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Prevalence of HPV in Oral and Oropharyngeal Squamous Cell Carcinoma at a Tertiary Care Centre

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ABSTRACT

Background: Oral and oropharyngeal squamous cell carcinoma (OSCC) represents a significant health burden with emerging evidence suggesting dual pathogenic pathways - one driven by traditional risk factors and another by human papillomavirus (HPV) infection. The relationship between HPV infection, vascular endothelial growth factor (VEGF) expression, and tumor characteristics remains incompletely understood, particularly in the Indian population.

Objectives: This study aimed to evaluate VEGF expression patterns in OSCC and their association with HPV E6/E7 oncoproteins, while additionally estimating HPV prevalence through viral oncoprotein detection. The study also examined correlations between VEGF expression and various clinicopathological parameters.

Methods: This hospital-based cross-sectional study examined 80 cases of histologically proven OSCC. Immunohistochemical analysis was performed for VEGF and HPV E6/E7 oncoproteins. VEGF expression was scored using an immunoreactivity scoring system (0-12), while HPV oncoprotein expression was evaluated using combined

percentage positivity and intensity scores (0-7). Results were correlated with clinicopathological parameters.
Results: VEGF expression was detected in 85% of OSCC cases, with 30% showing high expression (score 9-12), significantly higher than in adjacent dysplastic tissue (p=0.004). HPV prevalence, as indicated by E6 expression, was 37.5%, with lower rates of E7 expression for HPV16 (26.25%) and HPV18 (20%). A significant correlation emerged between VEGF expression and tumor differentiation (p=0.012), with higher expression in well-differentiated tumors. VEGF expression showed no significant associations with HPV oncoprotein status, age, gender, tumor size, lymph node involvement, or TNM stage.
Conclusions: The high prevalence of VEGF expression in OSCC and its significant correlation with tumor differentiation suggests its potential role as a prognostic marker. The independence of VEGF expression from HPV status, despite considerable HPV prevalence in the study population, indicates that angiogenic mechanisms might operate independently of viral oncogenesis. These findings suggest that anti-VEGF therapy might be beneficial regardless of HPV status, particularly in early-stage disease.
Keywords: Oral squamous cell carcinoma, oropharyngeal cancer, vascular endothelial growth factor, human papillomavirus, immunohistochemistry, tumor angiogenesis

INTRODUCTION

Oral and oropharyngeal squamous cell carcinoma (OSCC) represents a significant global health burden, with squamous cell carcinoma accounting for approximately 90% of all oral malignancies [1]. While traditional risk factors like tobacco use and alcohol consumption remain important, human papillomavirus (HPV) infection has emerged as a major etiologic factor, particularly for oropharyngeal cancers [2].

The incidence of HPV-associated oropharyngeal cancers is notably higher among men compared to women, and tends to affect younger adults with a history of multiple sexual partners [3,4]. HPV-16 and HPV-18 are the predominant high-risk types implicated in oral and oropharyngeal carcinogenesis [5]. The viral oncoproteins E6 and E7 play central roles in carcinogenesis through their interactions with tumor suppressor proteins p53 and pRb respectively [6,7].

HPV-positive OSCCs demonstrate distinct clinical and molecular characteristics compared to HPV-negative tumors. These cancers typically present at a younger age, show better response to treatment, and generally have improved survival outcomes despite often presenting at advanced stages [8,9]. The molecular basis for these differences may lie in the mechanism of viral oncogenesis, particularly the actions of E6 and E7 oncoproteins in promoting angiogenesis through vascular endothelial growth factor (VEGF) expression [10].

Despite growing evidence supporting HPV's role in OSCC, there remains a paucity of data from Indian populations regarding HPV prevalence and its association with angiogenic factors like VEGF. Understanding these relationships could have important implications for prognosis and treatment selection, particularly regarding the potential utility of anti-angiogenic therapies in HPV-positive versus negative cases [11,12].

This study aimed to evaluate the prevalence of HPV infection through immunohistochemical detection of E6 and E7 viral oncoproteins in oral and oropharyngeal squamous cell carcinoma cases at a tertiary care center, while also examining potential associations with VEGF expression and clinicopathological parameters. To evaluate the immunohistochemical expression of VEGF and its association with HPV E6 and E7 oncoproteins in OSCC, while examining correlations with clinicopathological parameters. Additionally, to estimate the prevalence of HPV infection in oral and oropharyngeal squamous cell carcinoma through immunohistochemical detection of viral oncoproteins.

MATERIALS AND METHODS

Study Design and Setting

This hospital-based descriptive observational cross-sectional study was conducted at the Department of Pathology in collaboration with the Department of Otorhinolaryngology, Lady Hardinge Medical College and Associated Hospitals, New Delhi, and Institute of Cytology and Preventive Oncology (ICMR), Noida between November 2014 and March

2016.

Study Population

Eighty newly diagnosed, histologically proven cases of oral or oropharyngeal squamous cell carcinoma were included after obtaining informed consent. Patients already on therapy for oral/oropharyngeal squamous cell carcinoma and malignancies other than squamous cell carcinoma were excluded.

Histopathological Examination

Biopsy specimens were fixed in 10% neutral buffered formalin for a minimum of 4 hours. Paraffin-embedded tissue blocks were sectioned at 3-4 µm thickness and mounted on poly-L-lysine coated slides. Hematoxylin and eosin (H&E) staining was performed using standard protocols [13].

Immunohistochemistry

Immunohistochemical staining was performed using a non-biotin polymeric technique [14]. Antigen retrieval was done using pressure cooking in a decloaking chamber (Biocare Medical) with citrate buffer (pH 6.0). The following primary antibodies were used:

- VEGF: Concentrated rabbit monoclonal antibody IgG Clone EP1176Y (Biocare Medical)
- HPV16/18 E6 Antibody (C1P5) - mouse monoclonal IgG1 (Santa Cruz Biotech)
- HPV16 E7 Antibody (ED17) - mouse monoclonal IgG1 (Santa Cruz Biotech)
- HPV18 E7 Antibody (N-19) - goat polyclonal IgG (Santa Cruz Biotech)

Detection was performed using Dako REAL™ Envision™ Detection System with DAB chromogen [15]. Appropriate positive controls were included for each marker.

Scoring System

VEGF expression was evaluated using an immunoreactivity score (IRS) calculated by multiplying staining intensity (0-3) with percentage positivity (1-4), yielding final scores of 1-12 [16]. Scores were categorized as:

- Low: 1-4
- Medium: 6-8
- High: 9-12

For E6 and E7, immunoreactivity scores (0-7) were calculated by adding percentage positivity (0-4) and staining intensity (0-3) scores [17].

For HPV oncoprotein expression, immunoreactivity scores (0-7) were calculated by combining percentage positivity (0-4) and staining intensity (0-3). Percentage positivity was scored as: <10% (0), 10-30% (1), 30-50% (2), 50-70% (3), and 70-100% (4). Staining intensity was scored as: no staining (0), mild (1), moderate (2), and intense (3). Cases were considered positive for viral oncoprotein expression when showing any detectable immunoreactivity.

Clinical Parameters

Detailed clinical information including age, gender, addiction history, tumor site, size, lymph node involvement, and TNM staging was recorded. Tumors were staged according to the TNM classification system [18] and histologically graded following standard criteria [19].

Statistical Analysis

Data was analyzed using SPSS version 16.0. Pearson's chi-square test was used for categorical variables and Pearson correlation for measurement scale variables. P-value <0.05 was considered statistically significant [20].

RESULTS

Demographic and Clinical Characteristics

The study included 80 cases of oral and oropharyngeal squamous cell carcinoma. The mean age was 54 years (range: 32-80 years), with maximum cases (51.25%) in the 41-60 age group. Male predominance was observed with a male-to-female ratio of 3.4:1 (77.50% males, 22.50% females).

Table 1: Distribution of Age and Gender (N=80)

Age Group (years)	Number (%)
21-40	17 (21.25)
41-60	41 (51.25)
>60	22 (27.50)

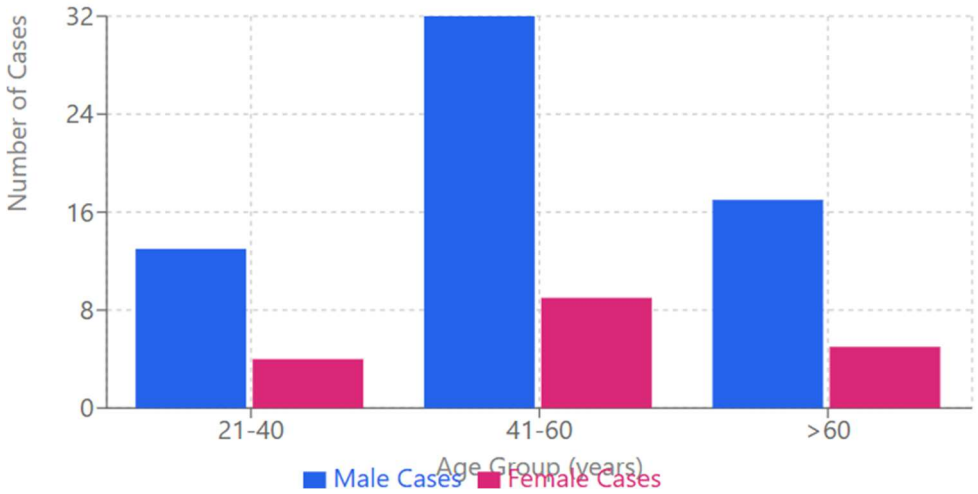

Fig 1: Bar graph showing age distribution by gender

Risk Factors and Site Distribution

Addiction habits (tobacco/smoking/alcohol) were present in 52 cases (65%). The tongue was the most common tumor site (28.75%), followed by cheek (26.2%).

Table 2: Distribution of Tumor Sites (N=80)

Site	Number (%)
Tongue	23 (28.75)
Cheek	21 (26.20)
Tonsil	10 (12.50)
Alveolus	8 (10.00)
Vallecula	6 (7.50)
Palate	5 (6.25)
Retromolar trigone	3 (3.75)
Floor of mouth	3 (3.75)
Lip	1 (1.20)

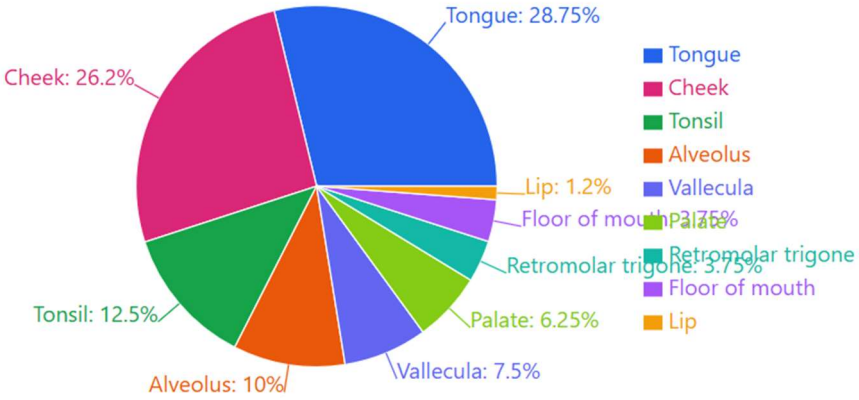

Fig 2: Pie chart showing distribution of tumor sites

Tumor Characteristics and Staging

Most tumors (47.50%) were ≤2 cm in size. Lymph node involvement was present in 33 cases (41.25%), with cervical nodes being most commonly involved (66.66%). According to TNM staging, maximum patients belonged to Stage I (30%).

Table 3: TNM Staging Distribution (N=80)

Stage	Number (%)
I	24 (30.00)
II	19 (23.75)
III	19 (23.75)
IVA	17 (21.25)
IVB	1 (1.25)

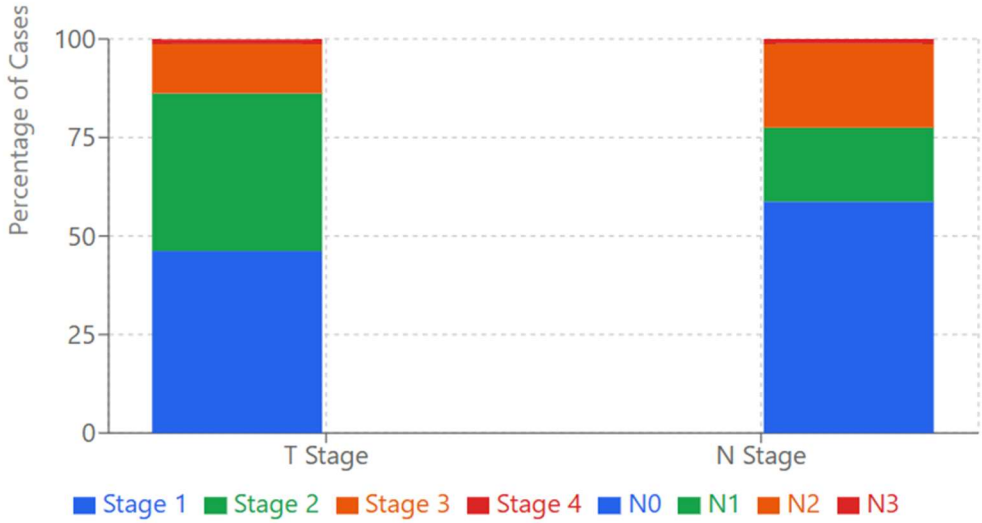

Fig 3: Stacked bar chart showing T and N staging distribution

Histopathological Findings

Moderately differentiated squamous cell carcinoma (MDSCC) was predominant (51.25%), followed by well-differentiated (WDSCC, 47.50%) and poorly differentiated (PDSCC, 1.25%) variants. All cases showed severe dysplasia in adjacent mucosa.

VEGF Expression Analysis

VEGF positivity was observed in 68/80 cases (85%) of OSCC. The distribution of VEGF expression scores was:

- High (9-12): 24 cases (30%)
- Medium (6-8): 19 cases (23.75%)
- Low (1-4): 25 cases (31.25%)
- Negative: 12 cases (15%)

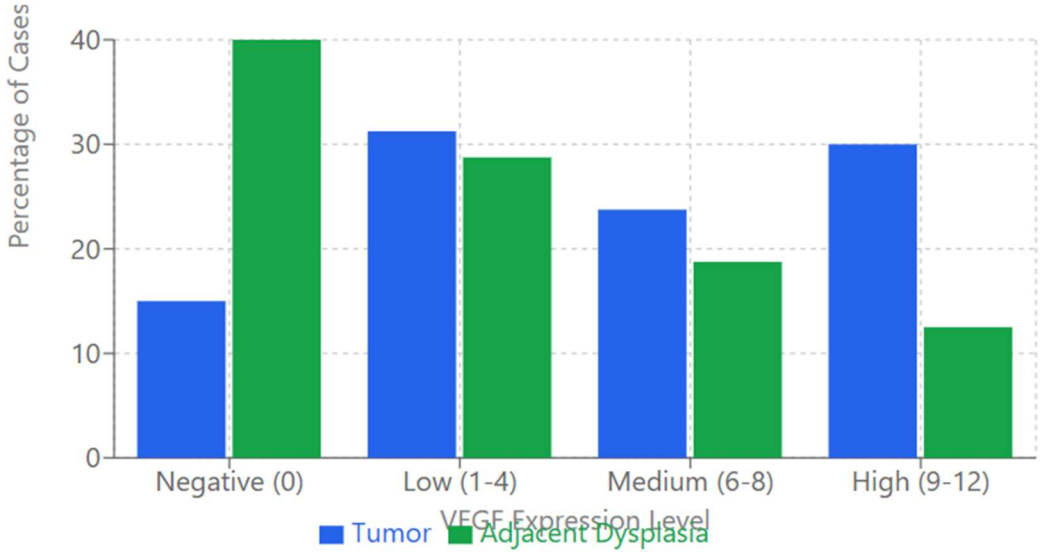

Fig 4: Bar graph comparing VEGF expression in tumor versus adjacent dysplasia]

HPV Oncoprotein Expression

Analysis of HPV oncoprotein expression revealed that 30 cases (37.5%) showed immunoreactivity for E6 (HPV16/18). Further characterization showed E7 (HPV16) positivity in 21 cases (26.25%) and E7 (HPV18) positivity in 16 cases (20%). When analyzed by scoring groups, 72.5% of cases had an E6 score of 0-3, while 27.5% showed scores of 4-7. For E7 (HPV16), 82.5% of cases scored 0-3 and 17.5% scored 4-7. Similarly, for E7 (HPV18), 90% of cases scored 0-3 and 10% scored 4-7.**Table 4:** Correlation of VEGF Expression with HPV Status

VEGF Score	E6+ (%)	E6- (%)	p-value
0-4	14 (46.7)	23 (46)	0.275
6-12	16 (53.3)	27 (54)	

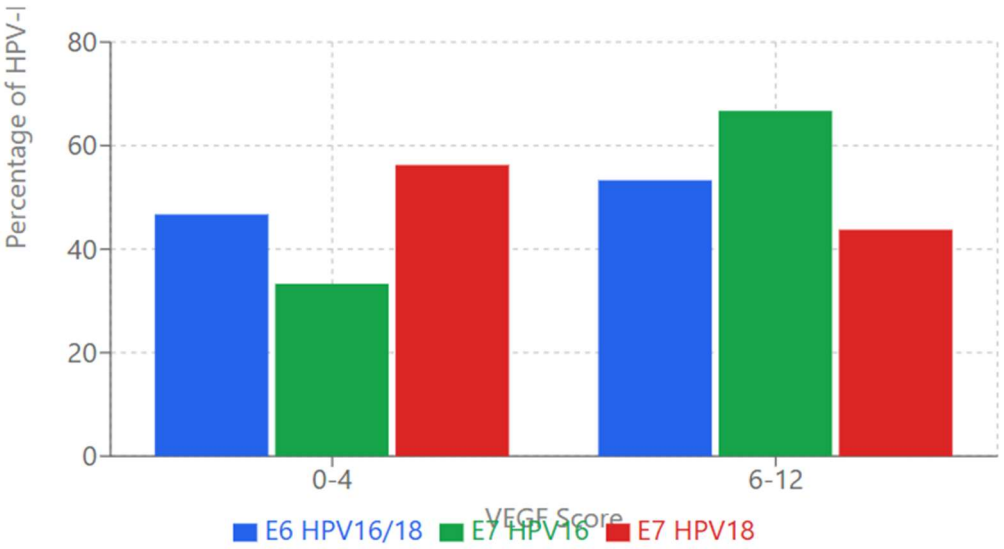

Fig 5: Multiple bar graph showing correlation between VEGF scores and HPV oncoprotein expression

Clinicopathological Correlations

A significant correlation was found between VEGF expression and tumor differentiation (p=0.012), with higher expression in WDSCC compared to MDSCC/PDSCC. VEGF expression showed no significant correlation with age (p=0.658), gender (p=0.368), tumor size (p=0.093), lymph node status (p=0.303), or TNM stage (p=0.226).

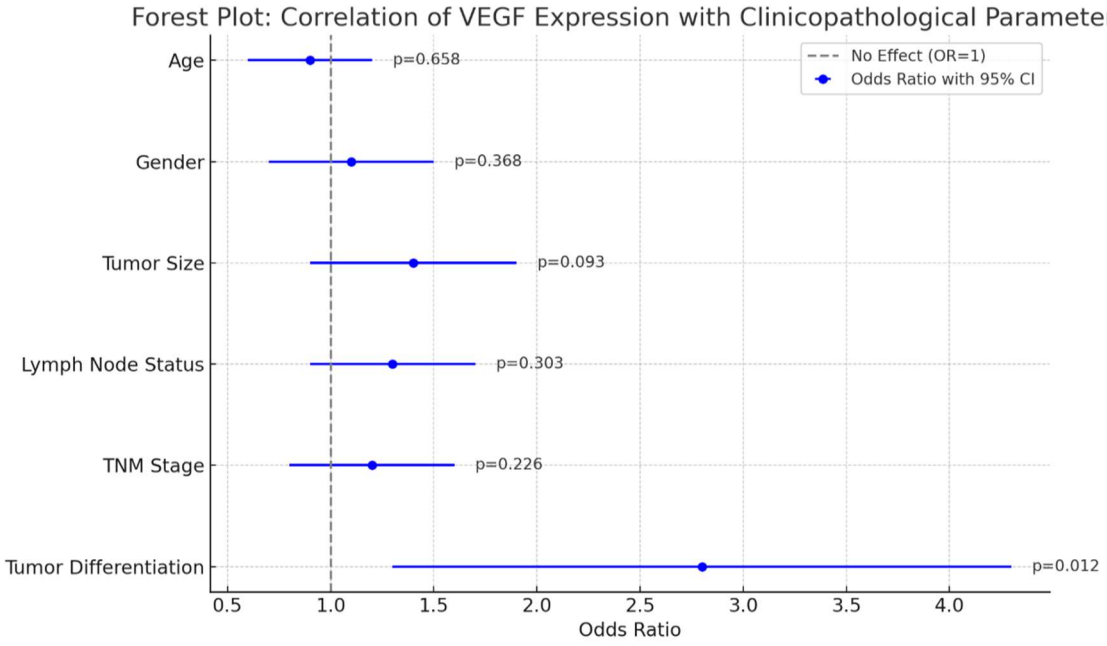

Fig 6: Forest plot showing correlation of VEGF expression with various clinicopathological parameters

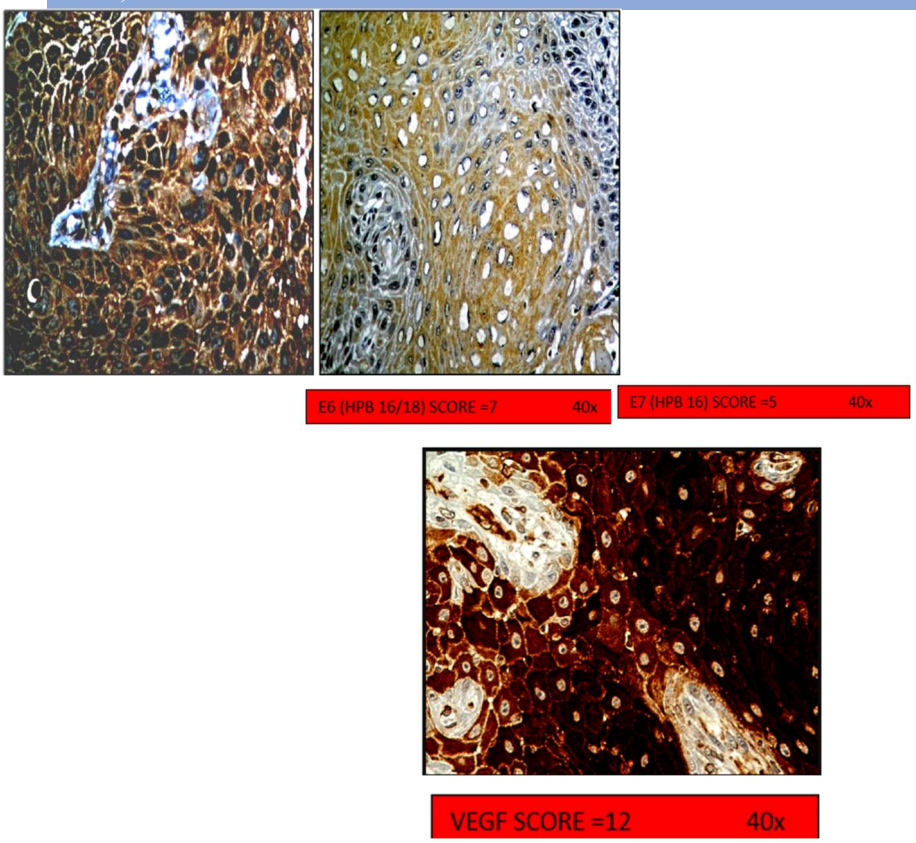

Figure 7: Immunohistochemical expression of VEGF in oral squamous cell carcinoma (OSCC) showing different staining intensities. (A) Strong cytoplasmic VEGF expression (3+) in well-differentiated OSCC. (B) Moderate VEGF expression (2+) with heterogeneous staining pattern. (C) High-power view demonstrating intense cytoplasmic and membranous VEGF immunoreactivity in tumor cells. (Original magnification: A,B ×200; C ×400; IHC-VEGF)

DISCUSSION

Our study provides important insights into the relationship between HPV infection, VEGF expression, and clinicopathological characteristics in oral and oropharyngeal squamous cell carcinoma in an Indian tertiary care setting.

Demographic and Clinical Profile

The mean age of 54 years with male predominance (3.4:1 ratio) in our study aligns with previous research. Cheng et al. [21] and Naruse et al. [22] reported similar age distributions, with maximum cases occurring after 50 years. The male preponderance observed in our study is consistent with findings by multiple researchers [23,24,25], though the ratio varies across populations. This gender disparity might be attributed to higher prevalence of risk factors among males, particularly in the Indian context.

Site Distribution and Risk Factors

The tongue emerged as the predominant tumor site (28.75%) in our study, followed by buccal mucosa (26.2%). This distribution pattern differs from some international studies but aligns with Indian population data. The high proportion of buccal mucosa cases likely reflects the prevalent habit of betel quid chewing in our population, as supported by Cheng et al. [21] who found 54% of their patients were betel quid chewers.

VEGF Expression Patterns

Our finding of VEGF positivity in 85% of OSCC cases is comparable to studies by Sappayatosok et al. [26] and Kukreja et al. [27], who reported positivity rates of 89.39% and 87.88% respectively. The significant increase in VEGF expression from dysplasia to carcinoma (p=0.004) supports its role in disease progression, as previously documented by Shilpi Arora et al. [28].

HPV Status and VEGF Correlation

The prevalence of HPV infection in our study (37.5% for E6 HPV16/18) falls within the range reported in literature. However, unlike Weinberger et al. [29], who found significantly higher VEGF expression in HPV-active tumors, we did not observe a significant correlation between HPV status and VEGF expression. This disparity might reflect population-specific differences or variations in detection methods.

Clinicopathological Correlations

The significant correlation between VEGF expression and tumor differentiation ($p=0.012$) aligns with findings by Marinescu et al. [30] and Astekar et al. [31], who reported higher VEGF expression in well-differentiated tumors. However, unlike some previous studies [32,33], we did not find significant correlations between VEGF expression and lymph node status or tumor stage. This difference might be attributed to variations in sample size and population characteristics.

The lack of correlation between VEGF expression and lymph node involvement in our study contrasts with findings by Shilpi Arora et al. [28] and Cheng et al. [21], who reported significant associations. This disparity warrants further investigation with larger sample sizes.

Age and Gender Considerations

The absence of correlation between VEGF expression and age/gender in our study is consistent with findings by multiple researchers [21,34,35], suggesting that these demographic factors may not significantly influence angiogenic mechanisms in OSCC.

Therapeutic Implications

Our findings regarding VEGF expression patterns, particularly their relationship with tumor differentiation, could have important implications for anti-angiogenic therapy. The lack of correlation between HPV status and VEGF expression suggests that anti-angiogenic treatments might be equally relevant for both HPV-positive and negative tumors, though this requires further validation through clinical trials.

Our study found HPV positivity in 37.5% of cases through E6 oncoprotein expression, with lower rates of E7 expression for both HPV16 (26.25%) and HPV18 (20%). This prevalence aligns with previous studies showing HPV infection rates between 20-60% in oral and oropharyngeal cancers, though rates vary significantly by geographic region and detection method. The higher prevalence of E6 compared to E7 expression might reflect differences in viral oncogene regulation or protein stability, though further molecular studies would be needed to confirm this observation.

Study Limitations and Future Directions

While our study provides valuable insights, certain limitations should be acknowledged. The single-center design and relatively small sample size might limit generalizability. Future multi-center studies with larger cohorts and long-term follow-up would be valuable to validate these findings and establish their prognostic significance.

CONCLUSION

This study provides significant insights into the complex relationship between HPV infection, VEGF expression, and clinicopathological characteristics in oral and oropharyngeal squamous cell carcinoma in the Indian population. The high prevalence of VEGF expression (85%) in OSCC cases, with a significant increase from dysplastic to carcinomatous tissue, reinforces its crucial role in disease progression.

The finding of HPV positivity in a substantial proportion of cases (37.5% for E6 HPV16/18) highlights the emerging importance of viral etiology in oral and oropharyngeal cancers. However, the lack of correlation between HPV status and VEGF expression suggests that angiogenic mechanisms might operate independently of viral oncogenesis in these tumors.

The significant association between VEGF expression and tumor differentiation, particularly its higher expression in well-differentiated tumors, could serve as a valuable prognostic indicator. The absence of correlation with other clinicopathological parameters such as age, gender, tumor size, and lymph node status suggests that VEGF expression

might represent an independent biological characteristic of these tumors.

These findings have important therapeutic implications, particularly regarding the potential utility of anti-angiogenic therapy in OSCC. The significant VEGF expression in precancerous lesions suggests that anti-VEGF therapy might be most beneficial when implemented early in the disease course, potentially even at the pre-malignant stage.

RECOMMENDATIONS

1. Larger, multi-center studies with long-term follow-up are needed to validate these findings and establish their prognostic significance.
2. Investigation of anti-VEGF therapy in precancerous lesions should be considered, given the significant VEGF expression observed in dysplastic tissue.
3. Development of standardized protocols for HPV detection and VEGF assessment would facilitate more accurate comparison across studies.
4. Future research should focus on understanding the molecular mechanisms underlying the relationship between tumor differentiation and VEGF expression.
5. Clinical trials evaluating the efficacy of anti-angiogenic therapy in both HPV-positive and negative OSCC are warranted, given the independence of VEGF expression from HPV status.

These insights contribute to our understanding of OSCC pathogenesis and may help guide therapeutic decision-making, particularly regarding the implementation of targeted anti-angiogenic strategies.

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