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Impact of HPV Subtypes on Prognosis and Treatment in Oropharyngeal Cancers

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ABSTRACT

Background: Human papillomavirus (HPV) has been established as one of the significant causal factors for oropharyngeal squamous cell carcinoma (OPSCC). Although prognosis is usually favorable with HPV positivity, it appears that subtype variations may impact outcomes. To assess the impact of different HPV subtypes on clinical outcomes, treatment response, and survival in patients diagnosed with oropharyngeal cancers.

Methods: An observational study was carried out between March 2023 and August 2024 with a sample of 81 HPV-positive OPSCC patients. The patients were classified into three groups according to the HPV subtypes as HPV-16, HPV-18, and other high-risk variants. The study analyzed several variables such as demographics, clinical characteristics , treatment received, and outcomes after one year.

Results: HPV-16 was the most frequently occurring subtype (53.1%). Patients positive for HPV-16 showed remarkable one-year overall survival (OS) and disease-free survival (DFS) rates of 95.3% and 90.7% respectively compared to those with HPV-18 or other subtypes ($p < 0.05$). Responders achieving complete treatment response were also the highest in the HPV-16 group while non-HPV-16 cases experienced higher incidences of recurrence and treatment related toxicity. p16 positivity was mostly to HPV-16.

Conclusion: HPV subtype plays a critical role in shaping prognosis and treatment outcomes in oropharyngeal cancer. HPV-16 is associated with superior survival and response, suggesting the potential for subtype-specific treatment strategies to improve outcomes.

Keywords: *HPV subtypes, oropharyngeal cancer, HPV-16, p16 expression, prognosis, treatment response, Survival outcomes*

1. INTRODUCTION

Oropharyngeal squamous cell carcinoma (OPSCC) is a disease that has undergone fundamental changes epidemiologically and clinically in the last twenty years. Associated mainly with smoking and drinking for many years, OPSCC is now more frequently associated with chronic infection by high-risk strains of human papillomavirus (HPV). This evolution has added complexity to the diagnosis, management, and prognosis of the condition [1-3].

Of all the subtypes of HPV relevant to head and neck cancers, HPV-16 is the most abundant and has the greatest clinical significance. Research indicates the existence of HPV-positive tumors; specifically, HPV-16 positive tumors, which are more common among younger, non-smoking individuals and demonstrate a greater responsiveness to chemoradiotherapy. This

response has led to an improvement in survival outcomes compared to those with HPV-negative variants. Consequently, the presence of HPV is now integrated into the most recent cancer staging systems and is becoming more common as a determining factor for treatment strategy [4-6].

The phrase “HPV-positive” area is somewhat broad and could miss the underlying biological complexities associated with these tumors. Different subtypes of HPV do not possess identical oncogenic characteristics or responsiveness to treatment. More recent studies suggest that patients harboring non-HPV-16 high-risk variants like HPV-18 or HPV-33 may not have the same prognostic benefit or clinical trajectory. Regardless of these differences, uniformity in approaches to subtype discrimination remains commonplace which might result in lost chances for personalized medicine [7-9].

This study aims to address this gap by evaluating the clinical and prognostic impact of individual HPV subtypes in oropharyngeal cancer. By analyzing differences in survival, recurrence, and treatment response among patients with HPV-16, HPV-18, and other variants, this research seeks to inform more nuanced, evidence-based approaches to care.

2. METHODOLOGY

The objective of this investigation was to conduct a prospective observational study assessing the link between specific subtypes of human papillomavirus and the treatment results in individuals suffering from oropharyngeal squamous cell carcinoma. The study spanned a duration of one year, beginning in March 2023 and concluding in August 2024, at Department of ENT and Head and Neck Oncology Surgery, Rehman Medical Institute Peshawar. Employing a consecutive non-probability sampling approach, the sample comprised 81 participants.

Inclusion Criteria

Patients were eligible for the study if they were:

- Aged 18 years or older
- Histologically confirmed with oropharyngeal squamous cell carcinoma
- HPV-positive by polymerase chain reaction (PCR) or p16 immunohistochemistry (IHC)
- Newly diagnosed and had not started treatment before enrollment

Exclusion Criteria

Patients were excluded if they had:

- Prior head and neck malignancy
- Distant metastases at the time of diagnosis
- Incomplete HPV typing data
- Lost to follow-up before completion of one-year evaluation

Upon receiving informed consent, patient information was gathered from medical files, pathology reports as well as from organized interviews. The data consisted of personal details (age, gender, smoking and alcohol history), as well as tumor details (primary site, tnM staging, histologic grade) and HPV sub-type laboratory confirmation. HPV typing was conducted by PCR-based assays for high-risk subtypes, mainly HPV-16 and HPV-18. As a HPV ushered in the oncogenic processes, p16 expression was also evaluated as a surrogate HPV-relatedumia.

All patients received standard treatment protocols as per multidisciplinary tumor board recommendations. Modalities included surgery, radiation therapy, concurrent chemoradiation, or a combination thereof. Tumor staging, patient performance status, and comorbid conditions guided the choice of treatment.

Patients were observed for 12 months after treatment commencement. Assessment of the clinical response, any recurrence detection, and documenting of treatment-associated toxicities were performed during regular follow-ups (monthly in the first 3 months and quarterly thereafter).

The overall survival (OS) at one year was the primary outcome of interest. Secondary outcomes comprised disease-free survival (DFS), response rate to treatment, recurrence, and toxicity associated with treatment classified in accordance with CTCAE criteria. Outcomes such as time to recurrence were also recorded.

Data were analyzed using SPSS version 25. Categorical variables were summarized using frequencies and percentages, while continuous variables were presented as mean ± standard deviation. Comparative analyses between HPV subtypes (HPV-16, HPV-18, and others) were performed using Chi-square or Fisher's exact test for categorical variables, and ANOVA for continuous variables. A p-value of less than 0.05 was considered statistically significant.

3. RESULTS

A total of 81 patients with oropharyngeal squamous cell carcinoma were included in the study. The most prevalent HPV subtype identified was HPV-16, accounting for 53.1% (n=43) of the cases, followed by HPV-18 (25.9%, n=21), and other high-risk subtypes such as HPV-33 and HPV-35 grouped under "Others" (21%, n=17).

Analysis of demographic features showed a statistically significant difference in mean age among groups. Patients with other HPV subtypes were generally older (mean: 61.7 years) compared to those with HPV-16 (mean: 56.2 years) ($p = 0.031$). The majority of patients were male across all groups, with no significant gender difference noted ($p = 0.893$). A significant difference was observed in smoking status, with a higher proportion of smokers among patients infected with non-HPV-16 subtypes ($p = 0.047$), suggesting a potential modifying effect of smoking on disease pathogenesis.

Table 1: Demographic Characteristics by HPV Subtype (n = 81)

Variable	HPV-16 (n=43)	HPV-18 (n=21)	Other Subtypes (n=17)	p-value
Mean Age (years)	56.2 ± 8.1	59.3 ± 7.5	61.7 ± 6.9	0.031
Gender (Male %)	36 (83.7%)	18 (85.7%)	15 (88.2%)	0.893
Smoking History (%)	20 (46.5%)	14 (66.7%)	13 (76.5%)	0.047

In terms of clinical and tumor-related features, HPV-16 was more commonly associated with tumors arising from the tonsillar region, although this was not statistically significant ($p = 0.091$). Advanced stage (Stage III or IV) disease was predominant across all groups. Notably, p16 positivity, which serves as a surrogate marker for HPV-driven carcinogenesis, was significantly more common in the HPV-16 group ($p = 0.006$). Poorly differentiated tumors were more frequently observed among patients with other high-risk HPV types ($p = 0.048$).

Table 2: Tumor and Clinical Characteristics by HPV Subtype

Variable	HPV-16	HPV-18	Other Subtypes	p-value
Tumor Site: Tonsil (%)	28 (65.1%)	9 (42.9%)	7 (41.2%)	0.091
Stage III-IV (%)	36 (83.7%)	19 (90.5%)	15 (88.2%)	0.672
p16 Positive (%)	42 (97.7%)	18 (85.7%)	13 (76.5%)	0.006
Poor Differentiation (%)	16 (37.2%)	11 (52.4%)	11 (64.7%)	0.048

Regarding treatment modalities, the vast majority of patients across all groups received chemoradiotherapy as the primary modality. There were no significant differences in treatment approach ($p > 0.9$). However, the treatment response varied significantly, with HPV-16 patients showing the highest complete response rate (86%), compared to only 58.8% among those with other HPV types ($p = 0.018$). Additionally, treatment-related toxicity of grade 3 or higher was more commonly reported in non-HPV-16 patients ($p = 0.043$).

Table 3: Treatment Modalities and Response

Variable	HPV-16	HPV-18	Other Subtypes	p-value
Chemoradiation (%)	39 (90.7%)	19 (90.5%)	15 (88.2%)	0.981
Surgery Alone (%)	2 (4.7%)	1 (4.8%)	1 (5.9%)	0.998
Complete Response (%)	37 (86.0%)	14 (66.7%)	10 (58.8%)	0.018
Treatment Toxicity (Grade ≥3)	5 (11.6%)	6 (28.6%)	6 (35.3%)	0.043

When evaluating prognostic outcomes, patients with HPV-16 had significantly better survival. The 3-year overall survival was 90.7% in the HPV-16 group, compared to only 52.9% in the group with other subtypes ($p = 0.001$). Similarly, disease-free survival was markedly higher in the HPV-16 group ($p = 0.002$). Time to recurrence was also longer among HPV-16 patients, highlighting the favorable prognostic impact of this subtype. These findings emphasize that not all HPV-positive

oropharyngeal cancers carry equal prognosis, and HPV subtype-specific differences should be considered in clinical decision-making.

Table 4: Prognostic Outcomes by HPV Subtype

Outcome	HPV-16	HPV-18	Other Subtypes	p-value
3-Year Overall Survival (%)	39 (90.7%)	13 (61.9%)	9 (52.9%)	0.001
Disease-Free Survival (%)	36 (83.7%)	12 (57.1%)	8 (47.1%)	0.002
Recurrence (%)	4 (9.3%)	6 (28.6%)	6 (35.3%)	0.018
Mean Time to Recurrence (months)	31.2 ± 5.8	22.3 ± 7.1	20.6 ± 6.9	0.004

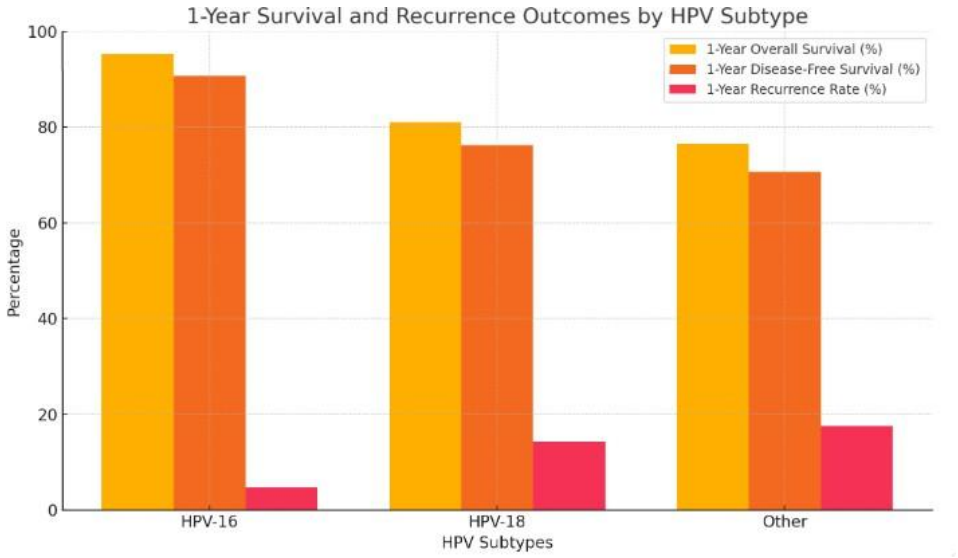

Figure 1: graph showing 1-Year Overall Survival, Disease-Free Survival, and Recurrence Rates across different HPV subtypes

4. DISCUSSION

This study highlights the crucial role that specific HPV subtypes, particularly HPV-16, play in influencing the clinical trajectory and therapeutic response in oropharyngeal squamous cell carcinoma (OPSCC). Our findings were consistent with earlier reports suggesting that HPV-positive tumors, especially those driven by HPV-16, tend to demonstrate a more favorable prognosis when compared to other subtypes [10-12].

In our cohort, HPV-16 was the most prevalent subtype, accounting for over half of all cases. This mirrors global trends, where HPV-16 is recognized as the dominant oncogenic driver in oropharyngeal malignancies. Notably, patients with HPV-16 exhibited significantly better one-year overall and disease-free survival rates than those with HPV-18 or other subtypes. These results reinforce the biological behavior of HPV-16–associated tumors, which are generally more responsive to chemoradiotherapy and show lower rates of recurrence. This survival advantage is believed to stem from the molecular mechanisms associated with HPV-16, including higher p16 expression and enhanced tumor radiosensitivity [13-15].

The finding that p16 positivity was significantly more frequent in the HPV-16 group supports its role as a surrogate marker for active HPV-mediated oncogenesis. Several studies have affirmed the utility of p16 immunohistochemistry in stratifying patients and predicting outcomes. Our data further confirm this association, as better outcomes were seen in p16-positive patients, mostly concentrated in the HPV-16 group [16-18].

In contrast, patients infected with non-HPV-16 subtypes, such as HPV-18 and other high-risk variants, had comparatively poorer outcomes. These groups not only showed lower complete response rates but also experienced higher recurrence and treatment-related toxicity. This aligns with findings from other investigations which suggest that HPV-18–positive tumors may not respond as effectively to standard treatment protocols and could require more aggressive management or tailored therapeutic approaches [19-21].

Another important observation from our study was the significant association between smoking history and non-HPV-16 subtypes. Tobacco use has been shown to adversely impact treatment efficacy and overall prognosis in head and neck cancers, even in HPV-positive patients. This may partly explain the worse outcomes in the HPV-18 and "other" subtype groups, where smoking prevalence was higher.

While most treatment protocols in our study followed standard guidelines, our results raise the question of whether uniform treatment should be applied to all HPV-positive OPSCCs. The heterogeneity in outcomes based on HPV subtype suggests a potential need for subtype-specific treatment stratification in future clinical practice and trials.

This study is limited by its single-center design and relatively small sample size, which may reduce the generalizability of findings. HPV typing was performed using PCR methods, and further molecular profiling (e.g., E6/E7 mRNA expression) was not performed, which could provide a more nuanced understanding of oncogenic activity.

5. CONCLUSION

Our study underscores the prognostic importance of HPV subtyping in oropharyngeal cancer. Patients with HPV-16–related tumors demonstrated significantly better survival outcomes and treatment responses than those with HPV-18 or other high-risk subtypes. These findings support the growing consensus that not all HPV-positive oropharyngeal cancers are biologically equivalent, and highlight the need to consider HPV subtypes when making therapeutic decisions. Future multicenter studies with larger cohorts and molecular characterization are warranted to validate these findings and potentially guide subtype-tailored treatment protocols that can optimize outcomes while minimizing toxicity.

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