Detection of oral potentially malignant lesions among tobacco users; Identafi and Microlux versus histopathology

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Abstract: Background: Detection of oral cancer in an early stage improves patient survival significantly and reduces morbidity and cost of treatment. Screening of high risk groups of individuals such as tobacco users has been achieved through many research projects using the devices such as Microlux and Identafi that have been invented to serve as aids in the examination of oral premalignant and malignant lesions. The aim of the current study was to evaluate Identafi and Microlux versus oral biopsy as a gold standard. **Methods**: The material of the study includes 39 oral lesions from tobacco users examined by conventional oral examination, Identafi, Microlux and histopathology. The findings of the study were recorded and statistically analyzed. The results of the 4 methods of examination (clinical, Identafi, Microlux and Microlux with toluidine blue) were compared with the histopathological findings that served as a gold standard. **Results**: Showed sensitivity of 80%, 80%, 100% and 100% respectively, while the specificity was 14.7%, 14.7%, 32.4% and 35.3% respectively. The accuracy was 56.5% for clinical examination, 48.7% for Identafi, 38.5% for Microlux and 35.9% for Microlux with toluidine blue. The contingency coefficient was 0.82%, 0.81%, 0.71% and 0.72% respectively. **Conclusion**: We can conclude that Identafi and Microlux can be used as aids to help identification of oral premalignant and malignant lesions. However we have to realize that still the histopathological examination is the most accurate method of diagnosis.
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Key Words: oral premalignant lesions, oral cancer, identafi, microlux, tobacco users.

1. Introduction:

Cancer of the oral cavity is usually preceded by oral potentially malignant lesions (OPL). Early OPL are difficult to identify, and the risk factors for these lesions are not the same all over the world.[1] Early detection of the malignant transformation of OPL is a major concern for public health strategies. The treatment of patients who have been diagnosed at an early stage of oral cancer is less aggressive. Morbidity of those patients is less and health costs are low. The recognition of individual risks is the most valuable tool, which depends on the availability of diagnostic aids to identify premalignant and malignant changes.[2,3]

Although conventional oral examination (COE) is of great value as a diagnostic method, there are limitations with this approach. While COE may be useful in the discovery of some oral lesions, it does not identify all potentially premalignant lesions, nor does it accurately detect the small proportion of biologically relevant lesions that are likely to progress to cancer.[4] This results in delay of patient management and worth prognosis.

Thomson stated that 36% of diagnosed oral squamous cell carcinoma patients had histologic criteria of dysplasia or carcinoma *in situ* in a biopsy that taken from normally appearing mucosa from the contralateral, corresponding anatomic location.[5]

Screening protocols of patients with possible OPL are useful. Determination of high-risk areas, distinctive clinical features, and staining manners with high specificity and sensitivity make detection of asymptomatic OPL possible. Early diagnosis leads to easily treated lesions, decreased post-treatment morbidity and increased survival rates.[6]

Furthermore, any technical approach which highlights OPL in an accurate manner will help clinicians in early detection and management of these lesions. Recently, the invention of noninvasive, diagnostic tools such as ViziLite, VELScope, Microlux and Identafi were evaluated.[7-9]

The aim of the current investigation is to assess the accuracy of the 2 devices Identafi and Microlux in detection of OPL in tobacco users versus the gold standard, the histopathology.

2. Material and methods

The study included 39 tissue biopsies taken from oral lesions of suspicious premalignancy or malignancy. The study was a part of a research included 599 subjects of smoking and/or smokeless tobacco users in Jeddah, Saudi Arabia having been selected from population clusters such as from companies, factories, universities and school students, and from groups of visitors attending special events in some general and private hospitals. The study was evaluated and approved by the local ethics committee at King Abdulaziz University, Saudi Arabia. The research was done voluntarily on subjects of ≥18 year old males and females between 2011 and 2013.

Clinical oral examination was done by the ordinary operatory light of a portable dental chair using disposable dental mirrors and palpation. This examination was done independently by oral medicine consultants. Clinical examination was repeated using the screening device, Identafi® system (Star Dental-Dental EZ, Lancaster, PA, USA) as manufacturer's instruction was previously described.[10, 11]

The examination was further repeated by using the Microlux/DL kit. The influence of toluidine blue (TB) with Microlux/DL was also assessed by using 1% TB[12] as mouth rinse for one minute before using Microlux/DL. All measurements were repeated and photographing of all lesions was done by means of Canon camera (33- EOS550D 18/15)
The COE, Identafi® and Microlux with and without TB diagnostic results were recorded for each lesion.

Tissue biopsies were obtained from suspicious lesions (Lesions showing well defined margins, red color, mixed red and white components, ulcerations, size more than 1 centimeter and lesions of ventro-lateral tongue or the floor of the mouth) by using either scalpel or punch technique under local anesthesia at Faculty of Dentistry clinics. The specimens obtained were routinely processed and stained with hematoxylin and eosin staining and examined microscopically by one consultant pathologist, who was blinded to the examination's results. Photo documentation was obtained prior to the surgical biopsy of the cases.

Data Analysis: The research data was analyzed using SPSS version 16.0 (SPSS, Chicago, Illinois, USA). A less than 0.05 P- value was considered statistically significant. For each examination technique and sensitivity were calculated where as the gold standard of test accuracy was the histopathologic diagnosis of biopsies read by the assigned pathologist.

3. Results

The oral histopathology laboratory has received 39 biopsies for diagnosis out of the 599 studied cases. Table 1 revealed that 22 cases (56.4) out of the 39 were diagnosed as Smokeless tobacco keratosis (Fig 1), 5 (12.8%) as dysplasia (Figs 2-4), 4 (10.3%) as hyperkeratosis (Fig 5), 4 (10.2%) as leukoplakia (Fig 6), 2 (5.1%) as epithelial hyperplasia (Fig 7), 1 (2.6%) as oral submucous fibrosis (Fig 8) and 1 (2.6%) as lichenoid reaction (Fig 9).

Concerning the cases of dysplasia revealed by the current work which were 5 cases, they all showed mild degree of dysplasia (Figs 2-4). The dysplastic changes revealed included basilar hyperplasia, loss of polarity, hyperchromatism and little pleomorphism.

Table 2 showing the detailed results of the biopsies taken whereas every case of the 39 biopsied cases were evaluated clinically, by using Identafi, Microlux without and with TB and histopathologically.

Table 3 showed high sensitivity for the clinical (80%), Identafi (80%), Microlux (100%) and Microlux with toluidine blue (100%) examination methods compared with the histopathological diagnostic method. However low specificity for the previous methods of diagnosis was found (14.7%, 14.7%, 32.4% and 35.3% respectively) when compared with the histopathological method.

Table 4 shows agreement of the different methods of examination of suspicious lesions clinically, by the 2 devices (Identafi and Microlux with and without toluidine blue) with the gold standard provided by biopsy examination, whereas the accuracy of clinical examination was 56.5%, 48.7% for Identafi, 38.5% for Microlux and 35.9% for Microlux with toluidine blue. The contingency coefficient was 0.82%, 0.81%, 0.71% and 0.72%respectively.

Table 1: Results of biopsied cases

Histopathological results	Number	%
Smokeless tobacco keratosis	22	56.4
Dysplasia	5	12.8
Leukoplkia	4	10.2
Hyperkeratosis	4	10.2
Epithelial hyperplasia	2	5.2
Oral submucous fibrosis	1	2.6
Lichenoid reaction	1	2.6
Total	39	100

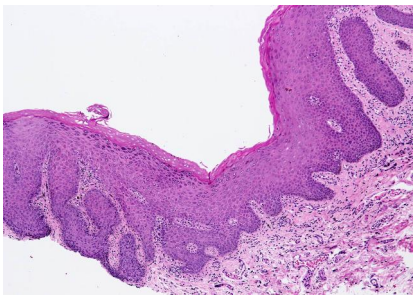

Fig. 1: Smokeless tobacco keratosis.

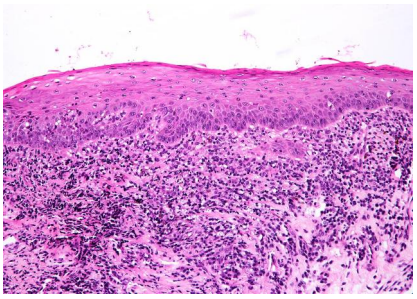

Fig. 2: Mild Epithelial dysplasia: Cellular changes found in the lower layers of surface epithelium.

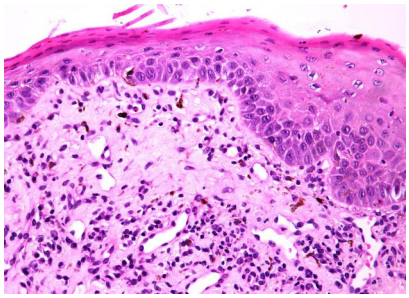

Fig. 3: Mild Epithelial dysplasia: Cellular changes involve the basilar and suprabasilar layers of epithelium.

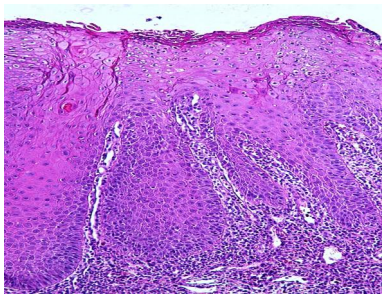

Fig. 4: Moderate epithelial dysplasia: Cellular changes extend to the middle layers of surface epithelium.

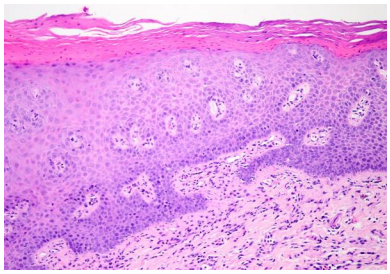

Fig. 5: Hyperparakeratosis and acanthosis.

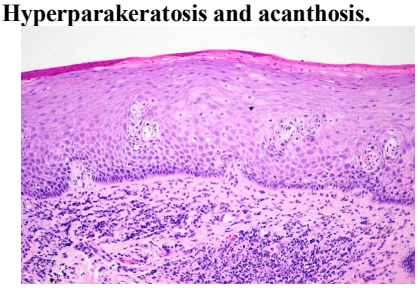

Fig. 6: Leukoplakia showing hyperparakeratosis and moderate acanthosis.

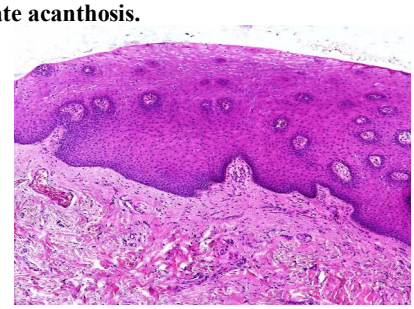

Fig. 7: Epithelial hyperplasia showing acanthosis of the surface epithelium.

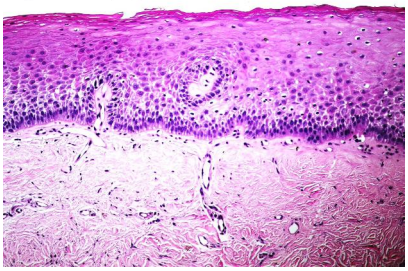

Fig. 8: Oral submucous fibrosis (OSF) showing mild atrophy of the surface epithelium and fibrosis of the underlying connective tissue.

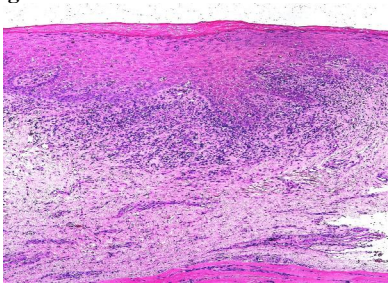

Fig. 9: Lichenoid reaction: showing mild acanthosis with keratosis of the surface epithelium and superficial connective tissue infiltration by chronic inflammatory cells.

Table 2: Detailed results of the biopsies taken

	Clinical	Identify	Microlux/DL	Microlux/DL+TB	Histopathology
1	Erytrholeukoplakia	Erytrholeukoplakia	Erytrholeukoplakia	Erytrholeukoplakia	Smokeless keratosis
2	Smokeless keratosis	Smokeless keratosis	Smokeless keratosis	Smokeless keratosis	Smokeless keratosis
3	OSF	OSF	OSF	OSF	Smokeless keratosis
4	Smokeless keratosis	Smokeless keratosis	Smokeless keratosis	Smokeless keratosis	Lichenoid reaction
5	Smokeless keratosis	Smokeless keratosis	Smokeless keratosis	Smokeless keratosis	Smokeless keratosis
6	Oral lichen planus	Oral lichen planus	Negative	Negative	Leukoplakia
7	Leukoplakia	Leukoplakia	Leukoplakia	Negative	Epithelial hyperplasia
8	Smokeless keratosis	Smokeless keratosis	Smokeless keratosis	Smokeless keratosis	Smokeless keratosis
9	Smokeless keratosis	Smokeless keratosis	Negative	Smokeless keratosis	Smokeless keratosis
10	Smokeless keratosis	Smokeless keratosis	Smokeless keratosis	Negative	Smokeless keratosis
11	Erytrholeukoplakia	Erytrholeukoplakia	Erytrholeukoplakia	Erytrholeukoplakia	Smokeless keratosis
12	Smokeless keratosis	Smokeless keratosis	Smokeless keratosis	Smokeless keratosis	Smokeless keratosis
13	Leukoplakia	Leukoplakia	Leukoplakia	Leukoplakia	Smokeless keratosis
14	Smokeless keratosis	Smokeless keratosis	Negative	Negative	Smokeless keratosis
15	Smokeless keratosis	Smokeless keratosis	Smokeless keratosis	Smokeless keratosis	Smokeless keratosis
16	Smokeless keratosis	Smokeless keratosis	Negative	Negative	Smokeless keratosis
17	OSF	OSF	OSF	Negative	OSF
18	Leukoplakia	Leukoplakia	Leukoplakia	Negative	Leukoplakia
19	Smokeless keratosis	Smokeless keratosis	Smokeless keratosis	Smokeless keratosis	Smokeless keratosis
20	OSF	OSF	OSF	OSF	Smokeless keratosis
21	Smokeless keratosis	Smokeless keratosis	Negative	Negative	Smokeless keratosis
22	Leukoplakia	Leukoplakia	Leukoplakia	Leukoplakia	Smokeless keratosis
23	Smokeless keratosis	Smokeless keratosis	Smokeless keratosis	Smokeless keratosis	Smokeless keratosis
24	Smokeless keratosis	Leukoplakia	Smokeless keratosis	Leukoplakia	Dysplasia
25	Leukoplakia	Leukoplakia	Leukoplakia	Leukoplakia	Dysplasia
26	Smokeless keratosis	Smokeless keratosis	Leukoplakia	Leukoplakia	Dysplasia
27	Smokeless keratosis	Smokeless keratosis	Smokeless keratosis	Smokeless keratosis	Smokeless keratosis
28	Negative	Leukoplakia	Negative	Negative	Hyperkeratosis
29	Leukoplakia	Leukoplakia	Leukoplakia	Leukoplakia	Leukoplakia
30	Negative	Leukoplakia	Negative	Negative	Hyperkeratosis
31	Leukoplakia	Leukoplakia	Leukoplakia	Leukoplakia	Hyperkeratosis
32	Smokeless keratosis	Smokeless keratosis	Smokeless keratosis	Leukoplakia	Dysplasia
34	Leukoplakia	Leukoplakia	Erytrholeukoplakia	Erytrholeukoplakia	Leukoplakia
35	Negative	Negative	Negative	Smokeless keratosis	Smokeless keratosis
36	Negative	Negative	Negative	Dysplasia	Epithelial hyperplasia
37	Negative	Negative	Leukoplakia	Leukoplakia	Hyperkeratosis
38	Negative	Negative	Leukoplakia	Leukoplakia	Dysplasia
39	Smokeless keratosis	Negative	Negative	Negative	Smokeless keratosis

Table 3: Validity of different methods of diagnosis of suspicious lesions versus histopathology

Diagnostic method	True +v	True-ve	False +ve	False -ve	Sn (%)	Sp(%)	PVP(%)	PVN(%)	Likelihood ratio		McNemar (P)
									+	-	
Clinical	4	5	29	1	80.0	14.7	12.1	83.3	0.94	1.36	0.000
Identify	4	5	29	1	80.0	14.7	12.1	83.3	0.94	1.36	0.000
ML	5	11	23	0	100	32.4	17.9	100	1.48	0.0	0.000
ML-TB	5	12	22	0	100	35.3	18.5	100	1.55	0.0	0.000

Table 4: Agreement of different methods of diagnosis of suspicious lesions versus histopathology

Diagnosis	Clinical		Identify		Microlux/ DL		Microlux/ DL + TB		Histopathology	
Negative	6	15.4	6	15.4	11	28.2	12	30.8	6	15.4
Smokeless keratosis	18	46.2	16	41.0	12	30.8	11	28.2	22	56.4
Leukoplakia	9	23.1	11	28.2	10	25.6	10	25.6	4	10.2
Erytrholeukoplakia	2	5.1	2	5.1	3	7.7	3	7.7	-	0.0
OSF	3	7.7	3	7.7	3	7.7	2	5.1	1	2.6
Lichenoid lesion	1	2.6	1	2.6	-	0.0	-	0.0	1	2.6
Dysplasia	-	0.0	-	0.0	-	0.0	1	2.6	5	12.8
Accuracy (% agreement)	56.5		48.7		38.5		35.9			
Contingency coefficient with histopathology	0.82**		0.81**		0.71*		0.72			

* $P < 0.05$ ** $P < 0.001$

4. Discussion

It has been well documented that the habitual using of tobacco either smoked or non-smoked is responsible for increased rate of oral cancer. Early detection and evaluation of OPL can decrease the mortality rate of this serious disease.[13]

Periodic clinical oral examination is the mainstay for early detection of oral cancer. It was shown to decrease mortality from oral cancer by 32% in high-risk patients.[14] However because of the various clinical pictures of OPL, it is necessary to biopsy these lesions for obtaining a histopathological diagnosis. Additionally, using adjunctive aids such as ViziLite, VEL Scope, Microlux/DL and TB, has been widely accepted to improve the effectiveness of diagnosis in large-scale screening for oral cancer.[7-9, 15]

The present investigation has been conducted in Jeddah, Saudi Arabia aiming for assessing the reliability of two new devices, Identafi that works the same as VELscope and Microlux that works the same as chemiluminescence (ViziLiteTM) in relation to the biopsy technique as a gold standard. To our knowledge, these 2 devices are used for the first time to detect early oral mucosal changes related to tobacco use among an adult sample selected from population clusters in Jeddah, Saudi Arabia.

Results of the current survey showed that out of the big research done which include 559 tobacco users subjects, only 39 cases were indicated and were available for biopsy as being suspicious for the presence of premalignant or malignant criteria. The results of the histological examination showed that the most prevalent cases were smokeless tobacco keratosis (56.4%), hyperkeratosis and epithelial hyperplasia (15.4%) that microscopically showing nonmalignant criteria such as hyperpara- or hyperorthokeratosis, acanthosis and edematous changes of the surface epithelium. Moreover the cases of leukoplakia (10.2%) showing also no malignant criteria. However only five cases (12.5%) among the 39 cases referred for biopsy proved to display dysplastic changes.
This accounts for a very low percentage in comparison with other studies, such as Jaber *et al.* [16] who followed up 630 patients with OPL. They found that the majority of these lesions (43.8%) were mild dysplasia, 30%were moderate and 24.7% were severe.

Regarding the methods of examinations used in the present study, it was found that all of them (clinical, Identafi, Microlux and Microlux with toluidine blue) possessed a high percentage of sensitivity, 80 to 100% but low percentage of specificity, 14.7 to 35.3% (Table 3) when they compared with histopathological examination method (gold standard). Also the values of accuracy of the 4 methods correlated with histopathological method were moderate to low, 56.5%, 48.7%, 38.5% and 35.9% respectively (Table 4).This leads to a conclusion that by the previous diagnostic devices (Identafi and Microlux), the suspicious oral lesions can be detected but cannot be distinguished from each other regarding the presence of premalignant or malignant criteria.

In the current study, examination of the suspicious lesions by Identafi demonstrated a sensitivity of 80%, a specificity of 14.7% and an accuracy of 48.7% when compared with the histopathology as a gold standard.

In accordance with our results, 126 patients with OPL were included in a study. Following a complete COE and examination with VEL scope, oral lesions were biopsied for histopathological evaluation. The results showed that out of 105 (83%) biopsies, 44 revealed epithelial dysplasia (29 mild, 8 moderate and 7 severe). The autofluorescence examination of these lesions by VELscope showed sensitivity and specificity of 84.1% and 15.3% respectively. The authors concluded that VELscope can be useful in detecting the OPL but is unable to distinguish between high- and low-risk ones.[17]

In a study done by Lane *et al.,* they investigated 44 precancerous or cancer lesions. Following COE, screening of the oral cavity of all patients was done by VELscope and areas of loss of autofluorescence were biopsied. The sensitivity and specificity of VELscope as a screening device demonstrated 98% and 100% respectively when compared to the histopathological method. The strength of this study is because it was directly compared to the histopathology as a gold standard and the presence of high degree of sensitivity which were similar to our findings. The high percentage of specificity in Lane *et al.* study was also encouraging. Therefore, the author concluded that this device might be considered as a suitable tool for screening of pre-cancer and cancer of the oral cavity. However, the study had a number of weaknesses such as a small sample size (n = 44) and the presence of history of oral dysplasia in those patients. This accounted for the high specificity of VELscope examination when it was compared with our results of Identafi (14.7).[18]

In contrast to our results, Scheer *et al.* (2011) used the VELscope to examine 64 patients at risk for oral cancer. After VELscope examination, biopsies were taken from all patients. A loss of autofluorescence was observed in 22 patients (34.4%) revealing intra-epithelial or invasive carcinoma. The VELscope identified the precancerous and cancerous areas with a sensitivity of 100% and a specificity of 80.8% compared with histopathology as gold standard. Again this high percentage of specificity of VELscope examination which was much higher than ours made the authors supported the concept of using VEL scope

in the early detection and distinguishing of OPL and malignant lesions from normal oral mucosa. However, the same device is not able to distinguish non-malignant from malignant or premalignant orallesions.[19]

Supporting the role of VELscope as a diagnostic tool, the accuracy of the VELscope was evaluated by Rana et al and they concluded that the additional use of the VELscope increased sensitivity of examination from 17 to 100% compared to COE alone in detecting OPL. They concluded that VELscope device can help in prevention or reducing the rate of occurrence of oral cancer.[20]

In a recent study, two examination methods were performed to examine 120 patients with OPL, white-light and an autofluorescence visualization by VELscope. Identified suspicious areas were biopsied. The diagnostic tool was compared regarding sensitivity and specificity. Based upon the results, using VEL scope leads to a higher sensitivity (22.0%), but low specificity (8.4%). It was concluded that The VELscope device can help the experienced clinician to find oral precursor malignant lesions.[21]

Concerning Microlux in our study that showed sensitivity of 100% and specificity of 32.4%, was similar to the results presented in a study done on suspicious lesions, whereas the ViziLite sensitivity was 100% and specificity ranged from 0-14.2. The conclusion of these authors supported the concept of superiority of COE and biopsy examination as gold standards for detection of OPL and oral cancer.[22]

Similar to our study regarding the sensitivity of Microlux or ViziLite, 40 patients with a previous history of OPL or oral cancer were examined by ViziLite. The device showed the maximum sensitivity (100%) and 14% specificity. The small sample size was one of the weak points in this study.[9]

Fifty five patients were also examined by ViziLite for assessment of OPL. Oral cavity examination was performed using the standard operatory light, and then repeated with the ViziLite. Incisional scalpel biopsy was taken from all lesions. ViziLite findings were compared with the microscopical diagnosis. ViziLite examination showed a sensitivity of 100%, specificity of 0.0% and an accuracy of 18.2%. The authors mentioned that using ViziLitein detecting the OPL provided little effect beyond COE alone.[7]

Awan *et al.* [23]in their study found that ViziLite system enhanced the visibility and sharpness of most OPL. In comparison with histopathology, the sensitivity and specificity of ViziLite system were 77.3% and 27.8%, respectively. It was concluded that although ViziLite has the ability to detect OPL and in particular improve the visualization of leukoplakias, it does not accurately distinguish dysplastic lesions. Therefore the device can only be used in screening or general examination of oral mucosa.

Comparing Chemiluminescence with 1% TB mouth rinse, the device was evaluated as a diagnostic toolfororal OPL and oral cancer. Sensitivity for Vizilite and TB was 100% and 70.3%, while the specificity was 14.2% and 25% respectively. The accuracy was 80.6% and 64.5% respectively. These results suggested that chemiluminescence is more effective as a diagnostic tool than TB in detection of OPL and cancer as well as in follow-up of patients treated for these serious lesions.[9]

In the current study, we used 1% TB as a mouth rinse before using Microlux. The method was compared with the histopathology as a gold standard. The results demonstrated a sensitivity of 100%, a specificity of 35.3% and an accuracy of 35.9%. In a similar manner, 41 visually identified OPL were examined by chemiluminescence and TB staining. Incisional biopsies were microscopically evaluated. It was found that ViziLite Plus system as a diagnostic tool may help in visualization of OPL that were not readily detectable with COE.[24]

Conclusion

The oral cavity should be carefully examined in tobacco users. Any changes in color or texture of oral mucosa should arouse suspicion of the presence OPL and/or oral cancer. Devices like Identafi and Microlux can be used as aids to help identification of these lesions. However we have to realize that still the histopathological examination is the most accurate method of diagnosis.

Conflict of Interest Statement

The authors declare any financial or personal relationship that could influence the results of this research.

Acknowledgments

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