

# Efficacy of Oral Brush Cytology in the Evaluation of Oral Premalignant Lesions: A Multiple Cohort Study

Abhay Kumar<sup>1</sup>, Ashwini Kumar<sup>2</sup>, Mhd. Ziya<sup>3</sup>

## ABSTRACT

**Introduction:** The Oral Brush Cytology using Liquid Based Cytology technique has been developed to improve efficacy of conventional cytology. Our objectives were to statistically prove its usefulness to diagnose premalignant and malignant oral cavity lesions in presence of clinical evidence.

**Material and methods:** 200 patients in 2 groups, 100 in each group with clinically diagnosed oral premalignant and malignant lesions respectively were selected. An oral brush cytology (LBC technique) followed by incisional biopsy were performed for every patient. Considering the histopathological diagnosis as the gold standard, the cytopathological scores were compared using statistical analysis of the samples.

**Results:** In premalignant cases, 86% cases were male and 14% were female, while in malignant lesions, 91% patients were males, and 9% were females. Older age group especially of 31-50 years was predominantly affected (68% of premalignant cases, 56% of malignant cases). Oral submucous fibrosis followed by leukoplakia were found to be most common premalignant lesions. Buccal mucosa for premalignant and tongue for malignant lesions were found to be the most common site involved. Either tobacco chewing or smoking or both were found to be most common predisposing habits for both premalignant and malignant lesions. Well differentiated Squamous Cell Carcinoma was diagnosed to be most common malignant lesion. The sensitivity, specificity, PPV and NPV of brush cytology were 94.7%, 91.4%, 91.8% and 94.5%, respectively.

**Conclusions:** The brush cytology using LBC technique is a non-invasive, inexpensive and reliable diagnostic tool which has a statistically significant specificity and sensitivity to diagnose dysplasia in early oral premalignant and malignant lesions where the treatment is most effective. Thus its use has the potential to reduce the poor mortality rate associated with oral malignancies.

**Keywords:** Oral Brush Cytology; Potentially Malignant Lesion; Squamous Cell Carcinoma

Tobacco smoking, or chewing, alcohol consumption and recently, the human papilloma virus infection are some of the major risk factors in the etiology of Oral squamous cell carcinoma (OSCC), the most common type (96%) of oral cancer, which usually develops from precancerous lesions and histopathologically follows a step-wise pattern of hyperplasia, dysplasia and squamous cell carcinoma.<sup>7-9</sup>

Despite significant advances in cancer treatment, early detection of oral cancer and its curable precursors remains the best way to ensure patient survival, improved quality of life, reduced mortality and public health costs.<sup>10-12</sup>

To diagnose the invisible precancerous lesions, random biopsies need to be taken, which is too invasive, hence, not feasible as a screening approach.<sup>13</sup>

The use of less expensive non-computer-assisted brush cytology using toothbrush and later confirmation by using scalpel biopsy, may have applications in resource challenged areas and could be a risk-free method in effectively diagnosing dysplastic epithelial changes or invasive oral cancer.<sup>14,15</sup> Oral exfoliative cytology is the cost effective and perhaps the best approach for the initial evaluation and diagnosis of the oral lesion.<sup>16,17</sup>

Since, 1990 liquid-based cytology (LBC) has been designed to improve the quality and quantity of conventional cytology. It reduces the problem related to sampling, helps in preparation of smears with high cellularity dispersed in a homogenous thin layer, reduction in false negative rates, clear background and thereby enhances sensitivity and quality of smear.<sup>16-18</sup>

Only a few studies, based on LBC technique used for oral cavity lesions, have been published in the literature, till date. Although diagnostic value of brush cytology or LBC technique have been published previously but lack of scalpel biopsy studies, in samples of different brush cytology results, have decreased their reliability.

Study was done with the aims and objectives to estimate the accuracy, Specificity, Sensitivity, Positive Predictive Value, Negative Predictive Value of index test (Oral Brush Cytology-LBC Technique) for the detection of premalignant and malignant disorders of the oral cavity in patients presenting with clinically evident lesions.

## MATERIAL AND METHODS

200 clinically diagnosed patients (2 groups), 100 with oral

<sup>1</sup>Professor, <sup>2</sup>Senior Resident, <sup>3</sup>Junior Resident, Department of ENT, U.P.U.M.S., Saifai, U.P., India

**Corresponding author:** Dr. Mhd. Ziya, Junior Resident, Department of ENT, U.P.U.M.S., Saifai, U.P., India

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## INTRODUCTION

The oral precancerous condition has been defined as ‘a generalised state associated with a significantly increased risk of cancer’. They are Leukoplakia, Erythroplakia, lichen planus, Oral submucous fibrosis, Discoid lupus erythematosus, Xeroderma pigmentosum, Epidermolysis bullosa, Sideropenic dysphagia, and Syphilis.<sup>1,2</sup>

Workshop, held in London in 2005, recommended the elimination of the term “precancer” and the use of the term “potentially malignant lesions” for oral lesions.<sup>3</sup>

Oral cancer, a major cause of cancer morbidity and mortality worldwide,<sup>4,5</sup> is having high incidence in South Asian countries like Srilanka, India, Pakistan, and Bangladesh. In India the incidence is 7-17/100,000 persons/year with 75,000-80,000 new cases reported annually.<sup>6</sup>

pre-malignant and 100 with malignant lesions, reported in the outpatient department of ENT Head and Neck Surgery, UPUMS, Saifai, India; were selected (irrespective of their age and gender) for the study by employing convenience sampling method. Patients with history of any treatment for the lesion (Medical/Surgical/ Radiotherapy), patients with severe oral submucous fibrosis, medically compromised patients, lesions contraindicated for LBC. eg. Lichen planus or patients who refused to undergo investigations were excluded. The objectives, methods, benefits and possible risks associated with the study have been explained to the patients and written consent was taken. Clearance from Institutional Ethical Committee was obtained.

A detailed history of the lesion in terms of duration, progress, associated symptoms, any treatment received and any adverse oral habit, if present, like tobacco smoking, quid or tobacco chewing and alcohol consumption was obtained.

All patients were subjected to a detailed ENT head and neck examination with thorough general medical examination.

An oral brush cytology (LBC) followed by incisional biopsy were performed for every patient. In cytopathology laboratory; the slides were prepared by using Liquid Based Cytology Technique.

We used a new system of classification, specific for oral cytodiagnosis (the Oral Bethesda system classification/criteria: Oral Bethesda)<sup>1</sup> (Table 1).

The incisional biopsy specimens were examined by the same pathologist and based on WHO criteria,<sup>3</sup> dysplasia and squamous-cell carcinoma were graded. Grading of dysplasia was done as mild, moderate, and severe and carcinoma in situ, while squamous cell carcinoma (SCC) was graded as well differentiated, moderately differentiated and poorly differentiated.

Considering the histopathological diagnosis as the gold standard, the cytopathological scores were compared.

## STATISTICAL ANALYSIS

SPSS® (Statistical Package for the Social Sciences) version 23 (South East Asia, Bengaluru, India) was used for statistical analysis. Chi-square or Fisher's exact test were used to compare proportions. Use of Kappa test was done to find significant association between two factors. ( $P < 0.05$ )

## RESULTS

Out of 100 pre-malignant cases, 86 cases were male (86%) and 14 were female (14%), with a male to female ratio of 6.14:1; while for malignant lesions, 91 patients (91%) were males, and 9 (9%) were females, with a male to female ratio of 10.1:1.

The age of the patients having pre-malignant lesions varied from 11 to 80 years which was subdivided into various groups.

1 patient in 11-20 years of age group, 16 patients in 21- 30 years of age group, 34 patients in 31-40 years of age group, 34 patients in 41-50 years of age group, 11 patients in 51-60 years of age group and in age group of 61-70 years, 4 patients were found.

The age of the patients having malignant lesions varied from 20 to 80 years. 8 patients in 21-30 years age group, 31 patients in 31-40 years of age group, 25 patients in 41-50 years of age group, 27 patients in 51-60 years of age group, 6 patients in age group of 61-70 years and 3 patients in age group of 71-80 years were affected.

The present study showed, out of total pre-malignant cases, 53 cases (53%) had oral submucous fibrosis followed by 40 cases of leukoplakia (40%), and only seven cases of Erythroplakia (7%).

In the patients with pre-malignant lesions, involvement of buccal mucosa in 66 patients, palate in 12 patients, tongue in 11 patients, lip in 6 patients, gingiva in 4 patients and floor of mouth in 1 patient were reported. While in the malignant cases, involvement of tongue in 45 patients, buccal mucosa in 34 patients, gingiva in 8 patients, lip in 7 patients, hard palate in 4 patients and floor of mouth in 2 patients were observed.

Out of the total pre-malignant cases, 79 tobacco chewer, 65 smokers, 59 alcohol consumers, and 13 betel nut chewers were reported. 50 cases were tobacco chewers plus smoker, 34 cases were tobacco chewers plus smoker plus alcohol consumer, 1 case had all the four habits of addiction and 5 cases were not having any addictions. Among all malignant cases in the study, 67 tobacco chewers, 73 smokers, 57 alcohol consumer, and 8 betel nut chewer were identified. 42 cases were tobacco chewers plus smoker, 30 cases were tobacco chewers plus smoker plus alcohol consumer, 1 case had all the four habits of addiction and 2 cases were not having any addictions.

In 100 pre-malignant lesions, 58 cases as NILM, 23 cases as LSIL, 05 cases as HSIL, 08 cases as SCC and 6 cases as inadequate sample on cytopathology were reported. Out of 100 malignant lesions, no case as NILM, 02 cases as LSIL, 03 case as HSIL and 90 cases as SCC were reported.

In patients with pre-malignant lesions, 54 cases with hyperkeratosis, 29 cases with mild dysplasia, 12 cases with moderate dysplasia, 4 cases with severe dysplasia and one case with carcinoma in situ were reported on histopathology.

Out of 100 malignant lesions, 53 cases with well differentiated SCC, 29 cases with moderately differentiated SCC, 12 case with poorly differentiated SCC, 4 cases with verrucous carcinoma, 01 case with basaloid carcinoma and 01 case as ameloblastic carcinoma were found.

In the study, 6 out of 100 pre-malignant lesions and 5 out of 100 malignant lesions, found to be inadequate in cytopathology, have been excluded for the statistical evaluation.

In our study, we found 90 cases as true positive, 8 cases as false positive, 5 cases as false negative and 86 cases as true negative.

The statistical sensitivity, specificity, PPV and NPV of brush biopsy were 94.7%, 91.4%, 91.8% and 94.5%, respectively.

The comparison was done between cytopathological and histopathological findings of pre-malignant and malignant lesions. Kappa test showed  $P < 0.05$ , suggestive of statistically significant. No cell (0%) has expected count less than 5. The minimum expected count was 45.26.

Abbreviation	Meaning
NILM	Negative for intraepithelial lesion or malignancy
LSIL	Low grade squamous intraepithelial lesion
HSIL	High grade squamous intraepithelial lesion
SCC	Squamous cell carcinoma

**Table-1:** Oral Bethesda system Criteria

## DISCUSSION

Scalpel biopsy, though a gold standard, is not able to diagnose all suspected premalignant and malignant lesions of oral cavity. In such cases, brush cytology offers an attractive alternative. This study was done to statistically prove its reliability.

In comparison to females, males are more often involved in habits of alcohol and tobacco consumption. We found male predominance in both premalignant and malignant lesions which is in accordance with some previous studies.<sup>14,19</sup> However another study<sup>20</sup> showed a slight female predominance with a male to female ratio of 1: 1.16, This is perhaps due to increase in the usage of shammah among women.

We found age group of 31-50 years predominantly affected (68% of premalignant cases, 56% of malignant cases). 83% of premalignant and 92% of malignant lesion occur after 30 year of age. Which is in accordance with some studies.<sup>14,21</sup> The overall age-related incidence of premalignant and malignant lesion suggests the onset and progression of genetic process caused by time-dependent factors.

In our study we found the buccal mucosa as a predominant site for premalignant lesion (66%) which is in accordance with previous studies.<sup>14,19,22,23</sup> But for malignant lesion tongue was predominantly involved site (45%) followed by buccal mucosa (34%) which is in accordance with a study.<sup>31</sup> In similar other studies,<sup>20-22</sup> they found buccal mucosa as most commonly involved site for malignancy. The difference in the site involved is probably due to indian habits of extensively placement of tobacco at different place, leads to continuous contact with the carcinogen. Besides, buccal mucosa is covered with a thinner, non-keratinized mucosa that provides less protection against carcinogen.

In our study most common type of oral premalignant lesion was OSMF (53%) followed by leukoplakia (40%), which is similar to some studies.<sup>19,24</sup>

In our study most common form of addiction found in patients of oral premalignant and malignant lesion were either tobacco chewing or smoking or both, which is in accordance with some studies.<sup>19,21,22,24</sup>

The results obtained in our study showed sensitivity (94.7%) is greater than specificity (91.4%) which is similar to a study.<sup>25</sup> Other studies<sup>14,17,18</sup> showed specificity greater than sensitivity. Similar to some previous studies, we found sensitivity (94.7%) and specificity (91.4%) were more than 90%.<sup>14,17,18</sup>

## CONCLUSION

The results of our study showed a statistically significant association between histopathological and cytopathological diagnosis of dysplasia or carcinoma.

The brush cytology using LBC technique has a statistically significant specificity and sensitivity to rule out premalignant and malignant lesion at therapy responsive early stage. In combination to clinical examination, it has capability to reduce their poor mortality rates. Thus, it is a convenient, non-invasive, inexpensive, cognizant, reliable diagnostic procedure that can be used in medically compromised patients.

This study supports the previous researches on oral brush cytology as a screening tool of oral lesions, but further studies with larger sample size are required to evaluate its role in oral premalignant and malignant lesions and to support the results

of our study.

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