The Diagnostic Value of Clinical Examination and Liquid Based Cytological Evaluation for Oral Potentially Malignant Disorders and Oral Malignant Lesions: A Preliminary Sample Study

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Abstract

Objective: The aim was to investigate the efficacy of clinical examination and of cytobrush with liquid based cytology [LBC] in detection of oral potentially malignant disorders [OPMDs] and malignant lesions.

Material and Methods: 34 patients with oral mucosal lesions who required histological examination for diagnosis were enrolled. After recording the clinical diagnoses, all lesions were stained with Toluidine blue solution in order to determine the biopsy site. The cellular samples were collected with cytobrush from the areas which required biopsy. Cytological samples were evaluated with LBC, whereas biopsied tissues were investigated with histological examination. Statistical analyses were used to compare the clinical, cytological and histological diagnoses and to determine the sensitivity, specificity, positive [PPV] and negative [NPV] predictive values, accuracy, positive [PLR] and negative [NLR] likelihood ratio, diagnostic odds ratio [DOR] of LBC and clinical diagnosis. Results: Of 34 lesions, 8[23.5%] were histologically diagnosed as malignant whereas 26[76.5%] were benign. The clinical diagnoses were 14[44.1%] malignant and 20 [55.9%] benign. The agreement between clinical and histological diagnoses was moderate [$\kappa=0.561$]. With LBC, 7 [20.6%] were diagnosed as malignant and 27[79.4%] were determined as benign. There was almost perfect agreement between LBC and histological diagnosis [$\kappa=0.915$]. The clinical diagnosis method had 100% sensitivity, 73.1% specificity, 53.3% PPV, 100% NPV, 79.41% accuracy, 3.40 PLR and 0.077 NLR, 44.20 DOR. Sensitivity, specificity, PPV, NPV, accuracy, PLR, NLR, DOR of LBC were calculated respectively as 87.5%, 100%, 100%, 96.3%, 97.06%, 45.00, 0.170, 265.00.

Conclusion: Although definitive diagnosis must only be made with histological evaluation of tissue after scalpel biopsy, LBC which had high sensitivity, specificity and Kappa value can be used as an adjunct method before surgical intervention.

1. INTRODUCTION

The International Agency for Research on Cancer and World Health Organization reported that 43.8 million people are living with cancer [within 5 years of diagnosis] worldwide, and over 18 million new cases of cancer and 9.5 million deaths due to cancer were observed in 2018 [1]. Even though detection of oral potentially malignant disorders [OPMDs] in early stages dramatically affects survival rates, unfortunately, 50% of patients have regional or distant metastases at the time of diagnosis, which reflects a significant diagnostic delay [2, 3].

By far, clinical examination which is followed by histopathological assessment that has been considered as the gold standard for definitive diagnosis has been used for detection of OPMDs and oral mucosal malignancies [3]. Additionally; immunohistochemical investigations which evaluate cell survival and apoptosis, cell proliferation and tumor suppression markers in order to assist early detection of various precancerous /cancerous lesions are among the most valuable diagnostic procedures [4, 5]. As with other fields of medicine, diagnostic approaches in oral cavity are going toward noninvasive, simple, inexpensive, painless and

accessible chairside methods such as cytology, brush biopsy, toluidine rinses, chemiluminescent devices, and autofluorescence spectroscopy [5, 6]. Among these, cytodiagnosis has been considered as a minimally invasive technique whereby individual cells are gathered from their tissue of origin and transferred to a cytology slide for microscopic examination of cellular morphology [7-9]. However, proper and adequate cellular sampling from all layers of the stratified epithelium, especially in highly keratinized mucosal lesions is challenging [8-11]. In order to overcome this problem, newer collection devices or “cytobrushes” and novel cytological examination techniques such as liquid based cytology [LBC] have been developed [12,13].

In the 1990s, LBC has been developed for the collection and preparation of cervical cytological samples. This method minimizes issues related to sampling, aids in preparation of high cellularity smears with homogeneous thin layer, causes reduction in false-negative rates, provides clear background, and consequently, enhances sensitivity and quality of smears [14]. In the literature, limited studies in oral cavity based on LBC technique have been published [8, 13-17].

Although diagnostic value of brush biopsy or LBC technique have been reported previously, the methods have some pitfalls: First, the reported values for sensitivity and specificity could be questionable since not all of samples undergo scalpel biopsy [16, 17]. Second, there are few studies which used both brush and scalpel biopsy techniques simultaneously and exactly from the same area [8, 13]. However, it has been stressed that obtaining specimen from different areas of the lesion would lead to inconsistent results between cytology and histological diagnosis. In order to overcome this problem, toluidine blue staining prior to conventional brush biopsy to define the areas within the lesion to be sampled has been proposed [18].

In line with this approach, the aim of the present study was to quantitatively investigate whether the LBC evaluation with cytobrush effectively detects the OPMDs and oral malignant lesions. At the same time, it was also aimed to analyze the accuracy of the specialists’ preliminary diagnosis for suspicious oral lesions and to investigate the accordance between clinical examination and histological diagnosis.

2. MATERIAL AND METHODS

2.1. Study Population

In this preliminary study, 34 individuals with oral mucosal lesions who required histological examination for definite diagnosis and treatment planning were recruited from September 2016 to March 2018 at the Ege University School of Dentistry Department of Oral and Maxillofacial Radiology, Izmir, Turkey. The study was conducted in full accordance with ethical principles, including the Declaration of Helsinki as revised in 2008. The study protocol was approved by the Ethics Committee of the Medical Faculty of Ege University [protocol no. 16-2/47]. The study protocol was explained, and written informed consent was received from each individual before enrollment in the study.

Inclusion criteria were referral for having suspicious oral lesions clinically diagnosed as oral potentially malignant disorders, or early malignant lesions requiring an incisional biopsy for definitive diagnosis. Patients who had a previous definitive diagnosis that was confirmed with histological examination and who have declared a history of any treatment [topical or systemic medications, radiation, chemotherapy] for this diagnosis were excluded. Additionally, the presence of any contraindication for a punch biopsy was accepted as an exclusion criterion.

The patients’ demographic data, duration and location of the lesions were recorded. Thorough extra- and intra-oral clinical examinations were performed by a specialist [PG] with expertise on oral mucosal lesions, under standard conditions using incandescent light and routine dental examination instruments.

After two weeks from removal of potential causative agents such as factors related to traumatic or inflammatory changes including ill-fitting dentures, non-hygienic/defective restorations, orthodontic brackets, cheek biting, all lesions were re-examined and were stained with Toluidine blue solution in order to determine the biopsy site, as described previously [18]. The cytological sample collection and punch biopsy procedures were performed on the dark stained areas of the lesion. In cases where no staining was observed, sample collection was completed on the areas that were most representative of the suspicious lesion.

2.2. Cytological Sample Collection

In order to collect cellular samples from oral epithelium, a standard plastic cytobrush [Teknokim Ltd.Şti, İstanbul, Turkey] was placed on the dark blue stained area and was rotated on the lesion site with pressure. After observing pinpoint bleeding which is the indicator of reaching the basal layer, the brush was immersed in the fixative solution for LBC and was agitated for 10 seconds.

2.3. Punch Biopsy

The punch biopsy was performed under local anesthesia using standard procedures and equipment [5mm punch, Kai Europe GmbH, Solingen, Germany] at the same appointment by a periodontologist [OO] subsequently and exactly from the same area where the brush was applied. The biopsy sample with a diameter of 5mm was immersed in 10% formalin glass tube supplied for transportation of the material to the pathology laboratory.

2.4. Liquid Based Cytological Evaluation

A single ThinPrep slide from each vial was prepared using the ThinPrep 5000 processor [Hologic, Inc., MA, USA] according to the manufacturer's instructions. Briefly, the slide preparation process involves collection of the cytology material on a membrane using a gentle vacuum, trapping cells on the filter and transfer filtered cells to the glass slide. After these procedures, slides were stained with Papanicolaou in Leica XL autostainer [Leica Biosystems Nussloch GmbH, Nussloch, Germany]. The pathologist was unaware of the clinical and histological diagnoses during LBC examination of the samples.

Cytological examination of the samples was completed by experienced cytopathologists [UA, AV] and were classified according to the diagnostic categories of cytological diagnoses: [1] inadequate sample: specimens without any cells or cells with diagnostic quality, [2] benign sample: ordinary, reactive or inflammatory cells, [3] suspicious [atypical] sample: sparse abnormal cells with vague diagnosis for malignancy, [4] malignant sample: cells with obvious malignant cells [17, 19].

2.5. Histological Examination

Oral biopsy specimens were fixed in formalin, embedded in paraffin, and processed for routine hematoxylin and eosin evaluation using standard techniques. All samples were examined by experienced cytopathologists [UA] blind to the clinical diagnoses; using Leica BME [Leica

Microsystems, Buffalo, USA] and OLYMPUS BX51 [Olympus Corp., Tokyo, Japan] microscopes in 4X, 10X, 20X and 40X magnifications.

2.6. Statistical Analysis

The summary statistics [accuracy, sensitivity, specificity, prevalence, true-positive/negative results, false-positive/negative results] were calculated to aid in the analysis of the diagnostic tests. The biopsies of severe dysplasia, carcinoma-in-situ or SCC were considered "malignant"; no dysplasia, mild and moderate dysplasia were accepted as "benign" [20].

Quantitative variables were analysed by T test as $\pm$ SD and for quantitative variables chi square and Exact Fisher tests were done. Sensitivity, specificity, positive predictive value [PPV] and negative predictive value [NPV] were calculated for LBC with cytobrush and clinical examination.

The differences between the test parameters and the lesions in malignant and benign lesion groups were determined with Mann Whitney U test. Diagnostic tests variations were assessed with McNemar test and the diagnostic agreements between the diagnostic tests and the histological diagnoses were determined by calculation of Kappa value.

3. RESULTS

A total of 34 individuals, 15 females [44%] and 19 males [56%] with suspicious oral mucosal lesions were enrolled. The patient and lesion characteristics, clinical, liquid based cytological and histological diagnoses of the lesions in the study are outlined in Table 1.

The mean age of the patients with malignant lesions was 54.3 ± 19.6 years, and patients with benign lesions were older [55.9 ± 14.5 years]; however, this difference was not significant [$p=0.827$]. Both in benign and malignant groups, males presented with more lesions [53.3% and 62.5%, respectively], but the gender variation did not reach statistical significance [$p>0.05$].

Of 34 patients, the lesion duration was more than 4 weeks in 23 [67.6%] patients, whereas the duration was between 2 to 4 weeks in 7 [20.6%] cases. Unfortunately, 4 [11.8%] individuals were unaware of their lesions. The duration was more than 4 weeks in 83.3% of the malignant lesions, whereas this was 70.83% in the benign group. There were no significant differences between lesion duration and their diagnosis [$p=0.084$] [Table 1].

Table1. Demographic variables, lesion characteristics and clinical, liquid based cytological and histological diagnoses of the lesions are summarized

gender	age	duration	lesion region	preliminary diagnosis		cytobrush	histology (gold standard)
m	55	>4 weeks	fornix mucosa	lupus lesion	benign	benign	lupus erythematosus
m	67	>4 weeks	buccal mucosa	leukoplakia	benign	benign	squamous hyperplasia
m	52	>4 weeks	x	SCC	malignant	malignant	carcinoma in situ
f	65	>4 weeks	FOM	SCC	malignant	benign	carcinoma in situ
f	72	>4 weeks	x	SCC	malignant	malignant	SCC
f	69	x	x	SCC	malignant	malignant	SCC
m	22	2-4 weeks	lateral tongue	SCC	malignant	benign	SCC
f	55	>4 weeks	x	leukoplakia	benign	benign	squamous metaplasia
m	40	x	x	leukoplakia	benign	benign	verrucous hyperplasia
m	47	x	x	SCC	malignant	malignant	adenoid cystic carcinoma
f	61	>4 weeks	FOM	leukoplakia	benign	benign	squamous hyperplasia
m	55	>4 weeks	alveolar crest	SCC	malignant	malignant	SCC
f	35	2-4 weeks	buccal mucosa	SCC	malignant	benign	erosive lichen planus
f	73	x	alveolar crest	SCC	malignant	benign	carcinoma in situ
m	40	>4 weeks	lateral tongue	leukoplakia	benign	benign	squamous hyperplasia
m	22	>4 weeks	tongue,buccal mucosa	white sponge nevus	benign	benign	white sponge nevus
m	61	>4 weeks	alveolar crest	leukoplakia	benign	benign	squamous hyperplasia
f	66	>4 weeks	palatine mucosa	nonspecific ulcer	malignant	benign	lichenoid reaction
f	68	>4 weeks	tongue	leukoplakia	benign	benign	lichen planus
f	78	>4 weeks	tongue,buccal mucosa	lichen planus	benign	benign	lichen planus
m	60	2-4 weeks	tongue	lichen planus	benign	benign	ulcerous inflammation
m	64	2-4 weeks	palatine mucosa	SCC	malignant	benign	nonspecific ulcerous inflammation
m	55	>4 weeks	tongue	leukoplakia	benign	benign	erosive lichen planus
f	51	>4 weeks	retromolar region	SCC	malignant	benign	squamous intraepithelial neoplasia 1
m	73	2-4 weeks	FOM	SCC	malignant	benign	squamous intraepithelial neoplasia 2
m	59	2-4 weeks	tongue	SCC	benign	benign	non-specific (lymphocyte infiltration+mild fibrosis)
f	57	>4 weeks	buccal mucosa	leukoplakia	benign	benign	squamous hyperplasia
m	68	>4 weeks	buccal mucosa	leukoplakia	benign	benign	lichen planus
f	60	>4 weeks	FOM	leukoplakia	benign	benign	squamous hyperplasia
m	36	>4 weeks	buccal mucosa	SCC	malignant	malignant	SCC
f	81	>4 weeks	retromolar region	SCC	malignant	suspicious cytology	SCC
m	29	2-4 weeks	buccal mucosa	leukoplakia	benign	benign	squamous hyperplasia
m	32	>4 weeks	retromolar region	leukoplakia	benign	benign	squamous hyperplasia

Lesions were observed similarly both at the non-keratinized and keratinized mucosa: 17 were reported at the non-keratinized tissues [9 [26.5%] at the buccal mucosa, 4[11.8%] at the floor of the mouth, 1[2.9%] at the fornix, and 3[8.8%] at the lateral tongue]. The remaining 17 were observed at the keratinized mucosa; 5[14, 7%] were at the alveolar mucosa, 3[8.8%] were at the palatal and 3 [8.8%] were at retromolar mucosa, and 6[17.6] were at the tongue. Most of the benign lesions [53.8%] were located at the keratinized oral mucosa, whereas 62.5% of malignant lesions were observed at the non-

keratinized oral mucosa; however, no significant differences were observed between the location of the lesions and diagnosis [$p=0.263$] [Table 1].

The histological diagnoses of the lesions are presented in Table 1. Of 34 lesions, 8[23.5%] were histologically diagnosed as malignant whereas 26[76.5%] were considered benign. On the other hand, the clinical diagnoses were malignant for 14[41.1%] and benign for 20[58.9%] [Table 2]. The agreement between clinical and histological diagnoses was $\kappa=0.561$, presenting a moderate level of agreement.

Table2. 2x2 contingency table for clinical examination compared to cytobrush biopsy (LBC). Histological evaluation was considered as the gold standard

Tests diagnostic characteristics	Clinical		Liquid Based Cytology (LBC)	
	value	95% confidence interval	value	95% confidence interval
Sensitivity	100.00%	(63.06%-100.00%)	87.5%	(47.35%-99.68%)
Specificity	73.08%	(52.21%-88.43%)	100.00%	(86.77%-100.00%)
Positive Likelihood Ratio (PLR)	3.40		45.00	
Negative Likelihood Ratio (NLR)	0.077		0.170	
Accuracy	79.41%	(62.10%-91.30%)	97.06%	(84.64%-99.93%)
Positive Predictive Value (PPV)	53.33%	(37.76%-68.28%)	100.00%	
Negative Predictive Value (NPV)	100.00%		96.30%	(80.61%-99.39%)
Diagnostic Odds Ratio (DOR)	44.20		265.00	

With LBC, 7[20.6%] were diagnosed as malignant and 27[79.4%] were determined benign [Table 2]. There was almost perfect agreement between diagnoses of LBC and histology [$\kappa=0.915$]. When the localization of the lesions was considered, the agreement between the clinical and histological diagnoses of the lesions was moderate both at the non-keratinized mucosa [$\kappa=0.541$, $p=0.125$] and keratinized mucosa [$\kappa=0.564$, $p=0.250$]. For LBC, the agreement was almost perfect both at the non-keratinized [$\kappa=0.850$, $p=1.000$] and keratinized mucosa [$\kappa=1.000$, $p=1.000$].

According to the results; sensitivity, specificity, positive [PPV] and negative [NPV] predictive values, positive [PLR] and negative [NLR] likelihood ratios of LBC were calculated respectively as 87.5%, 100%, 100%, 96.3%, 45.00 and 0.170 [Table 3]. The clinical diagnosis method had 100% sensitivity, 73.1% specificity, 53.3% PPV, 100% NPV, 3.40 PLR and 0.077 NLR [Table 3]. The overall accuracy and diagnostic odds ratio [DOR] of LBC [97.06% and 265.00, respectively] were higher than those of the clinical diagnostic method [79.41% and 44.20, respectively].

Table3. The sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), accuracy, positive predictive value (PPV), negative predictive value (NPV), and diagnostic odds ratio (DOR) of the clinical and LBC diagnostic tests are presented

Histological examination (Gold Standard)				
		Benign		Total
		Benign	Malignant	
Clinical Diagnosis	Benign	19	1	20
	Malignant	7	7	14
Cytobrush	Benign	26	1	27
	Malignant	0	7	7
		26	8	34

The clinical diagnosis was more successful in malignant lesions [sensitivity=1.000, PPV=0.530] and the method accurately detected all malignant mucosal alterations, but almost half of the benign lesions were also considered as malignant [specificity=0.731, NPV=1.000]. On

the other hand, the LBC accurately diagnosed all benign mucosal lesions [specificity=1.000, NPV=0.963], however, one of the malignant lesions were incorrectly diagnosed as benign with LBC [sensitivity=0.875, PPV=1.000].

Considering the localization of the lesions, both diagnostic tests were more accurate [clinical diagnosis $p=0.250$, $\kappa=0.564$; LBC $p=1.000$, $\kappa=1.000$] to detect the lesions located at the keratinized oral mucosa when compared to those observed on non-keratinized mucosal lesions [clinical diagnosis $p=0.125$, $\kappa=0.541$; LBC $p=1.000$, $\kappa=0.850$]. However, on both localizations, LBC provided more agreement with histological diagnoses.

All tested parameters were placed in a statistical model to determine the factors which were significantly important on the diagnostic efficacy of the test methods. Logistic regression analysis revealed that none of the variables were influential on the diagnosis of the lesions: [gender [$p=0.487$], age [$p=0.891$], duration of the lesion [$p=0.526$], lesion localization [$p=0.356$]].

4. DISCUSSION

The reports have revealed wide range of sensitivity, specificity, PPV and NPV for conventional cytology [14, 17, 21] because of the time lapse between the cytological and histological examinations, the selection of the same site for cytological and scalpel biopsy, the thickness of the lesion and the presence of necrosis and/or infection [22] and accompanying inflammation [20, 22].

Comparison of conventional brush biopsy with immediate scalpel biopsy revealed the efficacy of brush cytology in oral mucosal lesion diagnosis [23-27], with 96.3% sensitivity and 100% specificity for oral dysplasia or carcinoma [28]. On the other hand, others have reported high false positive and false negative results of brush biopsy [ranging between 30-84% for OSCC [22] and 63% for dysplastic lesions [27]. The variations between the results have been attributed to the fact that clinicians usually tend to forgo the scalpel biopsy for histological examination for the lesions with negative brush biopsy results [2, 25, 27]. Additionally, the limitations inherent to the brush cytology method such as receiving a small and particular region of the oral lesion [29], unsatisfactory sampling from the deeper layers of OPMDs with thick keratin layers [9, 22, 24] and from OSCC lesions with accompanying necrosis, infection or inflammation may cause variant results obtained with conventional brush biopsy [20, 21]. To overcome these, LBC has been introduced to oral mucosal lesion diagnosis. Studies using both conventional cytology and

LBC have reported better diagnostic performance with LBC due to overall advance regarding specimen adequacy, sample preservation, visualization of cell morphology and reproducibility [13, 16, 17].

In the present study, sensitivity, specificity, PPV and NPV of clinical examination were calculated as 100%, 73.8%, 53.33% and 100%, respectively. During clinical diagnosis, the specialists tended to consider the lesions mostly as malignant: in addition to 8 histologically malignant lesions, clinical diagnosis considered further 6 of benign lesions as malignant [specificity=73.08%, PPV=53.33%]. This approach appears to influence both the accuracy and diagnostic odds ratio [DOR] of clinical diagnosis on oral mucosal lesion diagnosis, as well [accuracy=79.41%, DOR=44.20]. Referral of the patients from other centers because of the presence of clinically suspicious oral mucosal lesions may influence the clinical decision of the specialists, and appears to lead them to misdiagnosis.

LBC accurately diagnosed all benign lesions, but failed to recognize 1 of 8 malignant lesions [sensitivity=87.5%, NPV=96.3%]. Considering that this case was a SCC lesion observed on the lateral tongue as a speckled white thickening, probably improper cell sampling from the deeper layers of the lesion for LBC [28] may be a reason for this false negative result.

Although benefit of LBC over conventional cytology has been reported [13, 16, 17, 27], few studies provided diagnostic test values for LBC. In this context, the present study has provided valuable information for the clinicians. Our results were in agreement with the literature, which revealed sensitivity of 75-97.6%, specificity of 68.8-100%, PPV of 76-100%, NPV of 76-90.6% for LBC in oral mucosal lesion diagnosis [8, 14, 17]. Nevertheless, the main limitation of the present preliminary study is its' low study sample size; the findings require confirmation with larger number of patients with oral mucosal lesions in further studies, which is being carried on.

Kappa value disclosed that there was almost perfect agreement between diagnoses of LBC and histology, whereas the agreement between clinical and histological diagnoses was moderate [$\kappa_{LBC}=0.915$, $\kappa_{clinical\ diagnosis}=0.561$].

Based on the results, high sensitivity, specificity, and Kappa value showed that LBC

is a suitable adjunct test for clinical use. Considering that hyperkeratinization of an oral mucosal lesion prevents collection of epithelial cells in both conventional cytology and LBC [9, 22, 28, 30], scalpel biopsy shall be preferred in such cases [30]. However, in other occasions, especially in erosive and ulcerative forms of OPMDs, minimally invasive LBC can be used as an adjunct to screen and evaluate clinically suspicious oral lesions, or to examine oral epithelium after oral oncological treatment [31]. Additionally, after providing further immunocytochemical and molecular analyses, DNA ploidy and mRNA expression with LBC [8], practitioners can inform their patients about abnormal findings which have a strong positive predictive value for dysplasia or carcinoma. Along with, it should be stressed that definitive and final diagnosis can only be made with histological evaluation of tissue after scalpel biopsy, and all adjunct methods can only assist the clinicians to determine the time and area for histological examination of the lesion.

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REFERENCES

- [1] International Agency for Research on Cancer/World Health Organization. <https://gco.iarc.fr/today/data/factsheets/cancers/39-All-cancers-fact-sheet.pdf>
- [2] Fedele S. Diagnostic aids in the screening of oral cancer. *Head Neck Oncol.* 1, 5 (2009)
- [3] Acha A., Ruesga M.T., Rodríguez M.J., et al. Applications of the oral scraped [exfoliative] cytology in oral cancer and precancer. *Med Oral Patol Oral Cir Bucal.* 10,95-102 (2005).
- [4] Bajpai M., Agarwal D., Bhalla A., VatchalaRani R.M., Kumar M. Unilateral lichen planus: A rare case report. *J Nat Sci Biol Med.* 5, 453-455 (2014).
- [5] Chandolia B, Rajliwal JP, Bajpai M, Arora M. Prognostic Potential of N-Cadherin in Oral Squamous Cell Carcinoma via Immunohistochemical Methods. *J Coll Physicians Surg Pak.* 27, 475-478 (2017).
- [6] Lingen M.W., Kalmar J.R., Karrison T., et al. Critical evaluation of diagnostic aids for the detection of oral cancer. *Oral Oncol.* 44, 10-22 (2008).
- [7] Sekine J., Nakatani E., Hideshima K., et al. Diagnostic accuracy of oral cancer cytology in a pilot study. *Diagn Pathol.* 12, 27(2017).
- [8] Alsarraf A.H., Kujan O., Farah C.S. The utility of oral brush cytology in the early detection of oral cancer and oral potentially malignant disorders: A systematic review. *J Oral Pathol Med.* 47,104-116 (2018).
- [9] Kujan O., Desai M., Sargent A., et al. Potential applications of oral brush cytology with liquid-based technology: results from a cohort of normal oral mucosa. *Oral Oncol.* 42, 810-818 (2006).
- [10] McCullough M.J., Prasad G., Farah C.S. Oral mucosal malignancy and potentially malignant lesions: an update on the epidemiology, risk factors, diagnosis and management. *Aust Dent J.* 55, 61-65 (2010).
- [11] Speight P.M., Epstein J., Kujan O., et al. Screening for oral cancer-a perspective from the Global Oral Cancer Forum. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 123,680-687 (2017).
- [12] Smith J.H. Cytology, liquid-based cytology and automation. *Best Pract Res Clin Obstet Gynaecol.* 25,585-596 (2011).
- [13] Hayama F.H., Motta A.C., Silva Ade P., et al. Liquid-based preparations versus conventional cytology: specimen adequacy and diagnostic agreement in oral lesions. *Med Oral Patol Oral Cir Bucal.* 10,115-122(2005).
- [14] Delavarian Z., Mohtasham N., Mosannen-Mozafari P., et al. Evaluation of the diagnostic value of a Modified Liquid-Based Cytology using OralCDx Brush in early detection of oral potentially malignant lesions and oral cancer. *Med Oral Patol Oral Cir Bucal.* 15, 671-676 (2010).
- [15] Arul P. Application of liquid-based cytology preparation in micronucleus assay of exfoliated buccal epithelial cells in road construction workers. *Indian J Dent Res.* 28,413-417 (2017)
- [16] Shukla S, Einstein A, Shukla A, et al. Comparison of specimen adequacy and smear quality in oral smears prepared by manual liquid-based cytology and conventional methods. *J Oral Maxillofac Pathol.* 19, 315-318 (2015)
- [17] Remmerbach T.W., Pomjanski N., Bauer U., et al. Liquid-based versus conventional cytology of oral brush biopsies: a split-sample pilot study. *Clin Oral Investig.* 21, 2493-2498(2017).
- [18] Güneri P., Epstein J.B., Ilhan B., et al. Clinical application of a digital method to improve the accuracy of color perception in toluidine blue stained oral mucosal lesions. *Quintessence Int.* 44, 619-627 (2013).
- [19] Scuibba J. Improving detection of precancerous and cancerous oral lesions. *J Am Dent Assoc.* 130,1445-1457 (1999).

- [20] Güneri P., Epstein J.B., Kaya A., et al. The utility of toluidine blue staining and brush cytology as adjuncts in clinical examination of suspicious oral mucosal lesions. *Int J Oral Maxillofac Surg.* 40,155–161 (2011).
- [21] Carreras-Torras C., Gay-Escoda C. Techniques for early diagnosis of oral squamous cell carcinoma: Systematic review. *Med Oral Patol Oral Cir Bucal.* 20, 305-315 (2015).
- [22] Trullenque-Eriksson A., Muñoz -Corcuera M., Campo-Trapero J., et al. Analysis of new diagnostic methods in suspicious lesions of the oral mucosa. *Med Oral Patol Oral Cir Bucal.* 14, 210-216 (2009).
- [23] Gupta A., Singh M., Ibrahim R., et al. Utility of toluidine blue staining and brush biopsy in precancerous and cancerous oral lesions. *Acta Cytol.* 51,788-794 (2007).
- [24] Mehrotra R., Gupta D.K. Exciting new advances in oral cancer diagnosis: avenues to early detection. *Head Neck Oncol.* 3, 33 (2011).
- [25] Omar E. Current concepts and future of noninvasive procedures for diagnosing oral squamous cell carcinoma--a systematic review. *Head Face Med.* 11, 16 (2015).
- [26] Goodson M.L., Smith D.R., Thomson P.J. Efficacy of oral brush biopsy in potentially malignant disorder management. *J Oral Pathol Med.* 46, 896-901 (2017).
- [27] Navone R., Pentenero M., Gandolfo S. Liquid-based cytology in oral cavity squamous cell cancer. *Curr Opin Otolaryngol Head Neck Surg.* 19, 77-81 (2011).
- [28] Mehrotra R. The role of cytology in oral lesions: a review of recent improvements. *Diagn Cytopathol.* 40, 73-83 (2012).
- [29] Driemel O., Kunkel M., Hullmann M., et al. Diagnosis of oral squamous cell carcinoma and its precursor lesions. *J Dtsch Dermatol Ges.* 5, 1095-1100 (2007).
- [30] Osaka R., Hayashi K., Onda T., et al. Evaluation of Liquid Based Cytology for Tongue Squamous Cell Carcinoma: Comparison with Conventional Cytology. *Bull Tokyo Dent Coll.* 60, 29-37 (2019).
- [31] Reddy S.G., Kanala S., Chigurupati A., et al. The sensitivity and specificity of computerized brush biopsy and scalpel biopsy in diagnosing oral premalignant lesions: A comparative study. *J Oral Maxillofac Pathol.* 16, 349-353 (2012).

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