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Original Article

Expression of P16 in Benign, Premalignant, and Malignant Lesions of Oral Cavity

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ABSTRACT

Background: *Oral cavity lesions range from benign to malignant, with squamous cell carcinoma being the most common cancer. p16, a cyclin-dependent kinase inhibitor linked to HPV-related oncogenesis, has emerged as a useful marker for differentiating these lesions. This study evaluates p16 expression in benign, premalignant, and malignant oral lesions.* ***Methods & Materials:*** *This cross-sectional observational study was conducted in the Department of Pathology at Sir Salimullah Medical College, Dhaka, Bangladesh, from 2017 to 2019. A total of 60 patients presenting with clinically suspicious oral cavity lesions were enrolled. The chi-square test was applied to determine the association between histological diagnosis and p16 expression. A p-value of <0.05 was considered statistically significant.* ***Result:*** *In this study of 60 patients with oral cavity lesions, the majority (56.7%) were between 41–60 years of age, with a male predominance (male: female = 1.85:1). Histopathologically, 90% of the cases were malignant, most commonly well-differentiated squamous cell carcinoma (43.3%) and moderately differentiated squamous cell carcinoma (36.7%). p16 expression showed strong staining exclusively in malignant lesions—most notably in early invasive squamous cell carcinoma (100%), followed by well-differentiated (53.8%) and moderately differentiated squamous cell carcinoma (40.9%). Benign and premalignant lesions showed only weak to moderate staining.* ***Conclusion:*** *The differential expression of p16 across benign, premalignant, and malignant oral lesions underscores their value as adjunct diagnostic tools. Increased p16 expression correlates with higher grades of dysplasia and malignancy.*

Keywords: *P16, Malignant Lesions, Oral Cavity*

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INTRODUCTION

Lesions of the oral cavity encompass a wide spectrum of pathological entities, ranging from benign hyperplastic processes to potentially malignant disorders (PMDs) and invasive carcinomas. Among these, oral squamous cell carcinoma (OSCC) is by far the most common malignancy, representing more than 90% of oral cancers globally [1]. OSCC is often preceded by a series of histological changes, commonly referred to as oral potentially malignant disorders (OPMDs), such as leukoplakia, erythroplakia, oral submucous fibrosis, and lichen planus. In high-risk populations—especially in South Asia where tobacco, betel quid, and alcohol use are prevalent—the progression from premalignant to malignant lesions contributes significantly to the cancer burden [2]. Histopathological assessment of biopsies remains the cornerstone for diagnosis and classification of oral lesions. However, morphological overlap between benign, dysplastic, and early malignant changes can make definitive diagnosis challenging, especially in small or poorly preserved specimens [3]. In such scenarios, the application of biomarkers can enhance diagnostic accuracy, improve prognostic stratification, and guide early intervention strategies. Among the molecular markers studied, p16INK4a (commonly referred to as p16) has received considerable attention. p16 is a tumor suppressor protein encoded by the *CDKN2A* gene, which plays a pivotal role in regulating the cell cycle by inhibiting cyclin-dependent kinases (CDK4 and CDK6). Its overexpression results in cell cycle arrest at the G1 phase [4]. In the context of head and neck cancers, p16 overexpression is widely recognized as a surrogate marker for high-risk human papillomavirus (HPV) infection, particularly in oropharyngeal squamous cell carcinoma [5]. However, the role of p16 in OSCC appears to be more complex, as overexpression has been observed even in HPV-negative tumors, possibly due to

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cellular stress or epigenetic changes affecting the *CDKN2A* promoter region [6]. P16, a tumor suppressor protein encoded by the CDKN2A gene, plays a vital role in regulating the cell cycle by inhibiting cyclin-dependent kinases 4 and 6, thereby preventing phosphorylation of the retinoblastoma (Rb) protein and halting cell proliferation at the G1 phase [7]. Alterations in P16 expression have been associated with a variety of malignancies, including cervical, head and neck, and oral cancers. In the context of oral lesions, P16 overexpression is often linked to high-risk human papillomavirus (HPV)-associated oncogenesis, although non-viral mechanisms may also contribute to its dysregulation [8]. Assessment of P16 expression may serve as a valuable biomarker for distinguishing between benign, premalignant, and malignant lesions of the oral cavity. Studies have shown variable P16 expression across these categories, with low levels in benign lesions, increased expression in dysplastic epithelium, and either overexpression or loss of function in malignant lesions, depending on the underlying pathogenesis [9,10]. Thus, evaluating P16 status could enhance diagnostic precision, facilitate early detection, and potentially guide targeted therapeutic strategies in oral oncology. Given this background, the present study aims to evaluate the expression patterns of p16 in a range of oral lesions, from benign to premalignant and malignant. By correlating these markers with histopathological grades and clinical data, we aim to explore their utility in early detection, diagnosis, and risk stratification of oral cavity lesions.

METHODS & MATERIALS

This cross-sectional observational study was conducted in the Department of Pathology at Sir Salimullah Medical College, Dhaka, Bangladesh, from 2017 to 2019. A total of 60 patients presenting with clinically suspicious oral cavity lesions were enrolled and analyzed. The study included patients of both sexes and varying age groups who presented with oral lesions and underwent biopsy for histopathological evaluation. All patients were selected through purposive sampling based on inclusion and exclusion criteria.

Inclusion Criteria

- Patients with clinically evident oral cavity lesions undergoing biopsy.
- Histologically confirmed benign, premalignant, or malignant oral lesions.
- Adequate biopsy tissue for both routine histopathology and immunohistochemistry.
- Informed consent is provided by the patient or legal guardian.

Exclusion Criteria

- Poorly preserved or inadequate biopsy specimens.
- Patients previously treated with chemotherapy or radiotherapy.
- Cases with inconclusive histopathological diagnosis.
- Recurrent lesions.

Detailed demographic and clinical data including age, sex, and lesion site were recorded. Biopsy specimens were collected using standard aseptic techniques and immediately fixed in 10% neutral buffered formalin. Following fixation, tissues were processed routinely and embedded in paraffin wax. Serial sections of 4–5 µm thickness were obtained and stained with Hematoxylin and Eosin (H&E) for histopathological examination. All H&E-stained slides were reviewed under light microscopy. Based on morphological features, the lesions were classified into three categories: Benign: e.g., squamous papilloma, Premalignant: e.g., leukoplakia with dysplasia, Malignant: e.g., squamous cell carcinoma (well and moderately differentiated), verrucous carcinoma, early invasive squamous cell carcinoma. Immunohistochemical staining for p16 was performed using a standard labeled streptavidin-biotin method. The intensity of p16 immunostaining was evaluated semi-quantitatively under light microscopy and classified as: Weak staining: Faint cytoplasmic and/or nuclear staining in <10% of cells. Moderate staining: Distinct staining in 10–50% of cells, Strong staining: Intense staining in >50% of cells. All data were compiled and analyzed using SPSS version 25.0. Descriptive statistics were used to summarize the data. Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were presented as frequencies and percentages. The chi-square test was applied to determine the association between histological diagnosis and p16 expression. A p-value of <0.05 was considered statistically significant.

RESULTS

Table – I: Distribution of the study patients by age (*n*=60)

Age (in years)	Number of Patients	Percentage
20-40	14	23.3
41-60	34	56.7
>60	12	20.0
Mean±SD	49.87±11.77	
Range (min-max)	25-73	

In the present study, the mean age of the patients with oral lesions was 49.87±11.77 years. The age ranged from 25 to 73 years. Most of the patients with oral lesions were 41 to 60 years old (56.7%) (Table I)

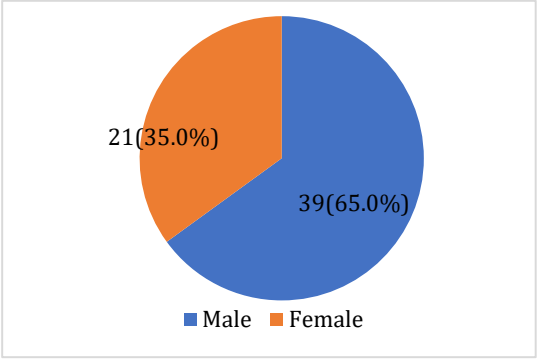

Figure – 1: Pie chart showing the sex distribution of the study patients (*n*=60)

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Regarding the distribution of the patients out of 60 patients, 65% patients were male and 35% patients were female. The male: female was 1:85:1. There was male preponderance in the present study. (Fig 1)

Table – II: Histopathological diagnosis of patients (*n*=60)

Histopathological Diagnosis	Number of patients	Percentage %
Squamous carcinoma, well-differentiated	26	43.3
Squamous cell carcinoma, moderately differentiated	22	36.7
Early invasive squamous cell carcinoma, well-differentiated	3	5.0
Verrucous papilloma	3	5.0
Squamous papilloma	3	5.0
Moderate dysplasia	2	3.3
Leukoplakia	1	1.7

In the present study, out of 60 cases, the most frequently diagnosed malignant lesions were squamous cell carcinoma, well-differentiated (43.3%), and squamous cell carcinoma, moderately differentiated (36.7%) followed by early invasive squamous cell carcinoma, well-differentiated (5.0%) and verrucous carcinoma (5.0%). Of the premalignant lesions, leukoplakia and moderate dysplasia were (1.7%) and (3.3%) respectively. The benign lesion was squamous papilloma (5.0%) (Table II).

Table – III: Patients with oral lesions according to histopathological diagnosis (*n*=60)

Type of lesions	Number of patients	Percentage %
Malignant	54	90.0
Benign	3	5.0
Premalignant	3	5.0

In the present study, among the 60 cases, 54 were histopathologically categorized as malignant, 3 cases were categorized as benign and 3 cases were categorized as premalignant lesions (Table III)

Table – IV: Distribution of p16 expressions according to histopathological diagnosis (*n*=60)

Histopathological Diagnosis	Weak staining		Moderate Staining (n=12)		Strong Staining (n=26)	
Benign lesion						
Squamous papilloma	2	9.1	1	8.3	0	0.0
Premalignant lesion						
Moderate dysplasia	0	0.0	2	16.7	0	0.0
Leukoplakia	1	4.5	0	0.0	0	0.0
Malignant lesion						
Early invasive squamous cell carcinoma, well-differentiated	0	0.0	0	0.0	3	11.5
Squamous cell carcinoma, well-differentiated	8	36.4	4	33.3	14	53.8
Squamous cell carcinoma, moderately differentiated	8	36.4	8	66.7	9	34.6
Verrucous carcinoma	3	13.6	0	0.0	0	0.0

In the present study, it was observed that most of the benign tumors show weak to moderate staining for p16. The premalignant lesions mostly show moderate staining for p16. The strong staining is only observed by malignant tumors. Among the malignant tumors, 53.8% strong staining is observed in well-differentiated squamous cell carcinoma, 34.6 % in moderately differentiated squamous cell carcinoma, and 11.5% is observed by early invasive well-differentiated squamous cell carcinoma. (Table IV)

Table – V: p16 expression in benign, premalignant, and malignant lesions (*n*=60)

Type of lesions	Weak Staining		Moderate Staining		Strong Staining (n=26)		P value
	n	%	n	%	n	%	
Benign	2	9.1	1	8.3	0	0.0	0.117^{ns}
Malignant	19	86.4	9	75.0	26	100.0	
Premalignant	1	4.5	2	16.7	0	0.0	

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In the distribution of the p16 expression in benign, malignant, and premalignant lesions, it was observed that 86.4% of cases (19) of malignant tumors showed weak staining. 75.0% (9) cases showed moderate staining and 26 cases showed strong staining. Among the benign tumors, 2 cases showed weak staining (9.1%), 1 case showed moderate staining (8.3%) and none showed strong staining. Of the premalignant lesions, one case showed weak staining (4.5%), 2 cases showed moderate staining (16.7%) and none showed strong staining. However, the differences achieved were not significant (p=0.117) among the three groups. (Table V)

Table – VI: p16 expression in benign and malignant tumors (*n*=57)

Type of lesions	Weak Staining		Moderate Staining		Strong Staining (n=26)		P value
	n	%	n	%	n	%	
Benign (3)	2	9.1	1	8.3	0	0.0	0.265^{ns}
Malignant (54)	19	86.4	9	75.0	26	100.0	

ns=not significant
p-value reached from the Chi-square test

The distribution of the p16 expression in benign and malignant it was observed that two-thirds of malignant tumors 19 (86.4%) showed weak staining, 9 (75.0%) moderate staining, and 26 (100.0%) cases showed strong staining when compared to p16 expression by benign tumors. 2 (9.1%) cases of benign tumor showed weak staining, 1 (8.3%)cases showed moderate staining and none showed strong staining. When compared the difference was statistically not significant (p=0.265). (Table VI)

Table – VII: p16 expression in benign and malignant tumors (*n*=6)

Type of lesions	Weak Staining		Moderate Staining		P value
	n	%	n	%	
Benign (3)	2	66.7	1	33.3	0.147^{ns}
Malignant (54)	1	33.3	2	66.7	

ns = not significant
p-value reached from the Chi-square test

The distribution of the p16 expression in benign and premalignant conditions was observed 2 (66.7%) of benign tumors showed weak staining and 2 (66.7%) of premalignant tumours showed weak staining. The difference was statistically not significant (p>0.05) between the two groups. (Table VII)

Table – VIII: p16 expression in benign and malignant conditions (*n*=57)

Type of lesions	Weak Staining		Moderate Staining		Strong Staining (n=26)		P value
	n	%	n	%	n	%	
Malignant	19	95.0	9	81.8	26	100.0	0.077^{ns}
Premalignant	1	5.0	2	18.2	0	0.0	

ns = not significant
p-value reached from the Chi-square test

The expression of p16 in malignant and premalignant conditions was observed that 26 malignant tumors showed strong staining (100.0%), 9 (81.8%) cases showed moderate staining, and 19 (95.0%) cases weak staining. In contrast, when premalignant lesions were compared, 1 (6.3%) cases showed weak staining, 2 (18.2%) cases showed moderate staining and none showed strong staining. The difference was statistically not significant (p>0.05) between the two groups. (Table VIII)

Table – IX: p16 expression in malignant oral lesions (*n*=54)

	EI SCC, WD (n=3)		SCC, WD(n=26)		SCC, WD (n=22)		VC (n=3)	
	n	%	n	%	n	%	n	%
Weak Staining	0	0	8	30.8	8	36.4	3	100.0
Moderate Staining	0	0.0	4	15.4	5	22.7	0	0.0
Strong Staining	3	100.0	14	53.8	9	40.9	0	0.0

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(EI SCC.WD=Early invasive squamous cell carcinoma, well-differentiated, SCC, WD=squamous cell carcinoma, well-differentiated, SCC, MD= squamous cell carcinoma. moderately differentiated, MEC= Mucoepidermoid carcinoma, VC= Verrucous carcinoma). The p16 expression in malignant oral lesions, it was observed that 14 (53.8%) cases of squamous cell carcinoma, well-differentiated (SCC, WD) presents strong staining,9(40.9%) cases of squamous cell carcinoma, moderately differentiated (SCC, MD)presents strong staining and 3 (100.0%) cases of early invasive squamous cell carcinoma, well-differentiated presents strong staining. While 3 (100.0%) cases of verrucous carcinoma present weak staining. (Table IX)

Table X: Comparison of p16 expression between squamous cell carcinoma (*n*=54)

Histopathological Diagnosis	Weak staining (n=19)		Moderate Staining (n=9)		Strong Staining (n=26)		P value
	n	%	n	%	n	%	
Early invasive squamous cell carcinoma, well-differentiated	0	0.0	0	0.0	3	11.5	0.132[ns]
Squamous cell carcinoma, well-differentiated	8	42.1	4	44.4	14	53.0	
Squamous cell carcinoma, moderately differentiated	8	42.1	5	55.5	9	34.0	
Verrucous carcinoma	3	15.7	0	0.0	0	0.0	

ns = not significant
p-value reached from the Chi-square test

When p16 expression was compared between 26 cases of well-differentiated squamous cell carcinoma and 22 cases of moderately differentiated squamous cell carcinoma, 14 cases of SCC, WD showed strong staining and 9 cases of SCC, MD showed strong staining and all cases of early invasive squamous cell carcinoma showed strong staining for p16. When staining intensity was compared between them it was found that the difference was statistically not significant ($p>0.05$) between two groups. (Table X)

DISCUSSION

In our cohort, males predominated (65%), and the most common age group was between 41–60 years. This demographic pattern echoes the findings of Warnakulasuriya et al. and Sankaranarayanan et al., who reported that OSCC is more common among middle-aged males with habits like tobacco chewing or smoking [1,11]. The male preponderance could be attributed to lifestyle factors and occupational exposures more prevalent among men in the studied population. Among the malignant lesions, well-differentiated squamous cell carcinoma was the most common subtype. This is consistent with the histopathological distribution observed in several studies across India and Southeast Asia, where well-differentiated OSCC is frequently diagnosed due to the prolonged course of lesion evolution and delayed healthcare-seeking behavior [12,13]. Premalignant lesions like leukoplakia and erythroplakia are considered important precursors to oral cancer and show a continuum of dysplastic changes that can be intercepted with timely intervention [14]. The p16 protein, a cyclin-dependent kinase inhibitor, plays a central role in cell cycle regulation by inhibiting CDK4 and CDK6, thereby preventing phosphorylation of the retinoblastoma (Rb) protein. In HPV-associated oropharyngeal cancers, p16 overexpression is used as a reliable surrogate marker due to viral-mediated inactivation of Rb [15]. However, in oral cavity lesions, p16 expression is more complex and may occur independently of HPV infection. Our study found strong p16 positivity predominantly in malignant lesions, especially in well- and moderately-differentiated SCC. This finding correlates with the observations of El-Naggar et al. and Lewis et al., who noted increased p16 expression in advanced neoplastic transformations within the oral cavity, even in HPV-negative tumors [16,17]. The upregulation of p16 in OSCC, in such cases, may be due to compensatory feedback mechanisms in response to Rb pathway disruption through non-viral mechanisms like mutations or promoter hypermethylation [18]. In premalignant lesions, p16 staining was moderate in most cases and weak in benign lesions. This graded expression reinforces the hypothesis that p16 upregulation increases progressively with the severity of dysplasia and malignant transformation, making it a potentially useful adjunct marker for histopathological grading [19]. Similar trends were reported in studies by Mendez et al. and Lingen et al., who emphasized the diagnostic significance of p16 in distinguishing high-risk oral lesions from benign entities [20,21]. Verrucous carcinoma cases in our study showed weak p16 staining, a finding that mirrors those of Chaturvedi et al. and Gorsky et al., suggesting that this well-differentiated variant of SCC follows a low-proliferative, less-aggressive molecular pathway not characterized by p16 overexpression [22,23].

Limitations of The Study

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community.

CONCLUSION

The differential expression of p16 across benign, premalignant, and malignant oral lesions underscores their value as adjunct diagnostic tools. Increased p16 expression correlates with higher grades of dysplasia and malignancy. p-16 can aid in early detection and accurate classification of oral

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epithelial lesions, ultimately contributing to better patient management and prognostication.

RECOMMENDATION

It is recommended that p16 immunohistochemistry be incorporated as supportive diagnostic tools in the routine histopathological evaluation of oral cavity lesions. Their combined use can enhance the detection of early dysplastic changes and improve the distinction between benign, premalignant, and malignant lesions, thereby facilitating timely intervention and more accurate prognostication. Further studies with larger cohorts and HPV correlation are encouraged to validate and expand upon these findings.

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