E-ISSN 2250-0944
ISSN 2250-1150
doi: 10.31838/ijprt/16.01. 655

Research Article

The Malignant Shift: Deciphering Clinical Predictors of Histological Dysplasia in Oral Mucosal Lesions

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Received: 19.03.2026, Revised: 06.06.2026, Accepted: 14.06.2026

ABSTRACT

Background: Oral mucosal lesions are diverse potentially malignant conditions that have varying risks of progression to oral squamous cell carcinoma. Although histological dysplasia is the most useful marker of malignant transformation, early clinical markers are vital for early diagnosis and intervention especially in resource-limited settings.

Objective: To determine clinical predictors associated with histological dysplasia in patients presenting with oral mucosal lesions.

Methods: The study was conducted in Department of Oral Medicine as an analytical cross sectional study for six months from July, 2025 to December, 2025. Patients with clinically suspected oral mucosal lesions were consecutively enrolled, resulting in 105 patients. The clinical assessment was performed in detail, including the type of lesions, their location, their colour, their surface characteristics, and risk habits. The data were analysed in SPSS version 24. The chi-square test and binary logistic regression were used and a p-value of ≤ 0.05 was taken to be statistically significant.

Results: A total of 53.3% cases showed histological dysplasia. Non-homogeneous lesion appearance, smoking, ulceration, induration, and lesions on the tongue and floor of mouth were significantly associated with dysplasia ($p < 0.05$). Non-homogeneous lesions (AOR 3.42), ulceration (AOR 4.15), induration (AOR 3.67), tobacco use (AOR 2.78), and high-risk sites (AOR 2.91) were independent predictors.

Conclusions: Histological dysplasia can be predicted from certain clinical characteristics in oral mucosal lesions. Prompt identification of these signs of high risk may help to timely biopsy and thus to prevent malignant transformation.

Keywords: Oral Mucosal Lesions, Histological Dysplasia, Oral Potentially Malignant Disorders, Leukoplakia.

INTRODUCTION

Oral mucosal lesions are a wide spectrum of pathological conditions from benign inflammatory changes to potentially malignant conditions to malignancies.[1] Of these, oral potentially malignant disorders (OPMDs) like leukoplakia, erythroplakia, oral submucous fibrosis and oral lichen planus have become significantly clinically important due to their potential to progress to oral squamous cell carcinoma (OSCC).[2] The behavior of oral mucosal lesions may be variable, and histological dysplasia is the most consistent prognostic sign of malignant progression, but early recognition and risk classification is a difficult task for both the clinician and the pathologist.[3]

Oral cancer is a significant health problem affecting about 377,000 people globally every year with 177,000 people dying each year.[4] The prevalence is disproportionately high in countries in South Asia, especially Pakistan and India, where tobacco use is prevalent, along with the use of betel nut, areca nut, gutka, naswar, and other smokeless tobacco products.[5] In Pakistan oral cancer is one of the most prevalent malignancies in male and is a rapidly increasing entity in the younger population due to early exposure to the carcinogenic chewing habits.[6]

Histopathological examination is regarded as the best diagnostic technique for the diagnosis of epithelial dysplasia and the assessment of malignant potential.[3] Dysplastic changes include architectural and cytological abnormalities, such as nuclear pleomorphism, hyperchromatism, increased nuclear-cytoplasmic ratio, abnormal mitoses, and loss of epithelial stratification.[7] The severity of dysplasia is graded as mild, moderate or severe, and the more severe the dysplasia, the greater the risk for malignant transformation.[8] However, in resource-limited settings, biopsy of all oral lesions might not always be possible and thus, the importance of having clinical predictors for early intervention and biopsy prioritization.[9]

Various clinical features have been suggested as markers of dysplastic transformation, including non-homogeneous appearance, duration of lesion, high-risk habits such as tobacco and areca nut use, induration, ulceration, lesion size, and anatomical location.[10] Lateral border and floor of the mouth lesions have a greater malignant potential.[11] Likewise, red and/or mixed red-white lesions have been demonstrated to carry a significantly higher risk of epithelial dysplasia than do uniform white plaques.[12]

The increasing prevalence of oral cancer and failure to recognize high-risk lesions should emphasize the need for easy-to-use but reliable clinical markers of histological dysplasia. The identification of clinically suspicious lesions in an early stage may allow timely biopsy, better surveillance, and decrease morbidity and mortality due to oral malignancies. Finding clinically detectable markers associated with dysplastic changes might be a feasible and cost-effective strategy for risk stratification and early detection in locations where access to medical care is limited. Hence, the aim of this study is to understand the clinical factors associated with histological dysplasia in oral mucosal lesions with the goal of filling the gap between clinical presentation and microscopic diagnosis and facilitating early detection of lesions which are at a risk of developing into malignancy. The purpose of the present study was to identify clinical predictors associated with histological dysplasia in patients with oral mucosal lesions.

METHODOLOGY

This hospital-based analytical cross-sectional study was conducted in the Department of Oral Medicine and Oral Pathology, over a duration of six months from July, 2025 to December, 2025. This study was designed to ascertain the clinical predictors of histological dysplasia in the patients who present with oral mucosal lesions. The sample size was determined by OpenEpi software where the prevalence of oral mucosal lesions in a previous study by Odukoya et al. where 57% of the lesions were reported to be of mild dysplasia.[13] The sample size was determined at 95 respondents for a 95% confidence, 10% margin of error and expected prevalence of 57%. The final sample size was expanded to 105 patients to enhance the statistical power and to make up for potential lack of data quality or biopsy size.

A non-probability consecutive sampling technique was used in this study. Oral mucosal lesions that were clinically suspected of potentially malignant condition such as leukoplakia, erythroplakia, oral submucous fibrosis, oral lichen planus, and mixed red white lesions of the oral cavity were included in this study. Those patients who agreed to clinical examination and histopathological biopsy evaluation were also included. The patients in the study were not those who had previously been diagnosed with oral squamous cell carcinoma, had a recurrent malignant lesion or had undergone prior treatment of an oral lesion (radiotherapy, chemotherapy, or surgical removal). Patients with purely inflammatory oral lesions, oral lesions of known infectious origin and oral lesions of known traumatic origin were also excluded. Furthermore, patients who refused the consent and patients with poor biopsy specimens which were not enough for histopathological evaluation were not included in the study.

During the study period patients with oral mucosal lesions were screened for inclusion and exclusion criteria. All eligible participants were informed of the purpose, nature and benefits of the study and written informed consent was obtained before they were enrolled. A detailed clinical history was obtained from all participants on a structured proforma which had been designed for the study. Data on demography such as age, sex, place of residence and occupation were gathered. Duration of lesion, associated symptoms (pain/burning sensation), tobacco smoking, betel nut chewing, areca nut chewing, alcohol consumption and history of oral lesions were also recorded.

Intra oral examination was carried out, with appropriate lighting, sterile mouth mirrors and gauze. All oral mucosal lesions were carefully

evaluated and documented based on their clinical characteristics such as the site of the lesion, its size, color, surface texture, homogeneity, ulceration, induration and number of lesions. Differential diagnosis of lesions was assigned on the basis of their clinical features as potentially malignant disorders like leukoplakia, erythroplakia, oral submucous fibrosis, oral lichen planus and mixed lesions.

After clinical exam biopsies were taken from the most representative area of the lesion, under local anaesthetic and in an aseptic condition. Larger lesions were biopsied incisonally and small lesions were excised for biopsy where possible. Biopsy samples were immediately fixed in 10% buffered formalin and submitted to histopathology laboratory for microscopic examination.

An experienced, blinded oral pathologist was used for histopathological examination to reduce observer bias. Tissue sections were prepared and stained with hematoxylin and eosin (H&E) stain. Epithelial dysplasia, as defined by the World Health Organization (WHO) was evaluated and graded on the basis of architectural and cytological abnormalities as no dysplasia, mild dysplasia, moderate dysplasia, and severe dysplasia.[14]

The data collected was entered and analyzed in Statistical Package for Social Sciences (SPSS) version 24. The continuous variables (age and lesion duration) were shown as mean ± SD, and the categorical variables (gender, clinical characteristics of lesions, risk habits, and presence of histological dysplasia) were shown as frequencies and percentages. The relationship between the clinical predictors (type of lesion, location, color, texture, risk habits) and histological dysplasia was evaluated by the Chi-square test or Fisher's exact test, as appropriate. Independent sample t-test was used for comparing the continuous variables of dysplastic group with non-dysplastic group. Binary logistic regression analysis was used to determine independent clinical factors predicting histological dysplasia. Univariate analyses were used to identify variables that were significant and included in the multivariate model. Odds ratios (OR) were adjusted for 95% confidence intervals (CI) to assess the strength of the association. For all analyses the criterion for statistical significance was a p-value of ≤ 0.05.

RESULTS

The study included 105 patients with oral mucosal lesion. The mean age of the participants was 46.8 ± 12.4 years, most of them were middle age. The male to female ratio of the study sample was higher than the female ratio and more than half of the study population was from urban areas (Table 1).

Table 1: Demographic Characteristics of Study Participants (N = 105)

Variable	Category	N (%)
Age (years)	Mean ± SD	46.8 ± 12.4
Age Group	18–30	18 (17.1)
	31–45	32 (30.5)
	46–60	38 (36.2)
	>60	17 (16.2)
Gender	Male	67 (63.8)
	Female	38 (36.2)
Residence	Urban	58 (55.2)
	Rural	47 (44.8)

The study population included many who were exposed to known risk factors for oral cancer. Tobacco use was the most common habit reported as being used, followed by the use of smokeless tobacco or chewing on areca nuts/betel. Many respondents said that they were exposed to several risk behaviors at the same time, reflecting the high level of behavioral risk factors among those experiencing oral mucosal lesions (Table 2).

Table 2: Risk Habits among Participants (N = 105)

Habit	Category	N (%)
Tobacco use	Yes	72 (68.6)
	No	33 (31.4)
Smokeless tobacco (naswar/gutka)	Yes	61 (58.1)
	No	44 (41.9)

Areca/betel nut chewing	Yes	49 (46.7)
	No	56 (53.3)
Combined habits (≥2 exposures)	Yes	44 (41.9)
	No	61 (58.1)

As far as the clinical presentation, the most common lesion type was leukoplakia followed by oral submucous fibrosis and oral lichen planus. The most frequent site of involvement was the buccal mucosa with lesions also noted on the tongue, floor of mouth, gingiva, and palate. Homogeneous and non-homogeneous lesions were found almost equally, and in a significant number of instances there was ulceration and induration (Table 3).

Table 3: Clinical Characteristics of Oral Mucosal Lesions (N = 105)

Variable	Category	N (%)
Lesion type	Leukoplakia	38 (36.2)
	Oral submucous fibrosis	24 (22.9)
	Oral lichen planus	19 (18.1)
	Erythroplakia	14 (13.3)
	Mixed lesions	10 (9.5)
Lesion site	Buccal mucosa	46 (43.8)
	Tongue	28 (26.7)
	Floor of mouth	12 (11.4)
	Gingiva/palate	19 (18.1)
Lesion appearance	Homogeneous	54 (51.4)
	Non-homogeneous	51 (48.6)
Ulceration	Yes	37 (35.2)
	No	68 (64.8)
Induration	Yes	41 (39.0)
	No	64 (61.0)

Histopathology showed that over 50% of the lesions showed epithelial dysplasia. The most common histological grade of dysplastic lesions was mild dysplasia, followed by moderate and severe dysplasia. On microscopic examination, a significant percentage of lesions examined did not exhibit dysplastic changes (Table 4).

Table 4: Histopathological Findings (WHO Grading Of Dysplasia) (N = 105)

Diagnosis	N (%)
No dysplasia	49 (46.7)
Mild dysplasia	27 (25.7)
Moderate dysplasia	18 (17.1)
Severe dysplasia	11 (10.5)
Overall dysplasia prevalence: 56 (53.3%)	

Bivariate analysis showed significant relationships between histological dysplasia with a number of clinical factors. High tobacco exposure, use of smokeless tobacco, non-homogeneous appearance of the lesion, lesions on the tongue or floor of the mouth, ulceration and induration were all significantly associated with the presence of dysplasia, and may be regarded as clinical markers of malignant potential (Table 5).

Table 5: Association of Clinical Factors with Histological Dysplasia

Variable	Dysplasia Present n (%)	Dysplasia Absent n (%)	p-value
Tobacco use	46 (82.1)	26 (53.1)	0.003
Smokeless tobacco	39 (69.6)	22 (44.9)	0.01
Non-homogeneous lesion	38 (67.9)	13 (26.5)	<0.001
Tongue/Floor of mouth site	29 (51.8)	11 (22.4)	0.004
Ulceration	31 (55.4)	6 (12.2)	<0.001

Induration	33 (58.9)	8 (16.3)	<0.001

Multivariate logistic regression analysis revealed that non-homogeneous lesion appearance, tobacco use, ulceration, induration and lesion location on the tongue or floor of the mouth were independent factors associated with histological dysplasia. These factors were particularly important when prioritising the biopsy of patients presenting with oral mucosal lesions, and ulceration was the strongest predictor, followed by induration and non-homogeneous lesion morphology (Table 6).

Table 6: Multivariate Logistic Regression Analysis of Predictors of Dysplasia

Predictor	Adjusted Odds Ratio (AOR)	95% CI	p-value
Non-homogeneous lesion	3.42	1.45–8.11	0.005
Tobacco use	2.78	1.21–6.41	0.016
Ulceration	4.15	1.62–10.62	0.003
Induration	3.67	1.41–9.54	0.007
Tongue/Floor of mouth site	2.91	1.12–7.56	0.028

DISCUSSION

In the present study, the clinical factors associated with histological dysplasia in oral mucosal lesions were determined and it was shown that non-homogeneous lesions, tobacco use, ulceration, induration and high risk anatomic sites such as tongue and floor of mouth were significantly associated with the presence of epithelial dysplasia. Histological dysplasia was found in the majority of clinically suspicious oral lesions (53.3%), suggesting that over half of the lesions in the present study were already dysplastic upon biopsy.

The incidence of dysplasia seen in this study is similar to that reported in recent literature. In a large clinicopathological study of 676 cases of oral leukoplakia, Kokubun et al. (2024) observed that about 41.9% of the men had epithelial dysplasia in the clinically diagnosed leukoplakia.[15] This lower prevalence rate than the current study could be explained by the differences in population habits, referral bias, or a narrower group of lesions (i.e., only leukoplakic lesions) in their study than the wider range of lesions included in the present study.

A similar population-based cohort study conducted by Firth et al. showed that patients with oral leukoplakia have a substantially higher risk of malignant transformation and that the risk of oral cancer is up to 40 times greater than in the general population.[16] This corresponds with the present study findings where a large percentage of dysplastic changes were observed and further highlighted the fact that clinically visible lesions are likely to be biologically active and therefore possess malignant potential.

Non-homogeneous lesions were strongly associated with the presence of dysplasia (AOR 3.42) that is consistent with recent oral pathology guidelines setting higher risk for malignant transformation for red or mixed red-white lesions than for homogenous white plaques. Furthermore, the position paper by Carlson et al. (2023) identifies erythroplakic and non-homogeneous lesions as more likely to be associated with high grade dysplasia and/or early carcinoma, highlighting the importance of clinical appearance as a risk stratification tool.[17]

Smoking was also a major predictor for the present study (AOR 2.78). This finding is consistent with the systematic evidence presented in the BMC Oral Health meta-analysis (2023) which found that smoking and smokeless tobacco use were strongly associated with the occurrence of oral potentially malignant disorders such as leukoplakia and dysplasia.[18] The positive correlation found in our study has been previously reported and is known to be carcinogenic, causing damage to epithelial DNA and dysplastic transformation, which are mediated by tobacco related nitrosamines.

The anatomical site distribution in this study found that dysplastic lesions were significantly associated with lesions involving the tongue and the floor of the mouth (AOR 2.91). This finding aligns with several recent studies including Kokubun et al. (2024) who found similar results of dysplastic changes in tongue lesions than in other intraoral lesions.[15] This could be attributed to the thinner epithelium, more vascularity, and more exposure to cancer-causing agents in these high-risk areas.

Additionally, in the present study, ulceration and induration were shown to be good predictors of histological dysplasia. The clinical symptoms are regarded as a sign of more

invasive changes of the deeper epithelium. The importance of clinical induration and surface ulceration in the identification of higher grade dysplastic changes and early malignant transformation has been highlighted in recent literature, and these are considered good red flag clinical signs.

Combined with previous research, results of the present study corroborate the global evidence that clinical examination is an important first step in the diagnosis of high-risk oral lesions.[19, 20] Alternatively, there is also a large amount of interobserver variation in grading dysplasia and the need for ancillary diagnostic techniques and models for more accurate early detection is highlighted. The prediction of dysplasia and the need to combine clinical and histopathological factors are further confirmed by emerging studies with digital pathology and the use of AI-based risk scoring. The present study reinforces the available data indicating that the clinical characteristics, such as lesion heterogeneity, high-risk habits and anatomical site, are strong indicators of histological dysplasia. In low resource areas, where it is not possible to routinely take biopsies of all lesions, these findings are even more relevant for clinical triaging to enable early intervention.

There are some limitations that should be taken into consideration while interpreting the results of the present study. The study was conducted in a single tertiary care hospital, which may not account for the generalizability of the findings. As the study was hospital-based, there could be referral bias, because the selected patients were likely to have advanced and symptomatic lesions. Secondly, it is difficult to draw temporal or causal conclusions from the cross-sectional design of the study and the development of histological dysplasia. Long-term follow-up would have been more convincing to show a transformation over time. Thirdly, the clinical features assessed, including size, texture and induration, were subject to some degree of clinical judgement which might lead to some inter observer variation, even though there was some attempt to ensure standardisation of examination procedures.

CONCLUSION

The present study brings to light the high prevalence of histological dysplasia among the clinically suspected oral mucosal lesions and reflects the aggressive biological nature of oral potentially malignant disorders. Clinical features of non-homogeneous lesion appearance, tobacco consumption, ulceration, induration, and high-risk anatomical areas (tongue and floor of the mouth) were found to be significant predictors of development of dysplastic transformation. The implications of these findings highlight the need for careful clinical examination as a valuable and inexpensive screening method for early detection of high-risk lesions, especially in resource-poor areas. The incorporation of these clinical parameters into the normal oral screening armamentarium may streamline the biopsy process, early diagnosis and the prevention of malignant transformation. It is important that specific clinical markers can effectively help to connect the dots between clinical suspicion and histopathology diagnosis, and ultimately help to improve outcomes in oral cancer prevention.

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