

Immunohistochemical Study of p53 Expression in Oral Squamous Cell Carcinoma and its Clinicopathological Correlation

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Abstract

Introduction: Oral squamous cell carcinoma (OSCC) is the most common malignancy of the oral cavity and represents a major public health problem in India due to its high incidence and late-stage presentation. Despite advances in treatment, prognosis remains poor, highlighting the need for reliable biomarkers to identify aggressive tumor behavior. The tumor suppressor protein p53 has been implicated in oral carcinogenesis and disease progression.

Objectives: To evaluate the immunohistochemical expression of p53 in oral squamous cell carcinoma and to assess its association with clinicodemographic and histopathological parameters.

Materials and Methods: This prospective, hospital-based cross-sectional observational study was conducted in the Department of Pathology, Government Medical College, Kota, from October 2023 to September 2024. A total of 61 histopathologically confirmed cases of OSCC were included. Immunohistochemical staining for p53 was performed using the DO-7 monoclonal antibody. p53 expression was assessed based on staining pattern and percentage positivity. Associations with clinicodemographic variables and histopathological features were analyzed using the chi-square test.

Results: Most patients were males in the fourth and fifth decades of life, with the buccal mucosa being the most commonly involved site. Well-differentiated squamous cell carcinoma was the predominant histological grade. Parabasal or diffuse p53 overexpression was the most frequent staining pattern, and overall p53 positivity was observed in 80.3% of cases. No significant association was found between p53 positivity and age, sex, tumor site, or histological grade. However, p53 positivity showed a statistically significant association with lymphovascular invasion and perineural invasion.

Conclusion: p53 immunohistochemical expression is common in OSCC and shows a significant association with adverse histopathological features, suggesting its potential role as an adjunct marker of tumor aggressiveness.

Keywords: Histopathology, Immunohistochemistry, Oral Squamous Cell Carcinoma, p53.

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Introduction

Cancer remains a major global public health challenge and is among the leading causes of morbidity and mortality worldwide. It ranks as the first or second leading cause of death before 70 years of age in the majority of countries. [1] According to GLOBOCAN 2020, approximately 19.3 million new cancer cases were reported globally, with India ranking third after China and the United States. Projections suggest a substantial rise in India's cancer burden, with an estimated

2.08 million cases by 2040, representing a 57.5% increase from 2020. [2] This rising trend is attributed to population aging, lifestyle changes, increased exposure to risk factors, and inadequate screening programs, particularly in developing countries. In India, cancer poses a growing health burden, with over 1.4 million new cases and more than 900,000 cancer-related deaths reported annually. [3] Oral, breast, and cervical cancers together account for nearly one-third of all cancer

cases in the country. [4] Among males, cancers of the lip and oral cavity are the most common, whereas breast and cervical cancers predominate among females. [5] The high prevalence of oral cancer in India is strongly linked to tobacco consumption and lifestyle-related risk factors.

Oral squamous cell carcinoma (OSCC) accounts for approximately 90% of all oral malignancies and represents the most common cancer of the head and neck region. [6] Globally, OSCC ranks among the most frequent malignancies, with a disproportionate burden in South and Southeast Asia. [7] In India, OSCC predominantly affects middle-aged and elderly males and is commonly associated with low socioeconomic status, poor nutrition, limited access to healthcare, and high-risk oral habits. Unlike Western countries where tongue cancer is predominant, the gingivobuccal complex, including buccal mucosa and retromolar trigone, is the most frequently involved site in India. [8]

A major concern in OSCC management is late-stage diagnosis, with nearly 70% of cases in India presenting at advanced stages (Stage III–IV), resulting in poor survival outcomes and five-year survival rates of around 20%. [9] Early detection significantly improves prognosis, with survival rates approaching 90% when diagnosed at initial stages. [10] Despite advances in surgical and adjuvant therapies, overall survival remains unsatisfactory, underscoring the need for reliable prognostic markers.

Immunohistochemistry has emerged as a valuable tool in tumor characterization, offering insights into tumor biology and prognosis. Among various biomarkers, the tumor suppressor gene p53 plays a central role in cell cycle regulation, DNA repair, and apoptosis. Mutations in TP53 lead to stabilization and accumulation of mutant p53 protein, making it detectable by immunohistochemistry. [11] Abnormal p53 expression has been implicated early in oral carcinogenesis and is associated with aggressive tumor behavior and poor prognosis. [12]

Given the high burden of OSCC in India and the lack of well-established prognostic biomarkers in routine practice, this study was undertaken to evaluate p53 immunohistochemical expression in oral squamous cell carcinoma and to assess its association with clinicodemographic and histopathological parameters, with the aim of exploring its potential prognostic significance.

Materials and Methods

This Prospective, Hospital-based Cross-sectional Observational study was conducted in the Department of Pathology, Government Medical College, Kota, after obtaining approval from the Institutional Ethics Committee. This study was

conducted from October 2023 to September 2024, followed by three months for data compilation, analysis, and manuscript preparation. The sample size was initially calculated as 60 cases at a 95% confidence level with an absolute error of 12%, based on an expected p53 positivity of 66.7% reported in Gupta S et al¹³. A total of 61 histopathologically confirmed cases of oral squamous cell carcinoma (OSCC) presenting during the study period, who gave written informed consent were included in the study. Patients with recurrent lesions, inadequately fixed specimens, and insufficient tissue for immunohistochemistry, incomplete clinical history, or unsatisfactory immunostaining were excluded from the study.

Demographic and clinical data, including age, sex, and personal habits such as tobacco chewing, smoking, and betel quid use, were recorded from hospital case records and supplemented through telephonic interviews when required. Biopsy or excision specimens from oral cavity lesions constituted the study material. All specimens were fixed in 10% neutral buffered formalin for adequate fixation, followed by standard gross examination and extensive sampling of representative areas. The tissues were processed routinely using automated tissue processors, embedded in paraffin, and sectioned at 4–5 μ m thickness. Hematoxylin and eosin-stained sections were examined under light microscopy for confirmation of diagnosis and histopathological grading.

Histological grading of OSCC was performed based on the degree of tumor differentiation, taking into account keratinization, nuclear and cellular pleomorphism, and mitotic activity. Tumors were categorized as well-differentiated, moderately differentiated, or poorly differentiated squamous cell carcinoma.

Immunohistochemical evaluation for p53 expression was carried out on formalin-fixed, paraffin-embedded tissue blocks. Sections of 2–3 μ m thickness were mounted on poly-L-lysine-coated slides. After deparaffinization and rehydration, antigen retrieval was performed using Tris-EDTA buffer (pH 9.0). Endogenous peroxidase activity was blocked, followed by incubation with a mouse monoclonal anti-p53 antibody (clone DO-7). Detection was achieved using an HRP-labelled polymer secondary antibody system, with 3,3'-diaminobenzidine as the chromogen. Slides were counterstained with hematoxylin, dehydrated, cleared, and mounted with DPX. Colon carcinoma tissue with known p53 overexpression served as the positive control, while negative controls were prepared by omission of the primary antibody.

p53 expression was assessed based on nuclear and/or cytoplasmic staining in tumor cells [table 1].

Cases showing staining in $\geq 10\%$ of tumor cells were considered p53 positive. Staining patterns were further categorized according to distribution and localization and interpreted as wild-type or mutant p53 expression. These findings were correlated with histological grade and clinicopathological parameters.[14]

Statistical Analysis: Data were entered into Microsoft Excel and analyzed using SPSS version 27.0. Quantitative variables were expressed as mean and standard deviation, while qualitative variables were presented as frequencies and percentages. Associations were assessed using the chi-square test, with a p-value < 0.05 considered statistically significant.

Results

[Table 2] The majority of patients were in the 40–49-year age group (34.4%), with a male predominance (63.9%). The buccal mucosa was the most commonly involved site (44.3%), followed by the tongue (18.0%) and mandible (13.1%). Histologically, well-differentiated squamous cell carcinoma was the most frequent subtype (65.6%). Swelling was the most common clinical presentation (65.6%). Lymphovascular invasion and perineural invasion were observed in 37.7% and 47.5% of cases, respectively. Tobacco use alone (52.5%) or in combination with alcohol (32.8%) constituted the predominant personal habits.

[Table 3] Parabasal or diffuse overexpression was the most frequent pattern (34.4%), followed by scattered (26.2%) and basal overexpression (21.3%). Null expression was noted in 18.0% of cases, while mid-epithelial and cytoplasmic patterns were not observed. Overall, p53 positivity in $\geq 10\%$ of tumor cells were seen in 80.3% of cases. [Table 4] In well-differentiated squamous

cell carcinoma, scattered (32.5%) and basal overexpression (27.5%) patterns were more frequently observed. Moderately differentiated tumors more commonly showed parabasal or diffuse overexpression (37.5%), while poorly differentiated carcinomas predominantly demonstrated parabasal or diffuse overexpression (80.0%). Null expression was observed across all grades, with higher proportions in moderately (31.3%) and poorly differentiated tumors (20.0%). This association between p53 expression pattern and histological grade was not statistically significant ($p > 0.05$).

[Table 5] p53 positivity across different age groups ranged from 66.7% to 91.7%, with the highest positivity observed in the 50–59-year age group; however, the association was not statistically significant ($p = 0.520$). Both males (79.5%) and females (81.8%) showed comparable p53 positivity, with no significant association with sex ($p = 0.826$). With respect to tumor site, p53 positivity varied from 33.3% to 100%, being highest in floor of mouth, gingiva, and retromolar trigone lesions; however, this association was also not statistically significant ($p = 0.469$). [Table 6] Percentage p53 positivity was highest in well-differentiated squamous cell carcinoma (85.0%), followed by poorly differentiated (80.0%) and moderately differentiated tumors (68.8%); however, this difference was not statistically significant ($p = 0.385$). p53 positivity was significantly higher in cases with lymphovascular invasion (95.7%) compared to those without LVI (71.0%) ($p = 0.044$). Similarly, perineural invasion–positive tumors showed significantly higher p53 positivity (93.1%) than PNI-negative tumors (68.7%) ($p = 0.039$).

Table 1: Major p53 IHC Patterns Identified in Invasive OSCC

Pattern	Description
Scattered	Heterogeneous nuclear staining in basal/parabasal layers.
Mid-epithelial (basal sparing)	Strong nuclear staining in mid-epithelial cells, basal layer spared.
Basal overexpression	Uniform strong nuclear staining in $\geq 80\%$ of basal cells, minimal parabasal.
Parabasal/diffuse overexpression	Strong nuclear staining in $\geq 80\%$ of basal cells with extension into parabasal.
Absent (null)	No nuclear staining in tumor cells; positive internal controls present.
Cytoplasmic	Cytoplasmic $\pm$ nuclear staining with internal control positivity.

Table 2: Clinicodemographic and Histopathological Profile of OSCC Cases

Variable	Category (n=61)	Number (%)
Age group (years)	30–39	13 (21.3)
	40–49	21 (34.4)
	50–59	12 (19.7)
	60–69	12 (19.7)
	70–79	3 (4.9)
Sex	Male	39 (63.9)
	Female	22 (36.1)
Site of lesion	Buccal mucosa	27 (44.3)
	Tongue	11 (18.0)
	Mandible	8 (13.1)
	Palate	5 (8.2)
	Maxilla	3 (4.9)
	Floor of mouth	2 (3.3)
	Gingiva	2 (3.3)
	Lip	2 (3.3)
	Retromolar trigone	1 (1.6)
Histological grade	Well differentiated	40 (65.6)
	Moderately differentiated	16 (26.2)
	Poorly differentiated	5 (8.2)
Clinical presentation	Swelling	40 (65.6)
	Ulcer	7 (11.5)
	Ulceroproliferative	6 (9.8)
	Others	8 (13.1)
Lymphovascular invasion	Present	23 (37.7)
	Absent	38 (62.3)
Perineural invasion	Present	29 (47.5)
	Absent	32 (52.5)
Personal habits	Tobacco	32 (52.5)
	Tobacco + alcohol	20 (32.8)
	Alcohol only	1 (1.6)
	None	8 (13.1)

Table 3: Pattern of p53 Immunohistochemical Expression in OSCC

p53 expression		Number (%)
Pattern of Staining	Scattered	16 (26.2)
	Basal overexpression	13 (21.3)
	Parabasal/diffuse overexpression	21 (34.4)
	Absent (null)	11 (18.0)
	Mid-epithelial	0
	Cytoplasmic	0
Percentage of Positivity	10-100 % Positivity	49 (80.3)
	0-9 % Positivity	12 (19.7)

Table 4: Association of Pattern of p53 Positivity with Histological Grading

Histology	Scattered	Basal Overexpression	Parabasal pattern/ Diffuse Overexpression	Absent (null)
WDSCC	13(32.5)	11(27.5)	11(27.5)	5(12.5)
MDSCC	3(18.8)	2(12.5)	6(37.5)	5(31.3)
PDSCC	-	-	4(80)	1(20)
Total	16(26.2)	13(21.3)	21(34.4)	11(18)

Table 5: Association of Percentage p53 Positivity with Age, Sex, and Site of Lesion in OSCC

Variable	Category	p53 Positive n (%)	p-value
Age group (years)	30–39 (n = 13)	10 (76.9)	0.520
	40–49 (n = 21)	18 (85.7)	
	50–59 (n = 12)	11 (91.7)	
	60–69 (n = 12)	8 (66.7)	
	70–79 (n = 3)	2 (66.7)	
Sex	Male (n = 39)	31 (79.5)	0.826
	Female (n = 22)	18 (81.8)	
Site of lesion	Buccal mucosa (n = 27)	23 (85.2)	0.469
	Tongue (n = 11)	8 (72.7)	
	Mandible (n = 8)	7 (87.5)	
	Palate (n = 5)	4 (80.0)	
	Maxilla (n = 3)	1 (33.3)	
	Floor of mouth (n = 2)	2 (100)	
	Gingiva (n = 2)	2 (100)	
	Lip (n = 2)	1 (50.0)	
	Retromolar trigone (n = 1)	1 (100)	

Table 6: Association of Percentage p53 Positivity with Histological Grade, Lymphovascular Invasion, and Perineural Invasion in OSCC

Variable	Category	p53 Positive n (%)	p-value
Histological grade	Well differentiated SCC (n = 40)	34 (85.0)	0.385
	Moderately differentiated SCC (n = 16)	11 (68.8)	
	Poorly differentiated SCC (n = 5)	4 (80.0)	
Lymphovascular invasion (LVI)	Present (n = 23)	22 (95.7)	0.044*
	Absent (n = 38)	27 (71.0)	
Perineural invasion (PNI)	Present (n = 29)	27 (93.1)	0.039*
	Absent (n = 32)	22 (68.7)	

Discussion

In the present study, oral squamous cell carcinoma was most frequently observed in middle-aged individuals, with a male predominance. This demographic pattern is comparable to the findings reported by Neeti Sindhwani et al [15], who documented a slightly higher mean age, and also aligns with earlier literature emphasizing age as an important epidemiological factor in oral malignancies. [16] The male preponderance noted in our cohort likely reflects the higher exposure of men to established risk habits like tobacco consumption in many Indian settings.

In the present study, the buccal mucosa was the most commonly involved site, followed by the tongue. This distribution closely parallels observations by Dundy G et al [17], who also reported buccal mucosa as the predominant site. The predominance of buccal mucosa involvement in Indian patients is frequently attributed to regional oral habits, particularly the placement of smokeless tobacco or betel quid in the gingivobuccal sulcus, which supports the site pattern seen in our cohort.

In the present study, well-differentiated squamous cell carcinoma formed the majority of cases, with fewer moderately and poorly differentiated tumors. A different grading distribution has been reported

by Abbas NF et al [18], suggesting that histological grade proportions may vary across populations and study settings.

Although tumor grade is clinically relevant, our findings indicate that p53 positivity was observed across all grades, without a statistically significant association between percentage p53 positivity and histological grade.

This observation is in agreement with Dundy G et al [17], who also did not find a significant grade-wise difference in p53 positivity. The absence of a consistent linear relationship between tumor differentiation and p53 positivity suggests that p53 overexpression may occur throughout OSCC progression and may not be sufficiently discriminatory when used alone to stratify tumors by histological grade. In the present study, diffuse/parabasal overexpression was the most frequent p53 staining pattern, followed by scattered and basal overexpression, while null expression constituted a smaller proportion. These findings reflect the heterogeneity of p53 expression in invasive OSCC. Similar observations have been reported in earlier work describing basal/suprabasal localization in dysplastic lesions and broader expression in invasive carcinomas. [19-21]

Abbas NF et al [18] also noted differences in distribution between dysplastic lesions and invasive

carcinomas, supporting the concept that expansion of p53 immunoreactivity beyond the basal compartment is more commonly encountered as lesions progress. Manjunath S et al [22] described a gradation of p53 expression with increasing epithelial atypia, further supporting the relevance of distribution patterns in the biological continuum from dysplasia to carcinoma. Differences in reported staining patterns across studies may also relate to technical variations and interpretative thresholds, which has been emphasized previously.

In the present study, the overall proportion of cases demonstrating $\geq 10\%$ p53 positivity was high, supporting p53 alteration as a frequent event in OSCC. This is consistent with studies reporting variable but often substantial p53 positivity in OSCC, including Manjunath S et al [22], Kajal V. Dave et al [23] and Rupa Das et al [24]. Reported positivity rates in the literature show wide variability (ranging from 36% to 80%), which has been attributed to methodological and scoring differences, as well as population-level variability in exposure profiles. [25,26] Despite this heterogeneity, the consistently high occurrence of p53 positivity across studies reinforces the value of p53 immunohistochemistry as a practical marker in OSCC evaluation, particularly when interpreted alongside histopathological parameters. [27,28]

In the present study, p53 positivity did not show a statistically significant association with age or sex, and similar findings have been reported in earlier studies. [23,24] The lack of demographic association suggests that p53 overexpression is more reflective of tumor-specific molecular alterations than patient-level demographic variables. In the present study, site-wise variation in p53 positivity was observed; however, the association was not statistically significant. This is consistent with Dundy G et al [17], who also reported no significant relationship between p53 expression and anatomical site, indicating that p53 alterations may represent a common molecular feature across OSCC arising from different oral subsites.

In the present study, p53 positivity was significantly higher in tumors showing lymphovascular invasion and perineural invasion. This association supports the relationship between p53 overexpression and aggressive histopathological behavior in OSCC. Giri et al [29] also reported higher TP53 expression in cases with lymphovascular invasion and perineural invasion, although statistical significance was not demonstrated in their study, highlighting that the strength of association may vary depending on sample size and study design. Importantly, both datasets point toward a consistent trend of increased p53/TP53 expression in tumors exhibiting invasive features, supporting the

potential utility of p53 immunohistochemistry as an adjunct marker when assessing biological aggressiveness in routine pathology reporting.

In the present study, p53 positivity did not show a statistically significant association with personal habit categories. Similar findings have been reported by Dundy G et al [17] and Abbas Ali Khan et al [30], suggesting that while tobacco and alcohol are central etiological factors in OSCC development, p53 immunoreactivity may not correlate directly with exposure history alone. [17,30] This may reflect the fact that p53 overexpression detected by immunohistochemistry represents a molecular event within the tumor and may be influenced by multiple downstream genetic and environmental interactions rather than the type of habit alone.

This prospective study employed a standardized p53 immunohistochemical protocol with systematic pattern-based assessment and correlation with key clinicopathological parameters, including lymphovascular and perineural invasion, enhancing the reliability and clinical relevance of the findings. However, the absence of TP53 gene sequencing and exclusion of premalignant lesions limited molecular confirmation and broader applicability.

Conclusion

In this study, most patients were in the fourth and fifth decades of life, with a higher proportion of males and a predominance of lesions involving the buccal mucosa. Well-differentiated squamous cell carcinoma was the most common histological type. On immunohistochemical analysis, parabasal or diffuse p53 overexpression was the most frequently observed pattern, followed by scattered and basal overexpression.

No statistically significant association was found between the percentage of p53 positivity and demographic variables, tumor site, or histological grade. However, p53 positivity showed a statistically significant association with lymphovascular invasion and perineural invasion, indicating a relationship with aggressive tumor features. These findings suggest that p53 immunohistochemistry may be useful as an adjunctive marker in the pathological evaluation of oral squamous cell carcinoma. However, confirmation of TP53 mutation status would require molecular sequencing, which was beyond the scope of the present study.

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