# PREMALIGNANT AND MALIGNANT LESIONS OF THE ORAL MUCOSA AND THEIR IMPACT ON PATIENTS' QUALITY OF LIFE

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**Summary**

*Patient quality of life is an increasingly common concept in the medical world, with the aim of integrating questionnaires on the patient's self-perception of illness and life into therapeutic management. Among the oral mucosal diseases with the most significant impact on quality of life, premalignant and malignant lesions are distinguished, with a prognosis that can influence not only quality of life but also its duration [1]. The majority of oral squamous cell carcinomas develop against the background of premalignant lesions of the oral cavity. A wide range of conditions have been implicated in the development of oral cancer, including leukoplakia, erythroplakia, oral lichen planus, actinic cheilitis, oral submucous fibrosis [2]. Oral mucosal lesions adversely affect quality of life, functional limitation, physical disability and psychological disability leading to social isolation.*

***Keywords:*** *erythroplasia, leukoplakia, lichen planus, squamous cell carcinoma, quality of life.*

*Received: 09.08.2023* *Accepted: 18.09.2023*

## Introduction

The World Health Organization defines quality of life as "each individual's perception of his or her position in life in the context of his or her culture and value system and in relation to his or her goals, expectations, standards and concerns". The need to link the perception of health with that of the ability to perform everyday activities leads to the concept of health-related quality of life. These concepts incorporate self-perception as an important component of health status assessment and promote understanding of how illness interferes with subjects' social lives [1]. Oral potentially malignant diseases (OPMD) are a group of chronic conditions with increased morbidity and mortality due to cancerous changes. Careful monitoring of these lesions by an experienced specialist is recommended to identify any malignant changes in the early stages to reduce the burden of cancer. Patients with OPMD have been documented to have significant health-related symptoms that affect QoL[3].

## Materials and Methods

A comprehensive literature search was conducted using PubMed, Elsevier databases in March 2023 using the terms "premalignant and

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malignant oral lesions" and "quality of life in patients with oral mucosal lesions". Studies and reviews were included if they described oral mucosal diseases and methods to quantify the impact on patients' lives, as well as approaches to their treatment, published in recent years.

## Results

### A. Potentially malignant oral conditions

#### *1. Erythroplasia*

Also called Bowen's disease of the mucous membranes, oral erythroplasia is much less common than genital erythroplasia. Smoking, excessive alcohol consumption, poor hygiene, repeated trauma, old age, human papillomavirus infections have been identified as risk factors for both erythroplasia and leukoplakia. [2] Clinically, it presents as an erythematous, slightly elevated, well-demarcated plaque with a polycyclic, lacquered appearance, asymptomatic, located mainly on the buccal floor. [4] It is less common than leukoplakia, but more likely to present with dysplasia or carcinoma, so any erythroplakia should be biopsied and examined histopathologically[2]. In a case series study, Shafer analysed biopsies of 65 cases of erythroplasia, all of which showed some degree of epithelial dysplasia: 51%-invasive SCC, 40% - carcinoma in situ or severe epithelial dysplasia, and the remaining 9% - mild to moderate dysplasia. There-fore, erythroplasia is a more worrying lesion than leukoplakia. Also, in a mixed erythroleukoplakia, the red component is more likely to show dysplastic changes than the white component; therefore, when choosing the biopsy site in a mixed lesion, the clinician should ensure that the specimen includes the erythematous component [5]. As treatment principles, surgical excision, topical 5-fluorouracil, curettage and electro/cryocautery, radiotherapy, laser therapy have been described. However, relapses are common, no current treatment has proven effective in preventing new lesions, and regular evaluation is essential [2]. Patients with oral potentially malignant disorders (OPMD), including oral leukoplakia and erythroplakia, proliferative verrucous leukoplakia, oral submucous fibrosis and oral lichen planus lesions, can be difficult to manage. A small proportion will undergo malignant development, determining the patient's cancer risk is key to making management decisions.

#### *2. Leukoplakia*

Leukoplakia consists of keratotic, whitish, polycyclic lesions with a shiny, opalescent surface, persistent, adherent, located on the oral mucosa, asymptomatic. It can affect any mucosa, but especially the lips, jugal mucosa, gums, lateral areas of the tongue[4]. Early (thin) leukoplakia appears as a slightly raised greyish-white plaque. As the lesion progresses, it becomes thicker and whiter, sometimes developing a skin-like appearance with fissures on the surface (homogeneous or thick leukoplakia). Some leukoplakia develop surface irregularities and are referred to as granular leukoplakia, others develop a papillary surface (verrucous leukoplakia) [6] Note that leukoplakia is a clinical term and the histopathological appearance is variable. The frequency of dysplastic changes varies between 15-39% in several studies. Malignant transformation occurs after variable intervals (1-20 years).[6] Treatment of leukoplakia includes various methods of excision (surgical, electrocautery, cryotherapy, CO2 laser, photodynamic therapy), topical treatment (5-fluorouracil, anti-inflammatory), systemic (vitamin A, beta-carotene), along with suppression of risk factors (smoking, alcohol consumption) and periodic re-evaluation. [4] In 2016, Lodi concludes that data on the treatment of leukoplakia are limited, therapies are effective but relapses and adverse effects are common[7].

In 2019, the first data from Australia on the quality of life of people with oral leukoplakia are published. Using both the Short Generic Health Questionnaire (SF-12) and the OPMD Questionnaire (OPMDQ), subjects reported poorer quality of life. compared to control individuals, in relation to age, gender, smoking and alcohol consumption. In 2023, 41 individuals with leukoplakia were interviewed based on the SF-12 and OPMDQ at four time points: at clinical diagnosis, at post-biopsy review, (confirmed diagnosis) and at 3- and 6-month follow-up controls. Results showed no significant differences in SF-12 scores over time. An overall

improvement in participants' quality of life was evident over the 6-month period investigated in the domains of psychological and social well-being and effect of treatment on daily life, as well as in the total OPMDQ score. Age, gender, medical condition, tobacco/alcohol use, lesion location, size, presence of dysplasia and treatment did not affect QoL scores over time[29].

***3. Actinic cheilitis***

It is considered a premalignant lesion, with the possibility of progression to squamous cell carcinoma in 6-10% of cases. It is predominantly located on the lower lip as a result of long-term exposure to UV radiation. [3] Clinically, the lesion progresses from a semi-mucous with a dry and scaly character, to accentuated hyperkeratosis, painful fissures, repeated bleeding, to deep fissures, hard-to-heal ulcerations, hyperkeratotic blocks. Usually asymptomatic, may manifest with pain, burning, anaesthesia. Histopathological examination reveals hyperkeratosis, solar elastosis, epithelial dysplasia of various degrees, perivascular inflammation. Both surgical (excisional vermilionectomy, cryotherapy, electrocautery, CO2 laser) and non-surgical methods (5-fluorouracil, imiquimod, trichloroacetic acid, phototherapy, DNA repair enzyme creams) are used for treatment [8]. A systematic review and meta-analysis (on 283 patients) showed that surgically treated lesions have a higher remission rate than non-surgically treated lesions (92.8% vs 65%) and lower recurrence rates (8.4 vs 19.2%)[8]. A 2021 systematic review of 699 patients shows that invasive therapies (partial surgery and laser treatments) had the best cosmetic and therapeutic results with few recurrences. Photodynamic therapy showed satisfactory results, while topical treatments were the least beneficial. The efficacy of photodynamic therapy was improved when combined with imiquimod 5%. When actinic cheilitis is treated, there is no risk of cancer progression. Larger studies are needed to confirm these results.[10] Another systematic review from 2022, which included 512 patients treated with laser concludes that laser therapy showed complete clearance of actinic cheilitis in 92.5% of patients (recurrence rate of 21.43%). Furthermore, it observed a very low frequency of malignant transformation after treatment (detected in only 3 of the 20 studies reviewed). Cosmetic results and patient satisfaction were also described as excellent in most studies. Laser therapy also shows superior results to treatment with topical anti-inflammatory and anti-neoplastic agents. However, there are no established treatment protocols regarding the physical parameters of the laser or the number of sessions required for correct treatment [11].

***4. Oral lichen planus***

Chronic inflammatory disease of the oral mucosa, predominantly affecting women over 50 years of age, with bilateral symmetrical distribution. Clinically 6 types have been described: reticular, papular, plaque, atrophic/erosive, ulcerative, bullous. [6] The reticular form has a whitish network appearance (Wickham's stripe), often located on the posterior buccal mucosa bilaterally. The plaque form is often located on the dorsal aspect of the tongue and is difficult to differentiate from leukoplakia. The papular form is characterized by the formation of papules, often on reticular lesions. The atrophic/erosive form is difficult to separate clinically, both manifesting as erythematous, atrophic lesions with fine, white, radiating streaks at the periphery. The appearance of an ulceration gives the ulcerative form, and the formation of bullae/broad epithelial separation - the bullous form. [12] In the current medical literature there are several reports of squamous cell carcinomas developed on the site of previous OPL lesions. However, there is ongoing debate about the possible premalignant nature of LPO. Results of studies examining malignant potential have varied significantly (reported malignant transformation rate ranging from 0% to 12.5%) [13]. It is still controversial whether biopsy should be performed for every OPL lesion. For erosive lesions, biopsy should be performed especially for those lesions with suspected dysplastic changes.[6] As treatment, corticosteroid ointment or spray is recommended in case of pain, burning, inflammation. For large, severe lesions, Triamcinolone is used intralesionally, along with oral Prednisolone. Severe multifocal lesions with ulceration advocate increasing the dose of Prednisolone. The combination of Levamisole, oral Prednisolone and Dexamethasone in orobase

has also been described in the literature [13]. The burden of LPO on patients' daily lives has been explored using qualitative methods to a limited extent. Studies demonstrate the association of OPL with oral discomfort and difficulty in eating, performing oral hygiene and speaking, as well as negative psychological consequences due to unpredictable clinical behaviour, chronicity and the potential for malignant transformation. A qualitative study using groups of patients with OPL highlights symptoms and triggers for exacerbation. The authors included patients from Ireland and the USA and defined triggers that contribute to pain in patients with OPL: tooth brushing, food intake, fluid intake, smiling, mouth breathing, talking and touching.[14] A study by Suliman et al. highlighted that oral health in patients with symptomatic lichen planus is associated with reduced quality of life compared to asymptomatic forms. Another similar result was obtained in the study by McGrath et al. which showed that patients with ulcer, erosions had lower levels of quality of life compared to asymptomatic patients. In 2021, in a study investigating the quality of life of patients treated for OPMD several patients reported experiencing severe pain (15.3%), burning sensation when eating spicy foods (36%), difficulty opening the mouth (15.3%), change in taste sensation (36.8%), limitation in eating desired foods (24.5%) and dry mouth (7.1%). Many patients felt very frustrated, depressed (9.2%) and reported that their condition affected their satisfaction with life (19.4%). However, no social relationships were affected nor did it add to their discomfort at social events or gatherings. Their main concern was the likelihood of progression to malignancy[27].

**B. Malignant lesions of the oral mucosa**

More than 90% of cases are squamous cell carcinomas, less than 10% - melanoma, lymphoma, salivary gland tumours[1]. Signs and symptoms raising suspicion of oral cancer are: persistent sores or pain, localised changes in mucosal appearance/consistency, persistent or growing formation, localised bleeding. Early disease may manifest as irregular white, red or mixed macules on the mucosa, more advanced ones appear as an elevated indurated nodule, often with an ulcerated surface. Local or systemic spread may result in dysphagia, odynophagia, dysphonia, otalgia, weight loss and lymphadenopathy. [6]

***1. Oral squamous cell carcinoma (OSCC)***

The first clinical sign may be a persistent fissure/small erosion/ulceration that bleeds slightly, often located on the tongue or the buccal floor. May become large, conopidiform, foul-smelling due to superinfection. [2] Accumulation of successive mutations causes epithelial changes preceding transformation to invasive carcinoma. Except in the case of very poorly differentiated tumours, the prototypic histological features are fairly constant[16]. Oral florid papillomatosis (OFP) represents the formation of multiple verrucous and papillomatous growths that converge to form plaques and vegetations. More common in male smokers aged 60-70 years, it is considered a low-grade malignant variant of verrucous CSC of the oral mucosa. It can sometimes develop areas of invasive carcinoma, requiring close monitoring and treatment aimed at definitive resolution[5]. POF treatment is eminently surgical by excision, electrocoagulation and CO2 laser, liquid nitrogen cryotherapy, chemotherapeutic agents, cytostatics and topical immunomodulators (retinoids, salicylic acid, trichloroacetic acid, podophyllin, podophyllotoxin, 5-fluoruracil)[2]. In 2022, Pedro et al describe treatment with imiquimod 5% in orabase on alternate days for 16 weeks supplemented with hyaluronic acid gel application [18]. In a 2021 study, 135 patients with CSCO were grouped according to treatment: surgery only, post-surgical radiotherapy (PRT) and post-surgical chemo-radiotherapy (PCRT). 12 Short Form Health Survey (SF-12) and Oral Health Impact Profile-14 (OHIP-14) items were used to assess HRQoL (general health-related quality of life) and OHRQoL (oral health-related) at 1 month and 6 months post-treatment, respectively. Results show that at 1 month post-treatment, patients who received PCRT had significantly lower mean values for the physical and mental domains of the SF-12 and higher mean values of the OHIP-14 subscale and overall score than those treated with surgery and PRT alone. Social

functioning, general health and bodily pain in the SF-12 and functional limitations, physical pain and physical disability among the OHIP-14 domains were highly affected. Although some physical domains in SF-12 showed significant improvement, mental domains remained a significant problem even after 6 months. However, OHRQoL was significantly reduced in all three study groups. [19] Given the high mortality rate, early detection results in better prognosis and survival rates and lower morbidity following treatment. [17] The first line of treatment for oral cancers is surgical excision, the aim being curative treatment with as few functional and aesthetic sequelae as possible. Combination with chemotherapy/radiotherapy can improve the chances in advanced stage patients. Surgical interventions range from simple wide local excision and primary closure to complex tongue/mouth/mandible resections with the need for locoregional flaps or microvascular free flap reconstruction. [5]. Although these invasive approaches may impose significant risks, removal of oral cancers is undoubtedly associated with improved patient outcomes. A 2020 study in Indonesia included 21 patients who were diagnosed with stage 3-4 oral CSC and about to undergo surgery. Results showed a significant decrease in postoperative oral pain and anxiety levels, while postoperative patient quality of life was significantly increased. Despite the invasive procedure that could cause postoperative effect, oral CSC patients in the study showed better quality of life after cancer removal[26]. Immunotherapeutic agents, particularly tyrosine kinase inhibitors and PD-1 inhibitors, are now used in combination with cisplatin-based chemotherapy or as monotherapy [19]. A 2021 study evaluated Adenovirus-p53 gene therapy, based on the observation that P-53 (tumor suppressor gene) mutations were identified in most cases of OPL and OSCC. Restoration of p53 function using recombinant p53 with adenovirus as delivery system resulted in complete tumor regression in murine models and cell lines. Approved in China in 2003, it has been shown to be effective alone and in combination with standard oral cancer and LPO regimens. However, a lack of studies in populations other than Chinese limits its potential. [18] Chemotherapy includes a wide range of agents: cisplatin, nitrosourea, dacarbazine, IL-2 immunotherapy, Imatinib, Dabrafenib and vemurafenib. [19] In terms of progrnostic, Chaudhry et al. reported that the median life span from diagnosis was approximately 18 months. Sampat and Sirsates reported that 79% of patients died within 5 years. In addition, Vairaktaris et al. showed that the 5-year survival rate of intraoral melanoma does not exceed 5-9% [21].

***2. Oral melanoma***

Oral melanoma is a very rare malignancy that progresses rapidly and is particularly aggressive. It accounts for 0.2% to 8% of all melanomas and 1-2% of all oral malignancies. Compared to other melanomas, mucosal ones have the lowest 5-year survival rate. [6] It usually presents as a brownish-brown macule or nodular lesion with varying shades of grey, red, purple or areas of depigmentation. Amelanotic lesions have also been reported. The aetiology, risk factors and pathogenesis of oral melanoma remain poorly understood. Primary melanomas of the oral mucosa mainly arise de novo, but up to 37% are preceded by pigmented lesions, persisting from months to years. Prosthetic irritation, infections and smoking have been listed as possible risk factors, but a direct relationship is not substantiated. For amelanotic oral melanoma, the absence of pigmentation is a diagnostic challenge, leading to delayed diagnosis, intrinsic aggressiveness with poor prognosis. Due to the rarity of the neoplasm, few case reports and almost no series have been published to date. As a result, it has been difficult to establish valuable data related to the quality of life of these patients.

## Discussions

Patients with oral mucosal disease have higher levels of anxiety, depression and lower quality of life. Psychological problems are related to their quality of life, suggesting that the psychological state of patients with oral mucosal lesions requires more attention from clinicians. [22] In an Arab population, mucocutaneous diseases with oral mucosal manifestations were reported to negatively affect quality of life scores, with the degree of impact directly related to the

number of oral lesions. A very strong negative impact on HRQoL has been reported in subjects suffering from burning mouth syndrome, who always show the worst scores regardless of the instru-ment used to measure QL(23). Another study in 2021 showed that pain and discomfort are patients' main experience in everyday life, affecting some aspects of lifestyle, such as dietary changes and restrictions in consumption of certain drinks and foods. Oral pain and functional limitations can interfere with social activities, causing embarrassment to patients. The unpredictable nature of premalignant and malignant lesions leads to frustration, self-doubt and uncertainty about the patient's future life. Those with lichen planus and leukoplakia had concerns about the malignant potential of the disease, and other patients had concerns about progression of the lesions [24]. In 2023, Rawan publishes a study in which quality of life scores in those with potentially malignant lesions were assessed and compared. The conclusion from the evaluation of 100 patients was that those with OPL had significantly higher scores than those with epithelial dysplasia, with those aged 40-64 being particularly affected. Independent factors leading to worsening quality of life were: intense pain, higher levels of stress and anxiety, use of topical corticosteroids. [24]

## Conclusions

A premalignant or malignant condition of the oral mucosa results in a deficiency; which in turn produces a disability and therefore affects daily activities on a regular basis. Oral cancer is predominantly a disease of the elderly, and for those with known epidemiological risk factors, there is sufficient time for examination of patients to detect precursor lesions and institute treatment before malignancy develops. Therefore, a healthy oral mucosa will contribute to the patient's well-being and contribute to their personal satisfaction and happiness.

## Bibliography


1. Kumar, Kapila et al. "Quality of life among Oral Potentially Malignant Disorder (OPMD) patients: A prospective study." *Journal of oral biology and craniofacial research* vol. 11,1, 88-91 (2021).
2. Abati S, Bramati C, Bondi S, Lissoni A, Oral Cancer and Precancer: A Narrative Review on the Relevance of Early Diagnosis. Int J Environ Res Public Health. 2020 Dec 8.
3. Gondivkar, Shailesh M et al. "Quality of life and oral potentially malignant disorders: Critical appraisal and prospects." *World journal of clinical oncology* vol. 9,4 (2018).
4. Pătrașcu, V., 2020. *Boli dermatologice și infecții sexual-transmisibile*. 5th ed. Craiova.
5. Waldron CA, Shafer WG. Leukoplakia revisited: A clinicopathologic study of 3256 oral leukoplakias. Cancer, 1975.
6. Neville, Brad W, and Terry A Day. "Oral cancer and precancerous lesions."(2002).
7. Lodi, Giovanni et al. "Interventions for treating oral leukoplakia to prevent oral cancer." *The Cochrane database of systematic reviews* vol. 7,7 CD001829. 29 Jul. 2016.
8. Muse, Mikel E. and Jonathan S. Crane. "Actinic Cheilitis." *StatPearls*, StatPearls Publishing, 22 September 2022.
9. Lai, Michela et al. "Treatments of actinic cheilitis: A systematic review of the literature." *Journal of the American Academy of Dermatology* vol. 83,3 (2020).
10. Bakirtzi, Katerina et al. "Treatment Options and Post-Treatment Malignant Transformation Rate of Actinic Cheilitis: A Systematic Review." *Cancers* vol. 13,13 3354. 4 Jul. 2021.
11. Ayen-Rodriguez, Angela et al. "Laser Therapy for the Treatment of Actinic Cheilitis: A Systematic Review." *International journal of environmental research and public health* vol. 19,8 4593. 11 Apr. 2022.
12. Rotaru, Doina Iulia et al. "Diagnostic Criteria of Oral Lichen Planus: A Narrative Review." *Acta clinica Croatica* vol. 59,3 (2020).
13. Chiang CP, Yu-Fong Chang J, Wang YP. Oral lichen planus - Differential diagnoses, serum autoantibodies, hematinic deficiencies, and management. J Formos Med Assoc. 2018.
14. López-Pintor, Rosa María et al. "World Workshop on Oral Medicine VIII: development of a core outcome set for oral lichen planus: a systematic review of outcome domains." *Oral surgery, oral medicine, oral pathology and oral radiology*, S2212-4403(23)00070-6. 3 Mar. 2023.

15. Wollina, Uwe et al. "Oral submucous fibrosis: an update." *Clinical, cosmetic and investigational dermatology* vol. 8 193-204. 13 Apr. 2015.
16. Watters, Carolina, et al. "Oral Mucosa Cancer." StatPearls, StatPearls Publishing, 10 June 2022.
17. Gonzalez, Mario. and Antonio Riera March. "Tongue Cancer." *StatPearls*, StatPearls Publishing, 13 September 2022.
18. Ruiz-Huertas, Pedro et al. "Oral florid papillomatosis: Topical treatment with 5% imiquimod in orabase." *Clinical and experimental dental research* vol. 8,4 (2022).
19. Shailesh M. Gondivkar, et al. "Oral and general health-related quality of life in oral squamous cell carcinoma patients- comparative analysis of different treatment regims", Journal of Oral Biology and Craniofacial Research, vol 11,2, (2021).
20. Zito, Patrick M., et al. "Oral Melanoma." *StatPearls*, StatPearls Publishing, 25 September 2022.
21. Hosmani, Jagadish et al. "Recombinant Human Adenovirus-*p53* Therapy for the Treatment of Oral Leukoplakia and Oral Squamous Cell Carcinoma: A Systematic Review." *Medicina (Kaunas, Lithuania)* vol. 57,5 438. 1 May. 2021
22. Aloua, Rachid et al. "Melanoma of the oral cavity: A silent killer." *Annals of medicine and surgery (2012)* vol. 62 182-185. 18 Jan. 2021.
23. Yang, C., Liu, L., Shi, H. *et al.* Psychological problems and quality of life of patients with oral mucosal diseases: a preliminary study in Chinese population. *BMC Oral Health* 18, 226 (2018).
24. Amir Reza Gandjalikhan Nassab ,et al. "Quality of Life in Patients with Chronic Oral Mucosal Conditions: A Qualitative Research". Pesquisa Brasileira em Odontopediatria e Clínica Integrada 2021.
25. Ashshi, Rawan A et al. "Quality of life in patients with oral potentially malignant disorders: oral lichen planus and oral epithelial dysplasia." *Oral surgery, oral medicine, oral pathology and oral radiology* vol. 135,3 363-371 (2023.)
26. Sjamsudin, Endang et al. "Assessment of oral cancer pain, anxiety, and quality of life of oral squamous cell carcinoma patients with invasive treatment procedure." *Oral and maxillofacial surgery* vol. 22,1 (2020): 83-90.
27. Kapur, Neharika et al. "Evaluation of quality of life in patients surgically treated for potentially malignant oral lesions." *Indian journal of cancer* vol. 58,3 (2021).
28. Frydrych, Agnieszka M et al. "Changes in quality of life over time in patients diagnosed with oral leukoplakia: A prospective longitudinal study." *Journal of oral pathology & medicine : official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology* vol. 52,3 (2023): 226-231.

Conflict of interest
NONE DECLARED

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