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Current Diagnostic Methods of Oral Squamous Cell Carcinoma: A Brief Literature Review

Oral Skuamöz Hücreli Karsinomun Güncel Tanı Yöntemleri: OSHK Tanı Yöntemleri Üzerine Kısa Bir Literatür Taraması

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ABSTRACT

Oral cancer remains a persistent biomedical challenge, with survival rates showing limited improvement over the years despite advancements in research and symptom-relieving therapies. Early detection is critical but the diverse and often painless or symptomatically ambiguous nature of oral cancer necessitates comprehensive screening and histological assessments. This study reviews publications from MEDLINE and Cochrane Databases (2002-2023), focusing on clinical manifestations and imaging modalities associated with oral cancer. Selection criteria include English-language publications, ensuring a contemporary understanding of oral cancer's clinical and imaging aspects. Although oral squamous cell carcinoma (OSCC) constitutes the majority of oral cancers, various malignancies such as salivary, soft and hard tissue sarcomas, and metastatic cancer can also manifest in the oral cavity. Additionally, while OSCC was associated with older individuals and a higher incidence in men, current literature suggests a more balanced distribution between genders and a decreasing age of onset. OSCC and oral potentially malignant lesions (OPML) are linked to tobacco, alcohol, and betel quid use. Late-stage diagnoses contribute to lower survival rates, emphasizing the need for early detection through clinical oral examinations, which can detect up to 99% of oral cancers. Clinically, histopathologically, or both, various lesions contribute to the complex landscape of oral cancers. Oral potentially malignant lesions (OPMLs) precede OSCC, encompassing conditions like leukoplakia, erythroplakia, submucosal fibrosis, and lichen planus. While the majority of OPMLs do not progress to cancer, early identification through comprehensive clinical examination is pivotal. This brief literature review contributes to the understanding of oral cancer's multifaceted nature, emphasizing the importance of early detection in improving survival rates.

Keywords: Oral cancer, squamous cell carcinoma, oral potentially malignant lesions

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ÖZET

Ağız kanseri, tanı ve tedavi yöntemlerindeki ilerlemelere rağmen yıllar içinde sınırlı iyileşme gösteren sağkalım oranları ile kalıcı bir sorun olmaya devam etmektedir. Erken teşhis kritik öneme sahiptir, ancak ağız kanserinin çeşitli ve genellikle ağrısız veya asemptomatik olması, kapsamlı tarama ve histolojik değerlendirmeler gerektirir. Bu derleme, ağız kanseriyle ilişkili klinik belirtilere ve görüntüleme yöntemlerine odaklanarak MEDLINE ve Cochrane veri tabanlarından (2002-2023) ilgili yayınları gözden geçirmektedir. Seçim kriterleri, ağız kanserinin klinik ve görüntüleme yönlerinin anlaşılmasını sağlayan İngilizce yayınları içermektedir. Ağız kanserlerinin çoğunluğunu oral skuamöz hücreli karsinom (OSHK) oluştursa da tükürük, yumuşak ve sert doku sarkomları ve metastatik kanser gibi çeşitli maligniteler de oral kavitede ortaya çıkabilir. Ayrıca, OSHK daha yaşlı bireylerle ve erkeklerde daha yüksek insidansla ilişkilendirilirken, mevcut literatür cinsiyetler arasında daha dengeli bir dağılım ve azalan bir başlangıç yaşı olduğunu göstermektedir. OSHK ve oral potansiyel malign lezyonlar (OPML) tütün, alkol ve betel quid kullanımı ile bağlantılıdır. Geç evre tanılar daha düşük sağkalım oranlarına katkıda bulunur ve ağız kanserlerinin %99'una kadarını tespit edebilen klinik ağız muayeneleri yoluyla erken teşhis ihtiyacını vurgular. Klinik, histopatolojik veya her ikisi birden, çeşitli lezyonlar oral kanserlerin karmaşık görüntüsüne katkıda bulunur. OPML'ler OSHK'lardan önce ortaya çıkar ve lökoplaki, eritroplaki, submukozal fibrozis ve liken planus gibi lezyonları kapsar. OPML'lerin çoğu kansere ilerlemezken kapsamlı klinik muayene yoluyla erken teşhis çok önemlidir. Bu kısa literatür incelemesi, ağız kanserinin karakterinin anlaşılmasına katkıda bulunmak ve erken teşhisin sağkalım oranlarını iyileştirmedeki önemini vurgulamayı amaçlamıştır.

Keywords: Ağız kanseri, oral skuamöz hücreli karsinom, oral potansiyel malign lezyonlar

1. INTRODUCTION

The term 'oral cancer' refers to cancers originating in the lip, mouth, oropharynx (1). Oral cancer has been depicted to be a continuous challenge for several decades, despite progress in research on this topic and therapeutic relief of symptoms, survival rates have not improved much over the years (2). As a collective, the 6th most common cancer is of the oral cavity and pharynx, with the number of cases worldwide ranging from 800,000 (in 2017) to 300,000 with a mortality rate of 145,000 (in the year 2020). This decrease could be associated with the ongoing education of the general public regarding the use of tobacco and alcohol; as these synergetic cofactors increase the risk of squamous cell carcinoma dramatically as has been supported by endless amounts of data resulting from research (3-5). Some advertisement claims have been made that smokeless tobacco can be safer in consumption, however this claim is incorrect with respect to oral cancer, as the US Department of Health and Human Service included it in the list of known carcinogens (6). In addition, another cause of dysplasia, according to John Hopkins Oncology Center, is Human Papilloma Virus type 16 and 18 (HPV16, HPV18) that is responsible for 18.9% of oropharyngeal cancers (7-9).

These particular components serve as top etiological precursors that help professionals diagnose squamous cell carcinoma in the oral cavity, lip vermilion and oropharynx. Yet identification is not always as basic due to signs and symptoms either being absolutely painless with no clear display of surface alterations or being painful ulcerations resembling other benign oral disorders. Hence regular check-ups, detailed screening examinations as well as biopsy and histological assessments of divergent looking lesions is an important factor of early detection and sufficient increase in survival rate of the patient. It is principal to note that the sublingual area of the tongue is the most vulnerable region liable for 40% of cases in 2002, as it is somewhat "forgotten" about during intraoral examination moreover due to pooling of saliva on the posterior areas that conceal clear signs of an anomaly (10). This brief literature review focuses on exhibiting clinical signs and symptoms of oral cancer and current diagnostic methods to help early identification and prevention.

The compilation of data presented in this study was systematically undertaken through an exhaustive literature review process. The literature evaluation encompassed a meticulous analysis of 9 research publications sourced from MEDLINE and Cochrane Databases. The inclusion criteria for the selected publications were based on their relevance to the clinical manifestations and imaging modalities associated with oral cancer. Specifically, publications written in the English language and published within the temporal scope of 2002 to 2023 were considered for inclusion in this brief literature review.

This literature review aimed to synthesize the existing knowledge and insights derived from a diverse range of research studies conducted over the specified timeframe. The selection criteria were designed to ensure the inclusion of studies that provide a contemporary understanding of clinical signs and imaging techniques pertinent to oral cancer. This brief literature review sought to offer and up-to-date evaluation of the existing literature, thereby contributing to the current understanding of clinical and imaging aspects related to oral cancer.

Oral Cancers: Beyond Squamous Cell Carcinomas (OSCCs)

Oral cancers predominantly manifest as OSCC, constituting over 90% of reported cases (5). However, the oral cavity presents a complex landscape, with various malignancies posing additional challenges. Salivary malignancies, soft and hard tissue sarcomas, and metastatic cancers are among the diverse array of neoplasms that can affect this anatomical region (11).

Primary Risk Factors for OSCC and OPML

OSCC and OPML share common risk factors, with tobacco, alcohol, and betel quid/areca nut use emerging as the foremost contributors. These risk factors disproportionately impact older adult males, forming a demographic profile susceptible to the development of oral malignancies. Notably, abstaining from these substances does not confer absolute immunity, signifying the multifactorial nature of oral cancer etiology (9,12).

Survival Challenges and Diagnostic Opportunities

The challenges in oral cancer survival rates are multifaceted. Gupta et al. highlight delayed diagnoses as a pivotal factor, stemming from patient delay, dentist delay, and various other contributing factors (13). Late-stage diagnosis significantly impacts survival outcomes. However, amidst these challenges, there exists a crucial window for improving prognosis (6-8).

Early Diagnosis as a Lifesaving Intervention

Diagnosing oral cancer in its early stages is pivotal for enhancing survival rates and reducing mortality. The diagnostic journey commences with a comprehensive clinical oral examination, a non-invasive yet highly effective approach (11). Through a thorough inspection of the oral cavity, clinicians can detect up to 99% of oral cancers. This underscores the significance of routine screenings and the potential for early intervention, offering a lifeline to patients at risk (14).

While OSCCs dominate oral cancer cases, a nuanced understanding of diverse malignancies and risk factors is essential. Timely and thorough clinical examinations, coupled with awareness of risk factors, are critical components in the collective effort to improve outcomes in oral cancer management (5, 6, 15).

Current Diagnostic Approaches

There are many different lesions that can be diagnosed either clinically, histopathologically, or both. Oral potentially malignant lesions (OPMLs) encompass various oral conditions and disorders that may precede the development of oral squamous cell carcinoma (OSCC). These include a range of clinically suspicious oral mucosal abnormalities such as leukoplakia, erythroplakia, submucosal fibrosis, and lichen planus. The majority of OPMLs, however, do not progress to cancer (16).

The prevalence, risk factors, transformation rate, treatment approach, and common locations of various OPMLs underscore the importance of comprehensive management strategies in dental practice. Leukoplakia, characterized by white patches on the oral mucosa, predominantly affects men and is associated with tobacco use. Its transformation rate of about 2-3% per year necessitates vigilant monitoring and biopsy for severe dysplasia. Erythroplakia, presenting as red lesions with high malignancy risk, is less common but poses a significant threat, particularly among individuals with a history of tobacco smoking and alcohol intake. The management typically involves excisional or incisional biopsy to rule out malignancy. Oral lichen planus, a chronic inflammatory disease affecting women aged 30 to 60, emphasizes the role of immunological factors and requires careful follow-up monitoring due to transformation risks. Submucosal fibrosis, prevalent in regions where betel quid chewing is common, highlights the importance of addressing cultural and behavioral factors in disease prevention. Lastly, chronic inflammation, often linked to irritation, underscores the significance of maintaining oral hygiene and addressing potential sources of irritation. Overall, a multidisciplinary approach incorporating preventive measures, regular monitoring, and targeted interventions is crucial for effectively managing oral potentially malignant lesions and reducing the risk of malignant transformation (12-16) (Table 1).

Table 1. The characteristics of oral potentially malignant lesions (OPMLs).

Oral Potentially Malignant Lesions	Description	Prevalence	Risk Factors	Transformation Rate	Treatment Approach	Common Location
Leukoplakia	A white lesion on the oral mucosa that cannot be removed either through clinical examination or histopathologically	1-3%, with a higher incidence in men	Tobacco, but can occur in non-smokers	About 2-3% per year	Biopsy and excision of the lesion is recommended.	Alveolar mucosa, buccal mucosa, palate, tongue, and floor of the mouth
Erythroplakia	A red lesion typically well delineated, posing a high risk of malignancy.	Between 0.02% and 0.2%	Tobacco smoking and alcohol intake	Not completely known, but it is thought to be much higher than leukoplakia.	Excisional or incisional biopsy is recommended	Soft palate, ventral tounge, floor of the mouth, and tonsillar pillars
Oral Lichen Planus	A persistent inflammatory condition, primarily affecting the skin but also capable of involving mucosal tissues.	Particularly women aged 30 to 60	Immunological Factors	Between 0% and 12.5%	Follow-up monitoring for transformation risks	Buccal mucosa, gingiva, and tongue
Submucosal Fibrosis	A chronic fibrotic lesion located on the oral mucosa, which impacts tongue mobility and restricts mouth opening.	Not Specified	In India and East Asian countries, betel quid chewing has been found to be the main etiologic factor	9%	Not specified	Buccal mucosa, tongue, lip, palate, and gingiva

The diagnostic landscape for OPMLs encompasses a variety of techniques aimed at early detection and accurate diagnosis. In clinical diagnosis, a trained examiner can visually detect OSCCs, but early OSCC can be asymptomatic (11). Early diagnosis and prompt initiation of treatment are paramount in effectively managing OPMLs. Timely identification of these lesions enables clinicians to intervene at a stage when the disease is still amenable to curative interventions, thereby improving patient outcomes and reducing morbidity and mortality associated with malignant transformation. Early diagnosis also facilitates less aggressive treatment modalities, potentially reducing treatment-related complications and improving patient quality of life. Furthermore, early detection allows for the implementation of preventive measures and risk reduction strategies, which may mitigate the progression of OPMLs to malignancy (15-16).

Additional precise diagnostic modalities are required beyond clinical examination to identify early lesions effectively and ascertain whether lesions are potentially malignant or benign. Biopsy and histopathology remain the gold standard, providing definitive confirmation of malignancy or dysplasia.

However, innovations in diagnostic techniques have expanded the armamentarium available to clinicians. Vital staining with toluidine blue emerges as a cost-effective adjunct, demonstrating higher sensitivity for detecting carcinoma in situ and highlighting abnormal areas of mucosa (16, 17). Biomarkers offer molecular insights into neoplastic changes within OPMLs, potentially aiding in risk stratification and prognosis assessment. Brush biopsy, exemplified by OralCDx, enables non-invasive sampling and computerized analysis of cytological samples, particularly useful for low-risk lesions (17).

Saliva-based diagnosis holds promise for detecting genetic alterations associated with oral cancer, offering a non-invasive and convenient screening approach. Optical systems, including optical spectroscopy, leverage light-tissue interactions to discern structural and biochemical alterations, providing valuable insights into tissue pathology (17-20). Optical Coherence Tomography (OCT) offers a non-invasive imaging modality for the evaluation of OPMLs and oral cancer. By utilizing near-infrared light to generate cross-sectional images of tissue microstructure, OCT enables real-time visualization of cellular and subcellular features within the oral mucosa. This technology provides high-resolution images with depth penetration, allowing for the assessment of epithelial thickness, architectural changes, and vascular patterns associated with OPMLs and OSCC. OCT has demonstrated promising capabilities in distinguishing between benign and malignant lesions, aiding in early detection and characterization of suspicious oral lesions. Moreover, its non-invasive nature and ability to provide immediate results make it a valuable tool for clinical evaluation and monitoring of disease progression. Overall, OCT holds significant potential for enhancing the diagnosis and management of OPMLs and oral cancer, offering a valuable adjunct to conventional diagnostic techniques in oral pathology (19, 20).

Tissue fluorescence imaging and spectroscopy utilize autofluorescence to identify precancerous and early cancerous lesions, offering objective and quantitative assessment. Additionally, DNA ploidy analysis and chemiluminescence enhance the diagnostic armamentarium by evaluating nuclear DNA content and leveraging chemiluminescent light to enhance mucosal abnormality detection, respectively (17, 18). The VELscope imaging system (The Visually Enhanced Lesion Scope, LED Dental, White Rock, British Columbia, Canada) has emerged as a valuable adjunct in the visualization and evaluation of OPMLs and oral cancer. This device utilizes tissue fluorescence to enhance the detection of abnormal cellular changes within the oral mucosa, providing clinicians with a non-invasive tool for early detection and monitoring of suspicious lesions. By emitting a safe blue light that excites natural tissue fluorescence, the VELscope highlights areas of concern that may not be readily visible under white light examination alone. This technology has demonstrated promising results in improving the identification of dysplastic and malignant lesions, thereby facilitating earlier intervention and improved patient outcomes. (21, 22).

However, it is essential to acknowledge the limitations of optical and fluorescence imaging of OSCC and OPMLs, including their reliance on visual interpretation and potential false-positive findings. Clinicians must undergo proper training to interpret images accurately and integrate them into the diagnostic workflow effectively. Overall, the integration of these advanced diagnostic techniques into

clinical practice holds the potential to improve OPML management, enabling earlier detection, risk stratification, and personalized treatment approaches (Table 2).

Table 2. Currently available diagnostic techniques

Diagnostic Technique	Description
Biopsy and Histopathology (17)	The examination should be of adequate size to encompass both suspicious and normal tissue.
Vital Staining (Toluidine Blue) (16, 17)	Toluidine blue staining serves as a cost-effective method for highlighting abnormal mucosal areas, selectively staining nuclear material in malignant lesions and OPMLs while sparing normal mucosa.
Biomarkers (17)	Encompasses a variety of molecular markers that elucidate neoplastic alterations within potentially malignant lesions.
Brush Biopsy (17)	Involves the use of a small nylon brush to collect cytology samples, subsequently analyzed via computer scanning and analysis (OralCDx) to visualize individual cells. Developed specifically for investigating mucosal irregularities that may not warrant biopsy due to low-risk clinical features.
Optical Systems (17, 19, 20)	Optical spectroscopy capitalizes on the interaction between light and tissue to discern structural and biochemical changes, aiding in the understanding of biological and microscopic characteristics.
Saliva Based Diagnosis (17)	Exfoliative cell samples have been utilized to identify genetic mutations in the oral epithelium of individuals at high risk for oral cancer and to detect microsatellite alterations in oral squamous cell carcinoma (OSCC). The prospect of utilizing saliva as a diagnostic tool for OSCC is particularly appealing, with promoter hypermethylation patterns of TSG p16, O6-methylguanine-DNA-methyltransferase, and death-associated protein kinase identified in the saliva of head and neck cancer patients.
Tissue Fluorescence Imaging (18, 21,22)	Employed in the screening and detection of OPMLs early cancerous lesions in various anatomical sites. Alterations in epithelial and stromal structure and metabolism influence tissue interaction with light, resulting in changes in tissue fluorophore distribution and autofluorescence emission upon stimulation with intense blue excitation light.
Tissue Fluorescence Spectroscopy (18)	Comprising a small optical fiber that generates diverse excitation wavelengths and a spectrometer for recording and analyzing tissue fluorescence spectra, offering objective interpretation of tissue fluorescence changes.
DNA Ploidy (17)	DNA ploidy entails the quantification of nuclear DNA content, with chromosomal imbalances during mitosis, termed aneuploidy, commonly observed in various cancers.
Chemiluminescence (18)	Examination with chemiluminescent blue/white light enhances the identification of mucosal abnormalities compared to conventional incandescent light.

2. CONCLUSION

Primary risk factors for OSCC and OPMLs include tobacco, alcohol, and betel quid/areca nut use. Despite these risk factors, early identification remains crucial in improving survival outcomes. Delayed diagnoses, attributed to delay, significantly affect prognosis. However, there exists a critical window for enhancing prognosis through early intervention.

Comprehensive clinical oral examinations serve as a cornerstone in the early diagnosis of oral cancers. Understanding the diverse manifestations of OPMLs, including leukoplakia, erythroplakia, submucosal fibrosis, and oral lichen planus, underscores the importance of vigilant monitoring and biopsy for severe dysplasia.

3. RECOMMENDATIONS

Innovations in diagnostic techniques, such as vital staining, biomarkers, brush biopsy, and saliva-based diagnosis, offer promising avenues for early detection and risk stratification. Optical coherence tomography (OCT), tissue fluorescence imaging, DNA ploidy analysis, and chemiluminescence provide valuable insights into tissue pathology, aiding in the differentiation between benign and malignant lesions. Integrating these techniques into clinical practice holds the potential to improve OPML management, enabling earlier detection and risk stratification.

REFERENCES

1. Shield, K. D., Ferlay, J., Jemal, A., Sankaranarayanan, R., Chaturvedi, A. K., Bray, F., & Soerjomataram, I. (2017). The global incidence of lip, oral cavity, and pharyngeal cancers by subsite in 2012. *CA: A Cancer Journal for Clinicians,* 67(1), 51-64.

2. Mauceri, R., Bazzano, M., Coppini, M., Tozzo, P., Panzarella, V., & Campisi, G. (2022). Diagnostic delay of oral squamous cell carcinoma and the fear of diagnosis: A scoping review. *Frontiers in Psychology,* 13, 1009080.

3. Warnakulasuriya, S. (2009). Global epidemiology of oral and oropharyngeal cancer. *Oral Oncology,* 45(4-5), 309-316.

4. Wimardhani, Y. S., Warnakulasuriya, S., Subita, G. P., Soegyanto, A. I., Pradono, S. A., & Patoni, N. (2019). Public awareness of oral cancer among adults in Jakarta, Indonesia. *Journal of Investigative and Clinical Dentistry,* 10(1), e12379

5. Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians,* 71(3), 209-249.

6. Janbaz, K. H., Qadir, M. I., Basser, H. T., Bokhari, T. H., & Ahmad, B. (2014). Risk for oral cancer from smokeless tobacco. *Contemporary Oncology/Współczesna Onkologia,* 18(3), 160-164.

7. Tricia Osuna, R. D. H., & Hopkins, S. (2010). Oral cancer diagnostic technologies. *CDHA Journal,* 24(1), 12-18.

8. Aragón-Niño, Í., Cuesta-Urquía, C., González-Martín-Moro, J., Morán-Soto, M. J., Pozo-Kreilinger, J. J., Pampín-Martinez, M. M., ... & Cebrián-Carretero, J. L. (2023). HPV infection in oral cancer, our experience: Prevalence, clinical implications, and current vaccination program in Spain. *Journal of Clinical and Experimental Dentistry,* 15(7), e584.

9. Katirachi, S. K., Grønlund, M. P., Jakobsen, K. K., Grønhøj, C., & von Buchwald, C. (2023). The prevalence of HPV in oral cavity squamous cell carcinoma. *Viruses,* 15(2), 451.

10. Rivera, C. (2015). Essentials of oral cancer. *International Journal of Clinical and Experimental Pathology*, 8(9), 11884.

11. Van der Waal, I., de Bree, R., Brakenhoff, R., & Coebegh, J. W. (2011). Early diagnosis in primary oral cancer: is it possible? *Medicina Oral, Patologia Oral Y Cirugia Bucal,* 16(3), e300-e305.

12. Neville, B.W. and Day, T.A. (2002), Oral Cancer and Precancerous Lesions. *CA: A Cancer Journal for Clinicians,* 52: 195-215.

13. Gupta, B., Kumar, N., & Johnson, N. W. (2019). Evidence of past dental visits and incidence of head and neck cancers: a systematic review and meta-analysis. *Systematic Reviews, 8*(1), 1-18.

14. Walsh, T., Liu, J. L., Brocklehurst, P., Glenny, A. M., Lingen, M., Kerr, A. R., ... & Scully, C. (2013). Clinical assessment to screen for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults. *Cochrane Database of Systematic Reviews,* 2013(11): CD010173.

15. Wong, T., & Wiesenfeld, D. (2018). Oral Cancer. *Australian Dental Journal,* 63 Suppl 1, S91–S99.

16. Abati, S., Bramati, C., Bondi, S., Lissoni, A., & Trimarchi, M. (2020). Oral Cancer and Precancer: A Narrative Review on the Relevance of Early Diagnosis. *International Journal of Environmental Research and Public Health,* 17(24), 9160.

17. Scully, C., Bagan, J. V., Hopper, C., & Epstein, J. B. (2008). Oral cancer: current and future diagnostic techniques. *Am J Dent,* 21(4), 199-209.

18. Fedele, S. (2009). Diagnostic aids in the screening of oral cancer. *Head & Neck Oncology,* 1(1), 1-6.

19. Gambino, A., Martina, E., Panzarella, V., Ruggiero, T., Haddad, G. E., Broccoletti, R., & Arduino, P. G. (2023). Potential use of optical coherence tomography in oral potentially malignant disorders: in-vivo case series study. *BMC Oral Health,* 23(1), 540.

20. Obade, A. Y., Pandarathodiyil, A. K., Oo, A. L., Warnakulasuriya, S., & Ramanathan, A. (2021). Application of optical coherence tomography to study the structural features of oral mucosa in biopsy tissues of oral dysplasia and carcinomas. *Clinical Oral Investigations,* 25(9), 5411–5419.

21. Cicciù, M., Cervino, G., Fiorillo, L., D'Amico, C., Oteri, G., Troiano, G., Zhurakivska, K., Lo Muzio, L., Herford, A. S., Crimi, S., Bianchi, A., Di Stasio, D., Rullo, R., Laino, G., & Laino, L. (2019). Early Diagnosis on Oral and Potentially Oral Malignant Lesions: A Systematic Review on the VELscope® Fluorescence Method. *Dentistry Journal,* 7(3), 93.

22. McNamara, K. K., Martin, B. D., Evans, E. W., & Kalmar, J. R. (2012). The role of direct visual fluorescent examination (VELscope) in routine screening for potentially malignant oral mucosal lesions. Oral Surgery, Oral Medicine. *Oral Pathology and Oral Radiology,* 114(5), 636–643.