

The Application of the Bethesda System for Reporting Cervical Cytology to Oral Cytology: An Institutional Study

Abstract

Classification of oral cytology remains controversial under the Papanicolaou system. A uniform classification system would reduce inter-observer variability and also establish well-defined thresholds for management. This study evaluated the diagnostic accuracy of Bethesda (2014) system for dysplasia and malignancy in comparison to the Pap classification system and histopathological gold standard. 806 patients presenting with oral lesions were subjected to cytological diagnosis at our institution from 2017 to 2019. 100 of these patients underwent simultaneous biopsy for these lesions (subjects of this study). PAP-stained cytological smears from these patients were classified according to PAP and Bethesda 2014 systems and compared with their histopathological diagnosis. Bethesda classification showed 52.9% sensitivity, 86.7% specificity, PPV of 90.2% and NPV of 44.1% for detecting malignant/pre-malignant oral lesions. Sensitivity, specificity, PPV and NPV of the PAP system was 70%, 80%, 89.1% and 46.6% respectively. Statistically significant association was found between histopathological diagnosis and Bethesda classification: Spearman's correlation coefficient being 0.537 ($p < 0.001$). The Bethesda classification system uses well-defined criteria. Our study suggests that it renders cytopathological diagnosis of oral lesions more rigorous and reproducible. Oral scrape cytology reported under the Bethesda system can present clinicians with more interpretable, objective and actionable reports

Keywords: Oral cytology, Papanicolaou classification, Bethesda classification, Squamous intraepithelial lesion, Squamous cell carcinoma

Introduction

Exfoliative cytology refers to the microscopic characterization of epithelial cells obtained from a surface mucosa. Since its popularization in 1940s by Papanicolaou and Traut, it has proved to be an invaluable tool in the detection of uterine cervical cancer.^[1-3] With respect to the oral cavity, cytology was first attempted by Montgomery and von Haam.^[4] It is a non-invasive technique whose role has been explored in the early identification of varied oral lesions like potentially malignant disorders, oral carcinomas, vesiculobullous disorders, fungal infections and viral infections.^[5-8]

Exfoliative cytology has been widely recognized for its role in the screening and diagnosis of gynecological malignancies.^[9] However, its application in the diagnosis of oral malignancies and suspicious lesions remains debatable with the literature being largely divided over its perceived practical relevance.^[2, 3, 10] One of the probable causes for the same may be the lack of a dedicated

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oral cytological grading system which not only provides diagnostic guidelines but also has high correlation with the histopathological diagnosis.^[11-13] So far, the original 'Pap class system' as given by George Papanicolaou^[11, 14] remains the mainstay for evaluation of oral cytology smears primarily due to lack of other grading systems. The Papanicolaou classification system was introduced to facilitate early detection of invasive cervical cancer and categorized the cervical smears into five classes based on their similarity to invasive cancer. The classification system lacked uniformity and histopathological correlation and hence was modified several times.^[15]

In contrast, the Bethesda system- which is now considered to be the gold standard in the fields of cervical, vaginal and thyroid cytology^[15-17]-was begot to promote worldwide standardization and to include the newly discovered role of human papillomavirus (HPV) in cervical cancer in the 1980's.^[18] The system reports on the specimen adequacy, general categorization

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and the interpretation of the smears.^[15] It has also been concluded that the Bethesda system allows for a more accurate reporting of suspicious and malignant lesions.^[19]

Interpretation and precise classification of abnormal squamous cell changes in oral scrape smears and tissue samples remains challenging and controversial via the Papanicolaou classification. Hence, there is a need to establish a uniform classification system that would provide clear-cut thresholds for management and reduce inter-observer variability. This study attempts to compare the Pap classification system^[15] with the Bethesda 2014 system^[20] as well as to determine the accuracy of the Bethesda system in predicting the oral potentially malignant disorders (OPMD) and malignant cases so as to allow us to establish its clinical applicability.

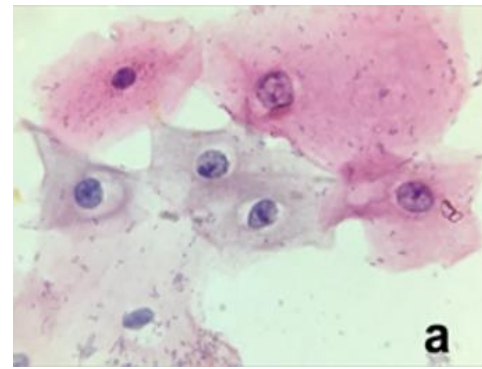
Materials and Methods

Study type, duration, and sample selection

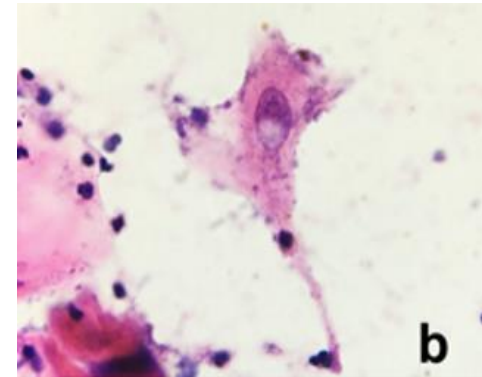
This retrospective pilot study was conducted at the dental center of a tertiary care hospital following approval from institutional ethics committee (IEC-720/04.10.2019, RP-31/2019) in accordance with the tenants of the Declaration of Helsinki. A total of 806 patients were subjected to oral cytological diagnosis at the division of Oral Pathology and Microbiology (following written informed consent) between the time period of April 2017 to Mar 2019. Amongst these patients, 100 subjects who simultaneously underwent a formal biopsy procedure were selected for the study. This criterion was followed in order to allow optimum matching between cytological and histopathological diagnosis and to prevent time related discrepancy between the diagnostic result of the two procedures due to temporal evolution of the lesion.

Procedure for cytological and histological analysis

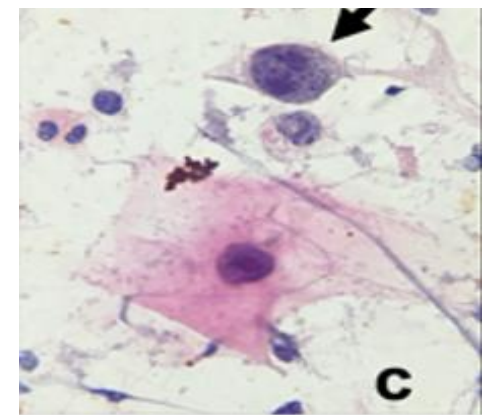
The cytological smears were prepared from the most representative site of the oral lesions via the wooden end of a sterile cotton swab stick which was rolled onto the chosen site for 20-30 seconds. Contact with the wooden end was constantly maintained during the mentioned duration followed by the smear preparation.^[21] The smears were subjected to conventional PAP staining procedure which had been previously standardized.^[22] The cytological smears were classified in accordance with both PAP and Bethesda (2014) systems under a light microscope followed by comparison with the histopathological diagnosis by oral pathologists. The smears were evaluated for various individual cytological features according to the Bethesda classification system (**Figures 1-3, Supplementary Table S1**) and scoring was done for each of the features to ensure holistic consideration and comparison of all the features during the final interpretation of the smears.



a)

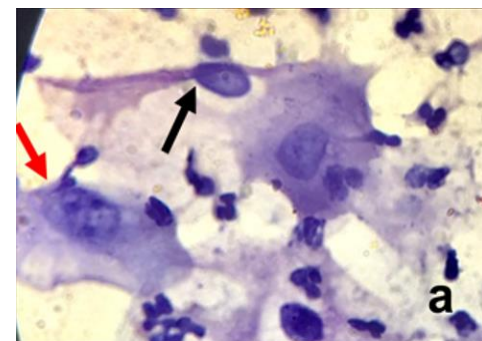


b)



c)

Figure 1. Perinuclear halo (mimicking a koilocyte) suspicious of HPV infection seen in a case of low grade squamous intraepithelial lesion (a). Keratinocyte with altered nuclear size in a high grade squamous intraepithelial lesion (b) Tadpole cell seen in a case of high grade squamous intraepithelial lesion (c).



a)

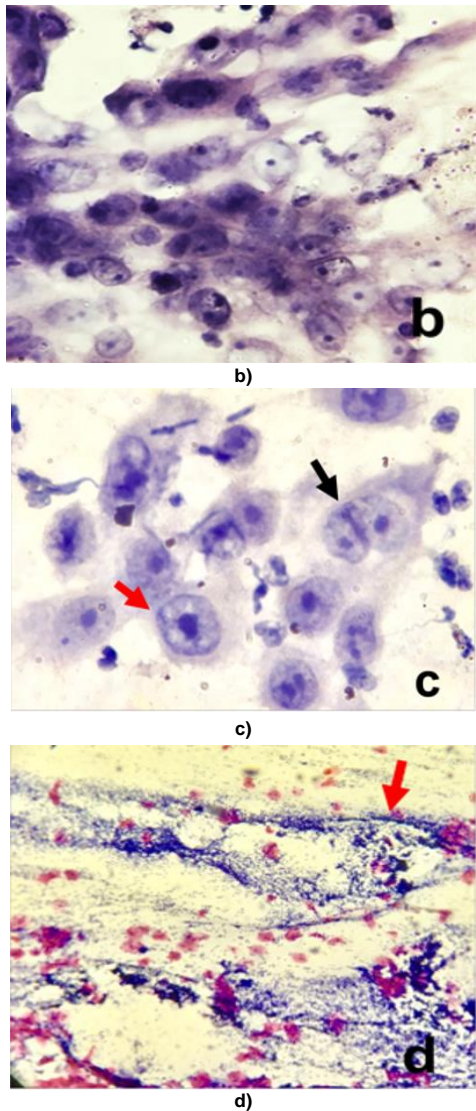


Figure 2. Cases of Squamous cell carcinoma showing atypical epithelial cells with coarse chromatin (red arrow) and pleomorphism (black arrow) (a). Epithelial cells also showed hyperchromatic nucleus with minimal cytoplasm and increased nuclear cytoplasmic ratio (b), macronucleolus (red arrow), multinucleated cells (black arrow) (c) and tumor diathesis (red arrow) (d).

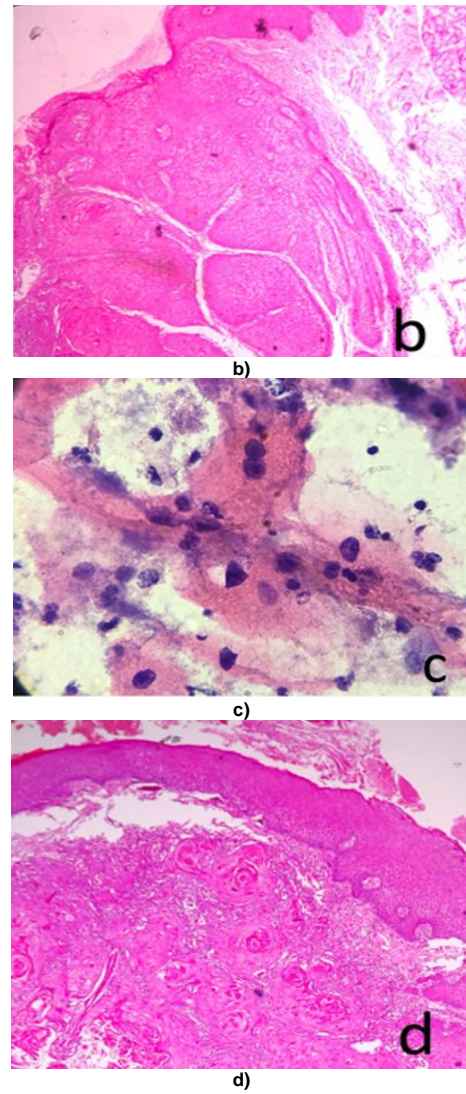
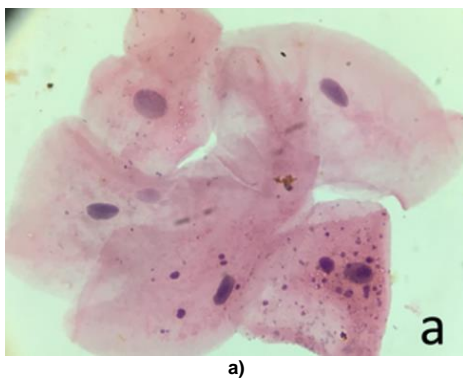


Figure 3. Cases of false negatives which were diagnosed as ASCUS (a) and LSIL (c) in cytology and verrucous carcinoma (b) and well differentiated squamous cell carcinoma (d) in histology.

Table S1. Scoring criteria for Bethesda classification

No.	Criteria	Scoring
1.	Cell size (Fig I)	P= parabasal, I= intermediate, S=superficial
2.	Presence of Koilocytes (Fig Ia)	0= absent, 1= present
3.	Nuclear size (Fig II a,b)	0= no change, 1= mild change, 2= marked change
4.	Nuclear contour (Fig II a,b,c)	0= regular, 1= mildly irregular, 2= markedly irregular
5.	Hyperchromatia (Fig II b)	0= absent, 1= mild, 2= marked
6.	Chromatin coarseness (Fig IIa)	0= absent, 1= mild, 2= marked
7.	Macronucleolus (Fig II c)	0= absent, 1= present
8.	Tumor diathesis (Fig II d)	0= absent, 1= present
9.	Tadpole cells (Fig.I c)	0= absent, 1= present
10.	Fiber cells	0= absent, 1= present

11.	Multinucleated cells (Fig II c)	0= absent, 1= present
12.	Loss of cohesion	0= absent, 1= present
13.	Mitotic figures	0= absent, 1= present

Following evaluation of the cytological features, the smears were classified as atypical squamous cells of undetermined significance (ASCUS), low grade squamous intraepithelial lesion (LSIL), high grade squamous intraepithelial lesion (HSIL) or squamous cell carcinoma (SCC) (**Supplementary Table S2**).^[23] The smears were also categorized via the PAP classification system based on the subjective adjudging of the oral smears for their similarity to invasive cancer (**Supplementary Table S3**) as described in the original classification.^[15]

Table S2. Features of Bethesda classification for epithelial cells.

Class	Features
ASCUS	<ul style="list-style-type: none"> Atypical cells with mature, intermediate type cytoplasm, including cells suggestive of koilocytes. Atypical squamous cells in atrophy. <ul style="list-style-type: none"> Atypical parakeratosis. Atypical repair. Intermediate size cells.
LSIL	<ul style="list-style-type: none"> Nuclear atypia-enlargement, irregular contour, hyperchromatia, slight chromatin coarseness. <ul style="list-style-type: none"> Cytoplasmic cavities. Keratinizing variant. Parabasal sized cells. Discrete cells or syncytium like groups.
HSIL	<ul style="list-style-type: none"> Nuclear atypia-enlargement, marked irregular contour, marked hyperchromatia, marked chromatin coarseness. <ul style="list-style-type: none"> Keratinizing variant.
SCC	<ul style="list-style-type: none"> Features of HSIL, plus. <ul style="list-style-type: none"> Macronucleolus Irregular chromatin distribution. <ul style="list-style-type: none"> Tumor diathesis. Tadpole and fibre cells.

Table S3. The Papanicolaou classification^[10]

Class	Description
I	Absence of atypical or abnormal cells
II	Atypical cytology, but no evidence for malignancy
III	Cytology suggestive of, but not conclusive for, malignancy
IV	Cytology strongly suggestive of malignancy
V	Cytology conclusive for malignancy

Biopsy was obtained from the most visually affected site for all the cases which had either clinically frank cancer or were suspicious for oral cancer/ oral potentially malignant disorder with atypical/ positive cytological test. Suspicious lesions

included any ulcerative lesions lasting for more than 2-3 weeks, leukoplakia >2cm in size, non-homogenous/ nodular/ speckled leukoplakia; lesions on the tongue and floor of mouth, leukoplakia not associated with tobacco/ arecanut habit (idiopathic leukoplakia), verrucous lesions; any long standing leukoplakia exhibiting changes in surface texture, colour, size, contour deviation, loss of mobility of intraoral or extra oral structures, loss of surface integrity and no or minimal/ partial response to therapy. On the basis of histopathological diagnosis, the cases were classified into three groups- malignancies, oral epithelial dysplasia and “others” (epithelial hyperplasia and verrucous hyperplasia without dysplasia, WHO Classification of Head and Neck tumors 2017).

Statistical analysis

Statistical analysis was done using IBM SPSS Statistics Version 21. For the purpose of analysis, the histopathological diagnosis of carcinoma and dysplasia were clubbed under one group and the non-dysplastic cases as the second group. Histopathological diagnosis was considered the gold standard against which the sensitivity, specificity, positive and negative predictive values of cytopathological methods were calculated. Spearman correlation test was used to study the correlation with histopathology.

For overall comparison with histopathological diagnosis and derivation of respective sensitivity, specificity, positive and negative predictive values (PPV and NPV), cytological lesions were grouped by PAP system of classification as:

- negative (Class I and Class II smears) and positive (Class III, Class IV and Class V) and;
- negative (Class I) and positive (Class II, Class III, Class IV and Class V).

Similarly, lesions identified by Bethesda system were grouped as:

- negative (ASCUS and LSIL) and positive (HSIL and SCC) and;
- negative (ASCUS) and positive (LSIL, HSIL and SCC).

In addition, sensitivity and specificity of each category/ class of detecting dysplasia or malignancy was also analysed.

Results and Discussion

The histopathological diagnosis of the 100 subjects selected for the study comprised of 17 cases of oral epithelial dysplasia, 53 cases of oral carcinomas and 30 cases falling under the category “others” (no dysplasia). 83% of the subjects were males and 17% were females with most of the subjects reporting to our tertiary care centre to be around 35-60 years of age. The case distribution in accordance with PAP classification and Bethesda system of classification with their histopathological correlation is detailed in **Table 1**.

Table 1. Histopathological and cytological correlation using Bethesda system of classification and PAP classification of cases

Histological division	Cytological Category (PAP classification)					Cytological Category (Bethesda classification)				Total
	Class I	Class II	Class III	Class IV	Class V	ASCUS	LSIL	HSIL	Malignancy	
Malignancy	3	7	14	18	11	8	11	10	24	53
Dysplasia	5	6	6	0	0	5	9	3	0	17
Others (epithelial hyperplasia without dysplasia)	13	11	5	1	0	19	7	2	2	30
Total	21	24	25	19	11	32	27	15	26	100

When the lesions classified according to PAP system as negative (Class I and Class II smears) and positive (Class III, Class IV and Class V) were compared with histopathology: the sensitivity and specificity of the PAP system was 70% and 80% respectively; NPV was 46.6% and PPV was 89.1%. Similarly, when the lesions identified by Bethesda system were classified as negative (ASCUS and LSIL) and positive (HSIL and SCC): Bethesda classification showed sensitivity of 52.9%, specificity of 86.7%, positive predictive value of 90.2% and negative predictive value of 44.06% for detecting histopathologically proven malignant/pre-malignant oral lesions.

However, when only Class I was relegated to the negative group with positive group consisting of Class II+Class III+Class IV+Class V (PAP classification) and comparison was done with histopathological diagnosis: sensitivity of 88.6%, specificity of 43.3%, PPV of 78.5% and NPV of 61.2%. were noted. Following comparison of Bethesda system (ASCUS considered negative group and LSIL+HSIL+SCC being positive group) with histopathology: The Bethesda classification showed sensitivity of 81.4%, specificity of 63.3%, PPV of 83.8% and NPV of 61.3%.

A statistically significant association was found between the histopathological diagnosis and the Bethesda classification with the Spearman’s correlation coefficient being 0.537 (p<0.001) (Figure 4).

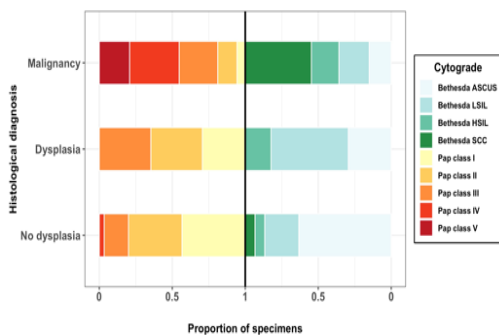


Figure 4. Graphical illustration of histopathological and cytopathological correlation of specimens using Bethesda classification and PAP classification

The sensitivity and specificity of the Bethesda system of classification was 52.9% and 86.7% respectively. Positive predictive value for the same was 90.2% whereas the negative predictive value was 44.06%. In comparison, the sensitivity and specificity of the Pap system of classification was 70% and 80% respectively. A significant association was found between the histopathological diagnosis and the Bethesda system of classification with the Spearman’s correlation coefficient being 0.537 with the p-value less than 0.001.

We also computed the sensitivity and specificity of each class for detecting dysplasia or malignancy except Class III of Pap classification as it was not possible to ascertain the ‘true positives’ in this class (Table 2).

Table 2. Class specific sensitivity and specificity for detecting dysplasia or malignancy.

Class/ Category	Sensitivity (%)	Specificity (%)
Class I (Pap)	68.42	85.86
Class II (Pap)	64.70	79.03
Class III (Pap)	-	-
Class IV (Pap)	46	96
Class V (Pap)	34.3	100
Bethesda system		
ASCUS	79.14	74
LSIL	53.84	64.91
HSIL	48.14	92.85
Malignancy	55.81	92.85

The computational parameters for each class have been defined in Supplementary Table S4. For the Pap classification, we found that the sensitivity decreased from class I to class V whereas vice-versa was true for the specificity which was 100% for Class V. We found a similar trend for the Bethesda classification as well. A notable finding was that both sensitivity and specificity was lowest for the LSIL lesions.

Table S4. Class specific parameters for computing sensitivity and specificity for detecting dysplasia or malignancy.

Class/ Category	Parameters
Class I (Pap)	True Positives: ‘Others’ lesions classified as Class I

	<p><i>False negatives:</i> ‘Others’ lesions classified as Class III, IV, V.</p> <p><i>False positives:</i> Malignancy +dysplastic lesions classified as Class I</p> <p><i>True negatives:</i> Malignancy +dysplastic lesions classified as Class III, IV, V.</p>
Class II (Pap)	<p><i>True Positives:</i> ‘Others’ lesions classified as Class II</p> <p><i>False negatives:</i> ‘Others’ lesions classified as Class III, IV, V.</p> <p><i>False positives:</i> Malignancy +dysplastic lesions classified as Class II</p> <p><i>True negatives:</i> Malignancy +dysplastic lesions classified as Class III, IV, V.</p>
Class III (Pap)	-
Class IV (Pap)	<p><i>True Positives:</i> Malignancy +dysplastic lesions classified as class IV.</p> <p><i>False negatives:</i> Malignancy +dysplastic lesions classified as classes I and II.</p> <p><i>False positives:</i> ‘Others’ lesions classified as Class IV</p> <p><i>True negatives:</i> ‘Others’ lesions classified as Classes I and II</p>
Class V (Pap)	<p><i>True Positives:</i> Malignancy +dysplastic lesions classified as class V.</p> <p><i>False negatives:</i> Malignancy +dysplastic lesions classified as classes I and II.</p> <p><i>False positives:</i> ‘Others’ lesions classified as Class V</p> <p><i>True negatives:</i> ‘Others’ lesions classified as Classes I and II</p>
Bethesda system	
ASCUS	<p><i>True Positives:</i> ‘Others’ lesions classified as ASCUS</p> <p><i>False negatives:</i> ‘Others’ lesions classified as HSIL and Malignancy.</p> <p><i>False positives:</i> Malignancy +dysplastic lesions classified as ASCUS</p> <p><i>True negatives:</i> Malignancy +dysplastic lesions classified as HSIL and Malignancy.</p>
LSIL	<p><i>True Positives:</i> ‘Others’ lesions classified as LSIL</p> <p><i>False negatives:</i> ‘Others’ lesions classified as HSIL and Malignancy.</p> <p><i>False positives:</i> Malignancy +dysplastic lesions classified as LSIL</p> <p><i>True negatives:</i> Malignancy +dysplastic lesions classified as HSIL and Malignancy.</p>
HSIL	<p><i>True Positives:</i> Malignancy +dysplastic lesions classified as HSIL</p> <p><i>False negatives:</i> Dysplastic lesions classified as ASCUS and LSIL.</p> <p><i>False positives:</i> ‘Others’ lesions classified as HSIL</p> <p><i>True negatives:</i> ‘Others’ lesions classified as LSIL and ASCUS</p>
Malignancy	<p><i>True Positives:</i> Malignancy +dysplastic lesions classified as Malignancy</p> <p><i>False negatives:</i> Malignancy lesions classified as ASCUS and LSIL.</p> <p><i>False positives:</i> ‘Others’ lesions classified as Malignancy.</p> <p><i>True negatives:</i> ‘Others’ lesions classified as LSIL and ASCUS</p>

Cytology has been recognized as a relatively rapid, cost effective, simple and a non-invasive procedure for making a provisional diagnosis that guides further investigational and treatment decisions by the clinician. Many investigators advocate its use as a screening test in suspicious oral lesions. [10, 18, 24, 25] Interpretation of the cytological features of the abnormal oral epithelial cells requires an objective grading system which would allow uniformity across the pathological spectrum as well as good inter-observer agreement. Though in few countries like US, where Oral CDx system is being used for rendering results and clinical recommendations. However, Oral CDx being an expensive device and lack of any other alternative, Pap system of classification is being used presently in most of the countries to study the oral epithelial cells even though cytological examination in other organ systems has increasingly favoured the Bethesda system (introduced in 1994).^[23, 26]

When compared with the histopathological diagnosis for thyroid and cervical neoplasms, the Bethesda system of cytopathology classification has been found to have a good predictive value.^[27-29] The Bethesda System for cervical cytology seemingly has been chosen among the other sites, because this system deals with squamous epithelium that is present both in cervix/vagina and the oral cavity.^[30] However, the major pathogenetic pathway that induce carcinoma of the two sites differ markedly. Virtually all squamous cell carcinomas and precursors of the cervix are HPV induced, only a minority of oral cancers fall into this category and will be missed frequently by cytology as they originate deeply within tonsillar crypts. The category of LSIL in TBS corresponds with active HPV replication in cases of cervical cytology nonetheless the lesions of the oral cavity are rarely associated with HPV except for oropharyngeal cases.

The same has been observed in the present study as evidenced by a high correlation coefficient. The present study is the first in published English literature which has attempted to compare the Papanicolaou classification with the Bethesda system (TBS) in the oral scrape cytology samples. Recently, Alsarraf *et al.*^[31] and Sekine *et al.*^[13] used a modified version of Bethesda system to classify oral potentially malignant disorders and oral cancer lesions in the Australian and Japanese population respectively, in a bid to determine its diagnostic accuracy. The reported sensitivity, specificity, and positive predictive and negative predictive values were in the range of 75%-93%, 50-84%, 62-81% and 75-90% respectively. Sekine *et al.* also indicated that histopathological examination should be recommended in cases with cytological diagnoses of LSIL, HSIL, and SCC which concurs with the findings of the present study (**Table 3**).

Table 3. Comparison of other studies assessing Bethesda system for reporting oral cytology

Authors	System used	Sensitivity (%)	Specificity (%)	Positive predictive value	Negative predictive value
Sekine J <i>et al.</i> 2017	Bethesda System	93.5- 77.8	50.6-83.9	62.4-81.0	89.8-81.1
Alsarraf A <i>et al.</i> 2018	Modified Bethesda Cytology system (Orcellex® brush biopsy with liquid-based cytology)	75	76	76	75
Present study	Bethesda system	52.9	86.7	90.2	44.06

Additionally, it is also recommended that cases exhibiting koilocytes and lesions with clinical suspicion should also be subjected for histopathological evaluation to rule out human papilloma virus lesions (especially HPV related dysplasia).

The results of the present study indicated that the Bethesda system has high specificity (86.7%) whereas the Pap classification is more sensitive (70%). The Bethesda system also showed higher specificity than vital staining technique and light-based detection or oral spectroscopy as reported by Macey *et al.* [32] in a comprehensive Cochrane meta-analysis. Macey *et al.* also concluded that based on the high sensitivity and specificity of cytology, it is the most useful adjunctive to histopathology. This furthers the role of oral cytology in screening of oral cancer, stressing the need to adapt a classification system for oral cytology which should use standardized terminology, can communicate clinically relevant information to the clinician and should be reliable, reproducible and uniformly accepted among pathologists around the globe.

Another noteworthy finding is the high positive predictive value obtained for the Bethesda system in this study, which can support its inclusion at the secondary level for the national cancer control programs. WHO advocates that the management of mouth cancer should be an integral part of national cancer control program.[33] At present, there is a paucity of a single effective screening procedure for the oral lesions. Hence, simple and inexpensive methods like cytology are more likely to succeed at a mass level in developing countries.

Literature states methodological weakness, sampling errors (lack of cellularity, technical errors), increased false negatives and false positives as known drawbacks of oral cytology techniques in the detection of OPMD and oral cancer. Similarly, few of the limitations of the present study are the false negatives in cytology when compared to histopathology resulting in delay in the diagnosis. Few of the ASCUS and LSIL cases in the study were histologically diagnosed as SCC (false negatives). These lesions in cytology showed mostly intermediate to superficial cells lacking significant nuclear atypia and other features of malignancy (**Figure 3**). This could possibly be because of inadequate sampling from the oral cytology instrument which missed the basal and parabasal cells where maximum dysplastic features are seen. Further unlike cervical SCC, oral SCC are mostly differentiated type (well differentiated SCC and verrucous carcinoma) showing normal superficial squamous cells, thus leading to

misdiagnosis. Likewise, oral epithelial cells can show inflammatory induced atypia further adding to the diagnostic perplexity. Additionally, due to limited sample size, comparison with larger sample size is recommended for concrete conclusion.

However, the sensitivity and specificity of oral cytology with reporting using Bethesda classification needs to be improved. Its rapidity, ease of use for clinicians and patients can help in early detection of oral precancer and cancer patients.

Conclusion

Bethesda classification system uses well-defined criteria making the pathological reporting of oral cytology more rigorous and uniform, helping the surgeons in making informed decisions. Thus, if oral cytological examination is performed in conjunction with the Bethesda system, it might have the potential to become a powerful diagnostic tool for detecting oral cancer.

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Conflict of interest

None.

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None.

Ethics statement

This study was approved by Ethics Committee of All India Institute of Medical Sciences, Delhi (IEC-720/04.10.2019, RP-31/2019). This research was conducted in accordance with the Declaration of Helsinki.

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