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Incidence of Human Papillomavirus-Related Squamous Cell Carcinoma of the Oral Cavity and Oropharynx and Outcomes After Treatment in a Population of Smokers and Non-Smokers: A Retrospective Study from a Tertiary Referral Center in India.

Seema Pati[1*], Shivali Thakur[2], Shubham Agrawal[3], Smriti Rathi[3].

[1]*Assistant Professor, Department of ENT, Abhishek I Mishra Memorial Medical College, Bhilai, Chhattisgarh, India.*

[2]*Assistant Professor, Department of ENT, 159 GH Military Hospital, Ferozepur, Punjab, India.*

[3]*Assistant Professor, Department of ENT, Shri Shankaracharya Institute of Medical Sciences, Bhilai, Chhattisgarh, India.*

Correspondence:
Seema Pati.
Assistant Professor, Department of ENT, Abhishek I Mishra Memorial Medical College, Bhilai, Chhattisgarh, India.

Email:
seema.cims@gmail.com

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Abstract

Background: Human papillomavirus (HPV) is an increasingly recognized etiological factor in head and neck squamous cell carcinoma (HNSCC), particularly oropharyngeal carcinoma. However, data from the Indian subcontinent remain sparse, where tobacco use is highly prevalent. This study aimed to determine the incidence of HPV-related oral cavity and oropharyngeal squamous cell carcinoma (SCC) and evaluate the impact of HPV status on treatment outcomes in a predominantly tobacco-using population. ***Methods:*** A retrospective descriptive cross-sectional study was conducted at Army Hospital (Research & Referral), Delhi. A total of 200 patients with histologically confirmed SCC of the oral cavity (n=54) or oropharynx (n=146) treated between May 2014 and February 2016 were included. HPV status was determined by p16 immunohistochemistry (IHC) on formalin-fixed paraffin-embedded tissue blocks. Kaplan-Meier survival analysis with log-rank testing was used to compare overall survival (OS) and disease-free survival (DFS) based on p16 status and smoking history over 36 months. ***Results:*** The cohort was predominantly male (86.5%), with a median age of 60 years in males and 57 years in females. Tobacco use was recorded in 88% of patients. HPV positivity (p16+) was identified in 17.8% of oropharyngeal and 9.25% of oral cavity SCCs. The 3-year OS for HPV-positive patients was 68% versus 55% for HPV-negative patients (p=0.43). The 3-year DFS was 56% (HPV+) versus 38% (HPV-) (p=0.36). Although trends favoured HPV-positive patients, no statistically significant survival advantage was observed, likely attributable to the high tobacco burden even among HPV-positive cases. ***Conclusions:*** The incidence of HPV-related HNSCC in this Indian population is substantially lower than reported in Western literature. High tobacco use—even among HPV-positive patients, appears to negate the prognostic survival benefit of HPV positivity. Routine p16 IHC testing is recommended for HNSCC patients, particularly those without a smoking or alcohol history. Adequately powered prospective studies are needed to define the true prognostic impact of HPV in India's unique epidemiological context.

Keywords: Human papillomavirus; oropharyngeal carcinoma; oral cavity squamous cell carcinoma; p16 immunohistochemistry; tobacco; head and neck cancer; India; survival analysis.

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide and the eighth leading cause of cancer-related death globally [1]. In India, HNSCC accounts for approximately 12% of all malignancies, representing a major contributor to cancer-related morbidity and mortality [1, 2].

The predominant risk factors in the Indian subcontinent are tobacco consumption, in its smoked and smokeless forms, and alcohol use. In contrast to this established paradigm, evidence from Western nations over the past two decades has implicated Human papillomavirus (HPV), a double-stranded DNA oncovirus, as an independent etiological agent in a distinct subset of HNSCC, particularly oropharyngeal carcinoma [3].

The American Joint Committee on Cancer (AJCC) 8th Edition and the National Comprehensive Cancer Network (NCCN) 2017 guidelines now classify HPV-positive oropharyngeal carcinoma as a separate entity with more favorable staging and prognosis compared to its HPV-negative counterpart [4-7].

HPV exerts its oncogenic effects primarily through two viral early proteins, E6 and E7. E6 inactivates the tumor suppressor protein p53, thereby preventing apoptosis and enabling unchecked cell cycle progression [5-7]. E7 destabilises the retinoblastoma (Rb) protein, leading to constitutive activation of cyclin-dependent kinases at the G1-S cell cycle checkpoint. As a downstream consequence, p16 (CDKN2A) expression is upregulated as a negative feedback mechanism [8]. This overexpression of p16, detectable by immunohistochemistry, serves as a validated and widely accepted surrogate marker for biologically active HPV infection in HNSCC. While robust data from North America and Europe demonstrate HPV prevalence rates of 40–72% in oropharyngeal SCC with significantly improved survival outcomes for HPV-positive patients, published literature from India is limited [8, 9].

The few Indian studies available report widely discordant HPV positivity rates (15–28% for oropharyngeal SCC) and variable survival outcomes [10-12]. A critical confounding factor in the Indian context is the overwhelmingly high prevalence of tobacco use, even among patients who test HPV-positive, a scenario that may substantially attenuate the known prognostic benefit conferred by HPV positivity.

This study was designed to (1) determine the incidence of HPV-related oral cavity and oropharyngeal SCC by p16 IHC in a North Indian tertiary referral population, and (2) assess the impact of p16 status on locoregional control, disease-free survival, and overall survival, stratified by smoking history.

MATERIALS AND METHODS

Study Design and Setting

This was a retrospective, non-interventional, cross-sectional descriptive study conducted at the Department of ENT and Head & Neck Surgery, Army Hospital (Research & Referral), Delhi Cantonment, a tertiary military referral center. The study was approved by the Institutional Ethics Committee (IEC) on 24 October 2017.

Patient Selection

All patients with histologically confirmed SCC of the oral cavity or oropharynx who completed cancer-directed treatment between May 2014 and February 2016, and for whom formalin-fixed paraffin-embedded (FFPE) tissue blocks were retrievable from the pathology archives, were included. Cases with distant metastases at presentation, inadequate tissue for histomorphology, or lost to follow-up were excluded. A total of 200 patients met the inclusion criteria.

HPV Detection by p16 Immunohistochemistry

FFPE tissue blocks were subjected to p16 IHC using a rabbit/mouse monoclonal p16INK4a antibody (CINtec, Biogenex) via an epitope retrieval technique with a high-sensitivity polydetector horseradish peroxidase/diaminobenzidine (HRP-DAB) system (Bio-SB).

Staining intensity was graded 0 (none) to 3 (strong), and the proportion of staining was graded 0 (none) to 3 (diffuse). The cell score (intensity × proportion, range 0–9) was calculated; scores of 0–1 were classified as negative and scores of 2–9 as positive. Slides were independently evaluated by two investigators, with any discordant cases resolved by consensus. Positive and negative controls were run with every batch.

Treatment

All patients received curative-intent multimodality treatment per standard head and neck oncology guidelines. Oral cavity cancers were managed with primary surgery (wide local excision with or without neck dissection) followed by adjuvant radiotherapy (RT) or concurrent chemoradiotherapy (CCRT) as indicated. Oropharyngeal carcinomas were treated with definitive CCRT (cisplatin + 70 Gy) or RT alone. HPV status was not known at the time of treatment planning and did not influence therapeutic decisions.

Follow-Up and Outcome Assessment

Patients were followed up at 3, 6, 12, 18, 24, and 36 months post-treatment. For the purpose of this analysis, outcomes at 1, 2, and 3 years were evaluated. Endpoints assessed were overall survival (OS), disease-free survival (DFS), and locoregional (LR) control.

Statistical Analysis

Categorical variables were expressed as frequencies and percentages. Associations between HPV status and clinicopathological variables were analyzed using Pearson, Kendall, and Spearman correlation coefficients.

OS and DFS were estimated using the Kaplan-Meier method, and survival curves were compared using the log-rank test. A p-value <0.05 was considered statistically significant. Statistical analysis was performed using STATA version 22.0.

RESULTS

Patient Demographics

A total of 200 patients were enrolled: 146 with oropharyngeal carcinoma and 54 with oral cavity carcinoma. The cohort was predominantly male (173 males, 27 females; M:F ratio ~6.4:1). The median age was 60 years for males and 57 years for females, with the largest proportion of patients (approximately 45%) in the 51–60 year age group.

Table 1. Baseline Characteristics of the Study Population

Characteristic	Oropharynx (n=146)	Oral Cavity (n=54)
Male	128 (87.7%)	45 (83.3%)
Female	18 (12.3%)	9 (16.7%)
Median Age (years)	60	57
Smokers	129 (88.4%)	28 (51.9%)
Alcohol Use	99 (67.8%)	39 (72.2%)
HPV Positive (p16+)	26 (17.8%)	5 (9.3%)
Stage III–IV	83.6%	100%

Tumor Characteristics

In oropharyngeal carcinoma, the tonsil was the most frequently involved subsite (57%), followed by the base of tongue (28%) and soft palate (12%). In oral cavity carcinoma, the tongue was the most common site (48%), followed by buccal mucosa (30%). The majority of patients presented with advanced disease: 83.6% of oropharyngeal carcinoma patients had Stage III or IV disease, and all oral cavity carcinoma patients presented with Stage III–IV disease. Moderately differentiated histology was the most frequent grade (47.5%), followed by well-differentiated (41.5%) and poorly differentiated (11%).

HPV Incidence

Overall HPV (p16) positivity was identified in 31 of 200 patients (15.5%). HPV positivity was detected in 26 of 146 (17.8%) oropharyngeal SCC cases and 5 of 54 (9.25%) oral cavity SCC cases. Among HPV-positive oropharyngeal patients, 77% were male, and 23% were female. In the HPV-positive oropharyngeal group, 81% were smokers, compared with 90% in the HPV-negative group—indicating high tobacco use in both groups.

Disease Outcomes at 3 Years

At 3-year follow-up, among all 200 patients, 86 (43%) died of disease, 83 (42%) had locoregional control, and 31 (16%) had disease recurrence. Oral cavity carcinoma carried a significantly worse prognosis: 59% died of disease versus 37% for oropharyngeal carcinoma. Among HPV-positive patients, 32% died, 58% achieved locoregional control, and 10% recurred. Among HPV-negative patients, 45% died, 38% achieved locoregional control, and 17% recurred.

Table 2. Disease Outcomes at 3-Year Follow-Up by HPV Status

Outcome	HPV Positive (n=31)	HPV Negative (n=169)
Died of Disease	10 (32%)	76 (45%)
Locoregional Control	18 (58%)	65 (38%)
Recurrence	3 (10%)	28 (17%)

Survival Analysis

Kaplan-Meier analysis revealed that HPV-positive patients had numerically superior survival outcomes across all subgroups, though these differences did not reach statistical significance.

Table 3. Kaplan-Meier Survival Outcomes at 3 Years by Site and HPV Status

Group	HPV+ OS	HPV- OS	HPV+ DFS	p-value (OS)
All Patients	68%	55%	56%	0.43
Oropharynx	65%	63%	54% vs 43%	0.47
Oral Cavity	80%	37%	56% vs 43%	0.36
Oropharynx – Smokers	76%	66%	—	0.28
Oropharynx – Non-Smokers	33%	20%	—	0.34
Oral Cavity – Smokers	85%	62%	—	0.11
Oral Cavity – Non-Smokers	50%	25%	—	0.42

Although statistical significance was not achieved, a consistent trend towards better survival was observed in HPV-positive patients across all subsites and smoking categories. The 3-year OS advantage for HPV-positive patients over HPV-negative patients was 13 percentage points overall (68% vs. 55%), and more pronounced in oral cavity SCC (80% vs. 37%).

DISCUSSION

This study reports one of the relatively few prospective-quality retrospective analyses of HPV-related HNSCC from a tertiary military referral center in North India. The 17.8% prevalence of HPV (p16+) positivity in oropharyngeal carcinoma observed in this study is broadly consistent with published Indian data from Bahl et al. (22.8%) and Murthy et al. (20%), and substantially lower than rates reported from Western series (40–72%) [10-15]. This divergence likely reflects the fundamentally different etiological landscape in India, where tobacco and alcohol, rather than sexual transmission of HPV, remain the dominant drivers of HNSCC. The high prevalence of tobacco use (88% overall) in this cohort is consistent with other large Indian series reporting tobacco use in 80–90% of HNSCC patients. Critically, even among HPV-positive patients in this study, 81% of oropharyngeal cases were current smokers—a pattern rarely observed in Western HPV-positive cohorts, where non-smoking status is virtually a defining characteristic [13-15].

This overlap likely explains why the expected survival advantage of HPV positivity was attenuated in this study. Ang et al. previously demonstrated that tobacco use increases mortality risk by approximately 1% per additional pack-year, independent of HPV status [8]. The absence of a statistically significant survival difference between HPV-positive and HPV-negative patients in this study, while not uncommon in Indian literature, has important clinical implications. P16 hypermethylation—driven by prolonged tobacco carcinogen exposure—may suppress p16 expression even in the presence of biologically active HPV, introducing discordance between p16 IHC and true HPV DNA status. This underscores the limitation of p16 alone as an HPV surrogate in high-tobacco-burden populations and supports the need for confirmatory HPV DNA testing (PCR for E6/E7) in select cases.

Despite the lack of statistical significance, the trend toward improved survival in HPV-positive patients—across all subgroups including smokers and non-smokers—is clinically meaningful. The magnitude of effect observed (13 percentage points in OS) is comparable to differences reported by Ritchie et al. (71% vs. 49%) and Licitra et al. (79% vs. 46%), both of which were statistically significant in larger cohorts [13]. The likely reason for non-significance in this study is the relatively modest sample size of HPV-positive cases (n=31), limiting statistical power. The advanced stage at presentation (84% Stage III–IV) in this cohort mirrors patterns reported across India and highlights the need for earlier cancer detection efforts. The higher mortality in oral cavity SCC (59%) compared with oropharyngeal SCC (37%) at 3 years is consistent with international data, reflecting the generally more aggressive course of tobacco-induced oral cavity cancers, which are typically HPV-negative [13-15]. Regarding preventive strategies, while HPV vaccines have demonstrated efficacy in preventing anogenital HPV infection, their role in preventing oropharyngeal SCC remains under evaluation. The U.S. FDA has not approved any currently available prophylactic HPV vaccine specifically for oropharyngeal SCC [16]. Given the relatively low HPV prevalence in India, the role of HPV vaccination in primary prevention of HNSCC in this population requires further investigation.

This study has several limitations. First, HPV status was determined by p16 IHC alone, without confirmatory PCR-based HPV DNA or E6/E7 mRNA testing, which is the gold standard for establishing biologically active infection. Second, the sample size of HPV-positive cases (n=31) may have been insufficient to detect a statistically significant survival difference. Third, quantitative tobacco exposure data (pack-years, duration, cessation status) and high-risk sexual behaviour history, an important HPV transmission risk factor, were not systematically collected. Finally, the retrospective design introduces potential selection bias.

CONCLUSION

The incidence of HPV-positive oropharyngeal and oral cavity SCC in this North Indian cohort (17.8% and 9.25%, respectively) is considerably lower than rates reported from Western populations, in keeping with the tobacco-dominated epidemiology of HNSCC in India. Although HPV positivity was associated with a numerical trend toward improved overall survival and locoregional control, this advantage was not statistically significant—likely due to the high tobacco burden even among HPV-positive patients, which appears to attenuate the prognostic benefit of HPV. P16 IHC remains a practical and sensitive surrogate marker for HPV and should be incorporated into routine diagnostic workup for HNSCC, especially in patients without significant tobacco or alcohol history. Large, prospective, multicenter studies with HPV DNA confirmation are needed to definitively characterize the prognostic impact of HPV in the Indian HNSCC population and to guide future treatment de-escalation strategies.

DECLARATIONS

Ethics Approval: Approved by the Institutional Ethics Committee
Consent: Written informed consent was obtained from all participants.
Conflict of Interest: The authors declare no conflicts of interest.
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