisting of interferon-gamma and five relevant signature genes was reported to significantly correlate with immunotherapy treatment response and survival in the KEYNOTE study.[32] In the future, clinical studies with more data emphasizing the relationship between HPV status, microenvironment signatures, and immunotherapy outcomes will potentially provide great value to these topics.

Furthermore, owing to its distinctive etiology and clinical attributes, HPV-associated HNSCC exhibits varied responses to treatment, distinct rates of secondary primary tumors, diverse recurrence rates, and disparate prognoses. Notably, contemporary experts in the field have proposed a 'de-escalation strategy' for managing HPV-associated HNSCC. This strategy aims to offer effective yet less toxic therapeutic approaches to patients in this category. It encompasses adjustments in the intensity of chemotherapy,

radiotherapy, and surgical interventions. However, it is paramount to underline that the specifics of this de-escalation strategy necessitate further exploration and substantiation through real-world evidence.

The present study delved comprehensively into the clinical characteristics of HPV-associated HNSCC within the southern Chinese population, with a pronounced emphasis on HPV status. However, the pursuit of a more profound understanding of HPV epidemiology and treatment comparisons remains an essential avenue for future investigation.

Conclusion

Our study provided the current prevalence of HPV-associated HNSCC in the southern China population and investigated several key factors that correlate to the HNSCC subgroup prognosis. Also, our data revealed a strong tonsil susceptibility of HPV-associated oropharyngeal HNSCC and a lower secondary primary tumor rate associated with HPV status.

Declarations

Ethics approval and consent to participate

The study received ethical approval from Sun Yat-Sen University Cancer Center (SL-B2023-374-01). The requirement for informed consent to participate has been waived by the Ethics Committee since this is a retrospective observational study only.

Consent for publication

Not applicable.

Author contributions

Mingyuan Du: Data curation; Formal analysis; Investigation; Methodology; Resources; Software; Supervision; Validation; Writing – original draft; Writing – review & editing.

Qiaohong Lin: Conceptualization; Data curation; Investigation; Methodology; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Shida Yan: Conceptualization; Investigation; Methodology; Supervision; Writing – original draft; Writing – review & editing.

Xianlu Gao: Investigation; Methodology; Software; Writing – original draft; Writing – review & editing.

Chulin Yang: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Writing – original draft; Writing – review & editing.

Zhaoyang Li: Methodology; Project administration; Validation; Writing – original draft; Writing – review & editing.

Wei Liao: Formal analysis; Investigation; Methodology; Project administration; Resources; Writing – original draft; Writing – review & editing.

Ankui Yang: Funding acquisition; Investigation; Methodology; Project administration; Validation; Visualization; Writing – original draft; Writing – review & editing.

Shuwei Chen: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Writing – original draft; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Original data were deposited with RDD Number (RDDA2024334478). Any additional information required to reanalyze the data reported in this paper is available from the lead contract upon reasonable request.

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