EGAS MONIZ SCHOOL of HEALTH & SCIENCE | INSTITUTO UNIVERSITÁRIO EGAS MONIZ

INSTITUTO UNIVERSITÁRIO EGAS MONIZ

MESTRADO INTEGRADO EM MEDICINA DENTÁRIA

RECURRENCE RATES OF ORAL LEUKOPLAKIA: A RETROSPECTIVE STUDY ON A PORTUGUESE POPULATION

Trabalho submetido por
Mafalda Baptista Dias Antunes
para a obtenção do grau de Mestre em Medicina Dentária

outubro de 2024

EGAS MONIZ SCHOOL of HEALTH & SCIENCE | INSTITUTO UNIVERSITÁRIO EGAS MONIZ

INSTITUTO UNIVERSITÁRIO EGAS MONIZ

MESTRADO INTEGRADO EM MEDICINA DENTÁRIA

RECURRENCE RATES OF ORAL LEUKOPLAKIA: A RETROSPECTIVE STUDY ON A PORTUGUESE POPULATION

Trabalho submetido por
Mafalda Baptista Dias Antunes
para a obtenção do grau de **Mestre** em Medicina Dentária

Trabalho orientado por
Mestre Pedro Trancoso

outubro de 2024

EGAS MONIZ SCHOOL of HEALTH & SCIENCE | INSTITUTO UNIVERSITÁRIO EGAS MONIZ

INSTITUTO UNIVERSITÁRIO EGAS MONIZ

MESTRADO INTEGRADO EM MEDICINA DENTÁRIA

RECURRENCE RATES OF ORAL LEUKOPLAKIA: A RETROSPECTIVE STUDY ON A PORTUGUESE POPULATION

Trabalho submetido por
Mafalda Baptista Dias Antunes
para a obtenção do grau de **Mestre** em Medicina Dentária

Trabalho orientado por
Mestre Pedro Trancoso

e coorientado por
Mestre Paulo Mascarenhas

outubro de 2024

AGRADECIMENTOS

Ao meu orientador, Prof. Doutor Pedro Trancoso, manifesto o meu mais profundo agradecimento por ter confiado em mim desde o início deste percurso. A sua disponibilidade constante e o seu compromisso foram fundamentais para a concretização deste trabalho. Agradeço não só pelos valiosos ensinamentos, mas também pela exigência que mostrou neste trabalho.

Ao meu coorientador, Prof. Doutor Paulo Mascarenhas, sou imensamente grata pelo apoio incondicional, mesmo nos momentos de maior incerteza. A sua experiência, e a serenidade que transmite foram essenciais ao longo deste processo. Obrigada por me ajudar ao longo deste trabalho, e por me incentivar a nunca perder de vista os meus objetivos.

Ao Instituto Universitário Egas Moniz, minha casa ao longo destes cinco anos, deixo um agradecimento especial. Foi aqui que vivi experiências transformadoras, momentos de alegria e superação. A todos os professores, colaboradores e colegas que tornaram esta caminhada possível, expresso a minha gratidão por fazerem deste lugar um espaço de excelência e acolhimento.

À minha mãe, meu porto seguro, agradeço do fundo do coração. A sua fé inabalável em mim e o seu apoio foram a minha maior força ao longo desta jornada. Ao meu pai, por me dar a certeza de que posso ir sempre mais longe. E ao meu avô, Dr. Aires Martins, a quem devo a concretização deste sonho, deixo o meu reconhecimento e amor eternos.

Por fim, aos meus amigos, quero expressar um agradecimento sincero. O vosso companheirismo, amizade e apoio foram indispensáveis e tornaram este percurso muito mais leve e gratificante.

Resumo

Objetivo: Avaliar a taxa de recorrência de leucoplasia oral e os fatores de risco associados, incluindo características epidemiológicas, clínicas e histopatológicas, em pacientes de uma clínica de Medicina e Cirurgia Oral em Portugal.

Materiais e métodos: Foi realizada uma análise retrospetiva de registos clínicos de leucoplasia oral desde 1992. Foram recolhidos dados sobre sexo, idade, localização da lesão, diagnóstico clínico e histopatológico, grau de displasia, tratamento e fatores de risco como consumo de tabaco e patologias sistémicas. Critérios de exclusão incluíram registos insuficientes, diagnósticos inconclusivos ou lesões brancas não diagnosticadas como leucoplasia. Os dados foram analisados entre outubro e dezembro de 2023.

Resultados: A taxa de recorrência foi de 36,4%, com a maioria dos casos apresentando uma ou duas recorrências; múltiplas recorrências foram menos comuns. A transformação maligna ocorreu em 3,0% dos casos. A idade média dos pacientes foi de 59,11 anos. A idade mostrou-se um fator de risco fraco, com aumento de 6,5% para recorrências múltiplas. As doenças respiratórias aumentaram o risco de recorrências múltiplas em 12,7 vezes. Patologias imunológicas mostraram um aumento do risco de recorrência em 9,35 vezes. Não fumadores apresentaram um risco de recidiva 16,6 vezes maior que os fumadores.

Conclusão: A recorrência de leucoplasia oral ocorreu em 36,4% dos pacientes, com a maioria tendo uma ou duas recorrências. Doenças respiratórias foram um fator de risco significativo para múltiplas recorrências, enquanto doenças imunológicas e o tabagismo também influenciaram o risco de recorrência da lesão . Contudo, o tabagismo não foi um fator determinante neste grupo. O estudo destaca a necessidade de monitorização cuidadosa e mais pesquisas para entender melhor os fatores de risco e recorrência da leucoplasia oral.

Palavras-chave: Leucoplasia oral, recorrência, estudo retrospetivo, patologia oral

Abstract

Objective: To evaluate the recurrence rate of oral leukoplakia over time and the associated risk factors, including epidemiological, clinical and histopathological characteristics, in patients from an Oral Medicine and Surgery clinic in Portugal.

Materials and methods: A retrospective analysis of clinical records of oral leukoplakia since 1992 was carried out. Data was extracted on gender, age, lesion location, clinical and histopathological diagnosis, degree of dysplasia, treatment and risk factors such as tobacco consumption and systemic pathologies. Exclusion criteria included insufficient records, inconclusive diagnoses or white lesions not diagnosed as leukoplakia. The data was analysed between October and December 2023.

Results: The recurrence rate was 36.4 %, with most cases present with a single or double recurrence, while multiple recurrences were relatively uncommon. Malignant transformation occurred in 3.0 per cent of cases. The average age of the patients was 59.11 years. Age was identified as a weak risk factor for multiple recurrences, with an associated increase of about 6.5% and respiratory diseases increase the risk multiple recurrences of oral leukoplakia in 12.7 times when present. Immunological pathologies showed an increased the risk of recurrence by 9.35 times. Compared to smokers, non-smokers showed an average increase in the risk of recurrence of around 16.6 times.

Conclusion: The recurrence of oral leukoplakia was observed in 36.4% of patients, with the majority presenting one or two recurrences. Respiratory diseases were identified as a significant risk factor for multiple recurrences, with an estimated odds ratio of 12.7. Other factors, including immunological diseases and smoking habits, were also found to influence the risk of recurrence. The study highlights the importance of close monitoring and underscores the need for further research to enhance understanding of the risk factors and recurrence of OL.

Keywords: Oral leukoplakia, recurrence, retrospective study, oral pathology

INDEX

INDEX OF FIGURES

INDEX OF GRAPH

INDEX OF TABLES

LIST OF ABBREVIATIONS

ARK - Alveolar ridge keratosis

CI - Confidence interval

DNA - Deoxyribonucleic acid

EBV - Epstein-Barr Virus

HIV - Human immunodeficiency virus

HPV - Human papillomavirus

KUS - Keratoses of unknown significance

MT - Malignant transformation

OHL - Oral hairy leukoplakia

OL - Oral leukoplakia

OPMP - Oral potentially malignant disorders

OSCC - Oral squamous cell cancer

OR - Odds ratio

PVL - Proliferative verrucous leukoplakia

UV - Ultraviolet

WHO - World health organization

I.INTRODUCTION

1.1. Concept of oral leukoplakia

The initial definition of the concept was established by the World Health Organization (WHO) in 1978, defining it as a white spot or plaque that cannot be clinically or pathologically characterised as any other disease (WHO, 1978). Subsequently, at the First International Conference on Oral Leukoplakia in 1984, the definition was revised to describe it as a white patch or plaque that cannot be clinically or pathologically characterised as any other disease and is not associated with any physical or chemical causative agent except tobacco use (Axell et al., 1984). At the 1996 International Symposium, the term was defined as a predominantly white lesion of the oral mucosa that cannot be characterised as any other definable disease and in 1997 the WHO followed the latest update stating that it is a predominantly white lesion of the oral mucosa that cannot be characterised as any other definable lesion, emphasising the change to the term 'lesion' instead of the previous 'disease' (Axéll et al., 1996).

Finally, the most recent definition from the WHO Collaborating Centre was "A predominantly white plaque of questionable risk after excluding (other) known diseases or disorders that do not confer an increased risk of cancer (Warnakulasuriya et al., 2007). During the latter meeting it has deliberately been decided to consider leukoplakia a potentially malignant- premalignant and precancerous are equivalent adjectives- disease and not a lesion since it is well known that cancer development not always occurs in or close to the leukoplakia but may also occur at other sites in the oral cavity or the head-and-neck region (Warnakulasuriya et al., 2007).

This oral lesion may present with atrophy or hyperplasia (acanthosis) and may or may not demonstrate epithelial dysplasia (Warnakulasuriya et al., 2007).

It is important to note that the term "leukoplakia" is used as a clinical diagnosis having excluded other clinically recognizable white or white/red lesions (Warnakulasuriya, 2019).

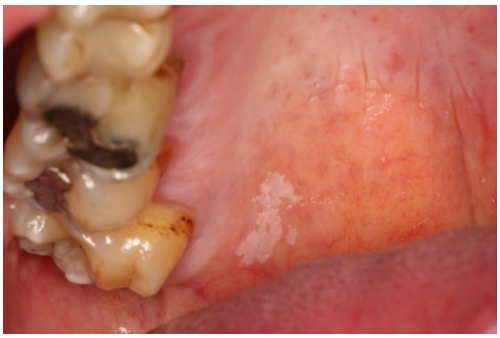


Figure 1- Oral leukoplakia (image provided by António Mano Azul and Pedro Trancoso)

1.2. Clinical Prevalence

Among the oral potentially malignant disorders, oral leukoplakia (OL) is the most frequently encountered entity in clinical practice. The global prevalence of oral leukoplakia has been estimated at 2.60% (Warnakulasuriya & Ariyawardana, 2016).

Although leukoplakia can affect both men and women of all ethnicities, it is more common in men, with a ratio of approximately 3:1, and the peak age of diagnosis is typically between the ages of 40 and 49, as consistently reported in various studies (Warnakulasuriya, 2019).

Population-based studies show that the prevalence of oral leukoplakia (OL) varies between continents, ranging from 2.53% in Asia to 0.33% in North America. The overall prevalence is 1.39%, with a global estimate of 3.41%. Prevalence rates vary widely within continents, ranging from 0.33% to 11.74%. A higher pooled estimated prevalence was found among males, smokers, and alcohol consumers (Mohammed & Fairozekhan, 2023; Zhang et al., 2023).

A study was conducted in Portugal (Porto) involving 727 people (277 men and 450 women) with an average age of 54 years old (ranging from 18 to 94). Participants were recruited through a mass media campaign and dental visits to a public hospital in Porto. Among those screened, 22 cases of potentially malignant disorders (OPMDs) were

reported, the majority of which were oral leukoplakia, accounting for 13 cases (59.1%) (Monteiro et al., 2014).

In addition, a 17-year retrospective study was conducted at the University Dental Clinic of the Portuguese Catholic University in Viseu. The study found that the prevalence of oral leukoplakia among attendants of the clinic was 12.09% (Aldagistani, 2022).

From a total sample of 1448 patients whose biopsies were analyzed in a Portuguese population over a period of 20 years, it was reported that among potentially malignant oral conditions, leukoplakia was the most commonly diagnosed (48.7%) (de Almeida et al., 2022).

	Sample size	Prevalence (n)	Prevalence %	Location	Year of publication	Data collection period
Monteiro et al., (2014).	727	13	1,78	Porto	2014	2010-2011
Aldagistani, (2022).	96	11	12,09	Viseu	2022	2004-2021
Almeida et al., (2022)	1448	135	9,33	Lisbon	2022	1990-2019

Table 1-Portuguese studies on oral leukoplakia in clinical samples in Portugal

1.3. Aetiology

The aetiology of oral leukoplakia is unknown being idiopathic in most cases, with the most commonly associated risk factor being the use of tobacco, either smoked or smokeless (Mohammed & Fairozekhan, 2023).

1.3.1. Tobacco

The most predominant risk factor associated with oral leukoplakia is the use of tobacco, whether smoked or smokeless, and this includes various forms of tobacco such as cigars, cigarettes, beedis and pipes (Mohammed & Fairozekhan, 2023).

In addition, compared to non-smokers, smokers are six times more likely to develop leukoplakia (van der Waal, 2009).

Oral leukoplakia and oral cancer share similar risk factors, including tobacco smoking, heavy alcohol consumption, betel nut chewing, older age (Villa & Sonis, 2018).

A Swedish study in which people with oral leukoplakia who were smokers were encouraged to quit showed that leukoplakia in smokers showed signs of reversal when smoking was either reduced or stopped altogether. Similarly, in a 10-year follow-up study in India, cessation of tobacco use led to a substantial fall in the incidence of oral leukoplakia (Warnakulasuriya et al., 2010) . These findings underscore the positive impact of smoking cessation on the regression and prevention of oral leukoplakia and highlight the importance of smoking cessation efforts in reducing the burden of this pathology.

As these patients may have a more aggressive natural history, it is important to document whether the patient with leukoplakia is a non-smoker (Warnakulasuriya, 2020).

1.3.2. Alcohol

There is no consensus in the literature on the influence of alcohol on the development and aetiology of oral leukoplakia.

Although various studies have explored potential risk factors for oral leukoplakia beyond tobacco use, none have demonstrated consistent and conclusive evidence. For example, while some research, such as - (Thomas et al., 2003), suggests that alcohol consumption might increase the risk of oral leukoplakia by 1.5 times, other studies have not found a

significant association. This discrepancy may stem from differences in study design or insufficient control for confounding factors like tobacco use (Hashibe et al., 2000).

1.3.3.HPV

The role of human papillomavirus (HPV) infection in oral squamous cell carcinoma (OSCC) and oral leukoplakia (OL) remains unclear, with conflicting results between studies (van der Waal, 2009).

While some evidence suggests that HPV, particularly types 16 and 18, may contribute to head and neck tumours, including OSCC, its exact role in oral malignancies is controversial, with studies showing different prevalence rates of HPV in OL and OSCC, and specific HPV genotypes have not been thoroughly investigated in OL (Yang et al., 2019).

Regarding the possible association of viruses such as HPV and Epstein Barr virus (EBV) with leukoplakia, the evidence remains inconclusive Bhargava et al., (2016), highlighting the need to re-evaluate the association of HPV with oral leukoplakia using consensus HPV primers.

In conclusion, although there are conflicting findings, some studies have indicated a potential correlation between HPV infection and OSCC and OPMD, highlighting the necessity for further investigation to elucidate this relationship and its implications for prevention and treatment strategies (van der Waal, 2009).

1.3.4. Candida

Candida albicans has the capacity to colonise the oral mucosal epithelium, which can result in the formation of a thick white plaque, medically termed "Candida leukoplakia" or "Candida hyperplasia". It remains uncertain whether there is a direct causal relationship between Candida and the development of epithelial dysplasia, or whether the fungus merely infects mucosa that has already undergone alteration (Aldagistani, 2022).

1.4. Clinical Diagnosis

Leukoplakia is a clinical term that is usually modified based on histopathological examination (Villa & Sonis, 2018). Consequently, the diagnosis of oral leukoplakia is dependent upon an expert oral clinicopathological examination.

A provisional diagnosis of leukoplakia is made when a predominantly white lesion on clinical examination cannot be clearly diagnosed as another disease or disorder of the oral mucosa (Warnakulasuriya et al., 2007). A diagnostic biopsy is indicated to confirm or modify this clinical diagnosis (i.e. oral lichen planus or hyperplastic candidosis) (Warnakulasuriya et al., 2020).

Clinically, leukoplakia can be broadly divided into homogeneous and non-homogeneous sub-groups based on color and morphology (thickness and texture) (Kumari et al., 2022; Villa & Sonis, 2018; Warnakulasuriya, Kujan, Aguirre-Urizar, et al., 2021).

The following criteria should be considered when making a clinical diagnosis of oral leukoplakia:
- A predominantly white patch/plaque that cannot be rubbed off. (Warnakulasuriya et al, 2020)
- No evidence of chronic traumatic irritation of the area (e.g., a sharp tooth rubbing against the tongue, a white patch on the alveolar ridge or retromolar pad from masticatory friction, a white patch on the gingiva from overzealous tooth brushing). (Warnakulasuriya et al, 2020)
- Is not reversible on removal of apparent traumatic causes, i.e. shows a persistent feature. (Warnakulasuriya et al., 2020)
- Does not disappear or fade with stretching (retraction) of the tissue.(Warnakulasuriya et al., 2020)
- By exclusion of other white or white/red lesions (Warnakulasuriya et al., 2020)
A patch of oral leukoplakia may vary in size from a quite small and circumscribed area to an extensive lesion involving a large area of the oral mucosa. (Warnakulasuriya, 2018)

Clinically, leukoplakia can be broadly divided into homogeneous and non-homogeneous sub-groups based on color and morphology (thickness and texture). (Kumari et al., 2022; Villa & Sonis, 2018):

- Homogeneous leukoplakia affects a circumscribed area and has well defined borders. A smaller subset may present with diffuse borders(Warnakulasuriya, 2018)

- Non-homogeneous leukoplakia typically present with more diffuse borders and may have red or nodular components. They are characterised by areas of erythema and areas of nodularity and verrucousity(Villa & Sonis, 2018). Non-homogeneous leukoplakia statistically carry a higher risk of malignant transformation (Carrard & Van Der Waal, 2018).

Non-homogeneous varieties comprise 3 clinical types and are usually symptomatic: Speckled-mixed, white and red in colour (also called erythroleukoplakia), but retaining predominantly white colour; Nodular-small polypoid projections, rounded, red or white prominences; Verrucous or exophytic - wrinkled or rippled surface appearance (Warnakulasuriya, 2018; Warnakulasuriya et al., 2007).

Leukoplakia is rarely multiple and rarely covers an extensive area of the mouth, and in contrast, one type of leukoplakia, called proliferative verrucous leukoplakia, is widespread and can affect multiple oral sites (Warnakulasuriya, 2019). Oral proliferative verrucous leukoplakia (PVL) is a distinct subtype of non-homogeneous leukoplakia that may involve a single large site, but is often multifocal, and often occurs on the gingiva, buccal mucosa, and tongue in both contiguous and non-contiguous areas of the oral cavity(Villa & Sonis, 2018). The main clinical criteria include (1) leukoplakic lesion with more than 2 oral sites, most commonly the gingiva, alveolar processes and palate, (2) presence of a verrucous area, (3) lesions that have spread or engulfed during the course of the disease, and (4) recurrence in a previously treated area (Warnakulasuriya, 2018). In addition to being multifocal and progressive, the lesion is characterised by a high rate of recurrence and malignant transformation (Pinto et al., 2020).PVL appears to be more common in older women and is usually not associated with tobacco smoking (van der Waal, 2009; Warnakulasuriya, 2018).

In a retrospective review of 1,676 clinically diagnosed oral lesions (OL), the majority of lesions were located on the tongue (28%), followed by the buccal mucosa (19%), the mandibular sulcus (15%), the palate (13%), the maxillary sulcus (11%), the floor of the mouth (11%), and the labial mucosa (2%) (Jones & Jordan, 2015).

In general, all cases of leukoplakia should be biopsied. In the specific instance of extensive leukoplakia, the necessity for multiple biopsies (commonly referred to as 'mapping') may be indicated (Carrard & van der Waal, 2017). As dentists in many areas may not be trained to perform incisional or excisional biopsies, referral to a specialist for these procedures is recommended (Carrard & Van Der Waal, 2018).

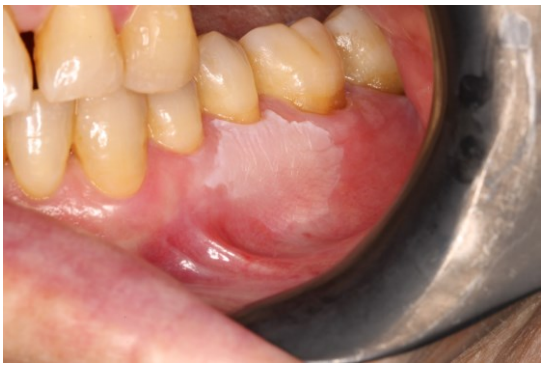


Figure 2 -A patch of homogeneous leukoplakia with a flat, thin, and uniformly white appearance (image provided by Antónnio Mano Azul and Pedro Trancoso)

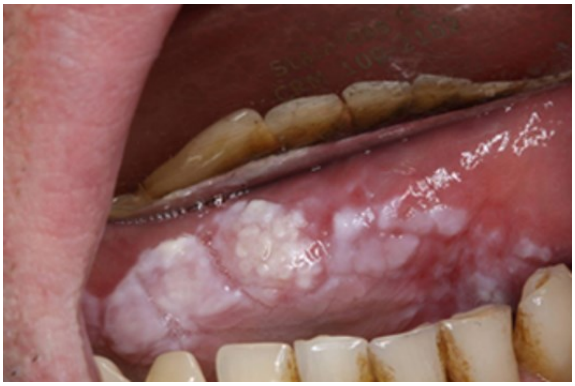


Figure 3- A patch of non- homogeneous leukoplakia affecting the lateral margin of the tongue with irregular boarders (image provided by António Mano Azul and Pedro Trancoso)

1.5. Histological Diagnosis

Leukoplakia is a clinical term that is usually modified on the basis of histopathological examination (van der Waal, 2015).

OL shows epithelial hyperkeratosis with or without epithelial dysplasia and is thought to progress from hyperkeratosis or hyperplasia to varying degrees of dysplasia (mild, moderate and severe) and finally to carcinoma in situ and/or OSCC. Absence of epithelial dysplasia does not disqualify oral leukoplakia as being a potentially (pre)malignant lesion, although the risk of malignant transformation of such leukoplakias is in most studies much lower than in case of the presence of epithelial dysplasia (Guimarães et al., 2020; van der Waal, 2019; Warnakulasuriya et al., 2007).

Dysplasia is assessed and graded on the basis of architectural disruption accompanied by cytological atypia, with the presence of dysplastic areas in the oral cavity epithelium being associated with an increased risk of malignant transformation (Guimarães et al., 2020; van der Waal, 2009).

The classification of mild, moderate and severe dysplasia is used when this architectural and cytological atypia affects less than one third, one third to two thirds and more than two thirds of the epithelium respectively (van der Waal, 2009). Carcinoma in situ is when the entire thickness of the epithelium is involved, with the dysplasia extending from the basal layer to the overlying mucosa without invading the underlying connective tissue(Mohammed & Fairozekhan, 2023).

While many leukoplakias show dysplasia or invasive OSCCs at the time of biopsy, some non-dysplastic keratotic lesions (KUS) also transform into invasive carcinoma over time (Villa & Sonis, 2018).

In cases where verrucous carcinoma, carcinoma in situ or invasive squamous cell carcinoma are diagnosed in addition to leukoplakia, the histopathological diagnosis

replaces the clinical diagnosis. Proliferative verrucous leukoplakia presents with a range of histopathological changes from hyperkeratosis with or without dysplasia to verrucous hyperplasia and verrucous carcinoma. It's debated whether verrucous hyperplasia is an early stage of verrucous carcinoma, with some authors making a distinction between the two (van der Waal, 2009).

Van der Waal & Axéll (2002) proposed a practical approach to the definitive diagnosis of leukoplakia by introducing four 'certainty factors' (C1, C2, C3 and C4): Based on various clinical features and characteristics, these factors help clinicians to assess the likelihood that a lesion is leukoplakia.

C1- Evidence from a single visit using inspection and palpation as the sole diagnostic means (provisional clinical diagnosis), including a clinical picture of the lesion.

C2- Evidence obtained by excluding suspected aetiological factors, e.g. mechanical irritation, with negative results during a follow-up period of 6 weeks (definitive clinical diagnosis).

C3 - As C2 but supplemented by a pre-treatment incisional biopsy in which no definable lesion is observed on histopathology (histopathologically supported diagnosis).

C4 - Evidence after surgery and pathological examination of the resected specimen.

Based on various clinical features and characteristics, these factors help the clinician to assess the likelihood that a lesion is leukoplakia.

1.6. Differential Diagnosis

The process of differential diagnosis is a systematic approach to identifying diseases. It works primarily by systematically eliminating possible causes. The clinician hypothesizes on the basis of the detection of a possible lesion during the clinical examination to reduce the diagnosis to a set of possibilities. Based on the results of the differential diagnosis, the physician can then choose therapeutic tests or specific complementary tests to arrive at a conclusive or definitive diagnosis.

Oral white lesions, including leukoplakia, are often investigated by biopsy to rule out the presence of dysplastic changes or cancer. Most white lesions are benign frictional keratoses or keratoses resulting from inflammatory conditions (e.g. lichen planus) and the diagnosis is usually clear from histopathology. As such, it is important to recognize its premalignant potential and treat it accordingly and differently from other white lesions (Villa & Woo, 2017).

The diagnosis is based on a combined clinical-microscopic assessment but usually becomes evident later in the course of the disease evolution (Warnakulasuriya, 2019).

Based on the present definition, a diagnosis of leukoplakia is one by exclusion of known, well-defined lesions and disorders that may occur in the oral mucosa, such as White Sponge Nevus, frictional keratoses (including alveolar ridge keratosis), chemical injury, acute pseudomembranous candidosis, leukoedema, Fordyce's spots/condition, skin graft, oral hairy leukoplakia (OHL), leukokeratosis, nicotinic stomatitis (smoker's palate), HPV lesions (e.g., condylomata/warts), geographic tongue/erythema migrans, and lichen planus or lichenoid lesions (van der Waal, 2019):

White sponge nevus - Noted in early life, family history, lesions are throughout the mouth; Genital mucosa may be affected. Occasionally a biopsy may be helpful (van der Waal, 2019; Warnakulasuriya, 2020).

Frictional keratosis- During clinical examination of a white patch, it is important to first look for a local traumatic cause. If this is evident, the white patch should not be considered a leukoplakia, but rather be designated as a frictional keratosis. These lesions are typically diffuse, and upon removal of the frictional source, they should resolve. It is important they are not regarded as an OPMD and must be distinguished from leukoplakia because the latter indicates a future cancer risk. Several terms are used for white patches induced by trauma: Frictional keratosis typically appears as a patch with diffuse borders; when found on alveolar ridges these are referred to as alveolar ridge keratosis (ARK); a white line along the occlusal plane is referred to as linea alba buccalis (Warnakulasuriya, 2020)

Morsicatio buccarum (Biting of lip, commissures or cheeks) is a condition characterized by chronic irritation or injury to the commissures and/or to the buccal mucosa, caused by

repetitive chewing, biting, or nibbling; Clinical aspect of irregular whitish- yellowish flakes, often bilateral, is rather diagnostic (Carrard & van der Waal, 2017).

Chemical burn- Known history of exposure to a chemical (e.g., an aspirin tablet - History of local application of aspirin tabletsor a caustic agent, e.g., sodium hypochlorite). The site of lesion corresponds to chemical injury, painful, resolves rapidly (Warnakulasuriya, 2020).

Acute pseudomembranous candidosis - An adherent white or white and red patch caused by a chronic fungal infection, usually *Candida albicans.* Somewhat questionable entity; some refer to this lesion as candida-associated leukoplakia. Mainly located in the commissures and the dorsum and the lateral borders of the tongue. Some use the results of antifungal treatment for establishing the diagnosis. Otherwise clinically indistinguishable from leukoplakia and can be easily wiped off (Carrard & van der Waal, 2017).

Leukoedema-Bilateral on buccal mucosae and disappears upon stretching (retracting). Predilection among some racial groups. Clinical diagnosis of a veil-like aspect of the buccal mucosa, bilaterally; tends to disappear when stretched. Occurs almost exclusively in middle-aged, dark-skinned people (Carrard & van der Waal, 2017; Warnakulasuriya, 2020).

Fordyce's spots/condition- <1 mm diameter, elevated, circular buff-colored spots/ papules distinctly demarcated from the normal surrounding lining mucosa (Warnakulasuriya, 2020).

Skin graft- Known history of a skin graft e.g. after vestibuloplasty (van der Waal, 2019).

Oral hairy leukoplakia - Bilateral keratosis with vertical striae, most commonly on the lateral margins of the tongue, but may focally affect other mucosal sites, especially in non-keratinised areas. Positive history of immunosuppression due to HIV disease or drugs - the latter often following organ transplantation or use of high-potency steroid inhalers More or less confined to HIV-infected patients, but may also occur in patients with immunocompromised status due to other causes. Almost exclusively bilateral on the edges of the tongue. Clinical appearance is not diagnostic (Flores-Hidalgo et al., 2018).

Nicotinic stomatitis (leukokeratosis nicotina palati or smokers' palate) - Greyish white palate with red spots (inflamed minor mucous glands). Smoking history. Usually a clinical diagnosis. Rarely becomes malignant. Regresses after cessation of the smoking habit (Carrard & van der Waal, 2017; van der Waal, 2019).

Papilloma and allied lesions, e.g. condyloma acuminatum, multifocal epithelial hyperplasia, verruca vulgaris- Clinical aspect; medical history. A biopsy may be helpful, including HPV typing (Carrard & van der Waal, 2017).

Keratotic lesions (including reverse smoking keratosis, sublingual keratosis, alveolar ridge keratosis, friction keratosis, sanguinaria-associated keratosis, tobacco pouch keratosis and keratosis of unknown significance) - Various aetiologies and clinical presentations; biopsy is indicated in many cases; some of the keratotic lesions carry an increased risk of malignant transformation (van der Waal, 2019).

Lesion caused by prolonged, direct contact of the oral mucosa with an amalgam or other dental restoration; often referred to as a lichenoid lesion - Disappearance of the lesion within an arbitrary period of 2-3 months after removal of the restoration; taking a biopsy prior to treatment is recommended (van der Waal, 2019).

Lichen planus (non-reticular types) and lichenoid lesions, including chronic Graft Versus Host Disease - Sometimes associated with typical cutaneous and mucosal lesions outside the oral cavity. Almost always bilateral. Several clinical subtypes of lichen planus may occur simultaneously. The erosive/erythematous type and the plaque type may be morphologically indistinguishable from leukoplakia. Heavy tobacco use favours the diagnosis of leukoplakia. Biopsy is not always diagnostic. The earliest presentation of proliferative verrucous leukoplakia may even mimic oral lichen planus (Carrard & van der Waal, 2017; van der Waal, 2019; Warnakulasuriya, 2019).

Lichen sclerosus - Atrophic, scarlike appearance; often cutaneous involvement as well. Rather typicical histopathology (Carrard & van der Waal, 2017).

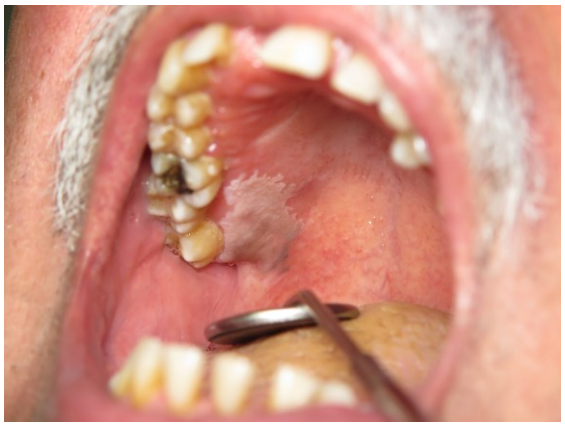


Figure 4-Oral leukoplakia (image provided by António Mano Azul and Pedro Trancoso)

1.7. Clinical Relevance

Oral cancer represents the 11th most common cancer worldwide, with an estimated 300 000 new cases, 145 000 deaths annually, and a 5-year survival rate of 50% to 60% (Paglioni et al., 2022).

Precancerous lesion and precancerous condition were proposed by the WHO in 1978, with the term precancer in itself suggesting a clinical presentation that may have a tendency to develop into cancer, implying that carcinogenesis is a two-step or multistep process. Subsequent studies have demonstrated that not all lesions with dysplasia develop into cancer, suggesting that it is patient-specific and further studies have indicated that cancer may develop in the contralateral or other apparently normal mucosa (Narayan & Shilpashree, 2016).

A recent consensus has therefore proposed the term, 'potentially malignant disorder' (OPMD), rather than precancer, stating that not all lesions and conditions described as precancerous may progress to cancer, but that there is a family of morphological changes, some of which may have an increased potential for malignant transformation (MT) (Guimarães et al., 2020; Narayan & Shilpashree, 2016).

Most oral squamous cell carcinomas (OSCCs) are preceded by oral potentially malignant conditions (OPMDs) (>50%). OPMDs represent a significant group of mucosal disorders

that may precede the diagnosis of oral squamous cell carcinoma (OSCC). The term conveys that not all lesions and conditions described will progress to cancer ; rather, there is an elevated probability of malignant transformation (MT) (Paglioni et al., 2022; Warnakulasuriya, et al., 2021)

Oral leukoplakia (OL) is the most common OPMD, with an average of 5% of oral leukoplakias progressing to cancer (Paglioni et al., 2022). The reported incidence of malignant transformation of oral leukoplakia varies considerably, from 0.13% to 34%, with observation periods ranging from 1 to 30 years. Therefore, early detection of leukoplakia is crucial to prevent its transformation into aggressive malignant OSCC, which is often difficult to treat (Farooq & Bugshan, 2020; Warnakulasuriya, 2019).

Next, when focusing on the risk of a specific site undergoing MT, it was found that the lateral tongue margin, followed by floor of the mouth, had the highest tendency for MT. (Ho et al., 2012; Narayan & Shilpashree, 2016; Pinto et al., 2020)

Another determinant included was the size of the OL, with evidence suggesting that the size/extent of the clinical lesion may be important, with those >200 mm2 surface area having a higher risk of MT compared to smaller lesions . Note that the area of the lesion is a characteristic that can be directly related to the time of appearance of the lesion; therefore, the longer the time of appearance, the greater the chances of MT (Paglioni et al., 2022a; Warnakulasuriya & Ariyawardana, 2016).

The association between age and malignancy may suggest that patients with persistent OL and longer exposure to associated risk factors are at greater risk of malignancy. Although OL is relatively rare in women compared to men, malignant transformation was found to be significantly higher in women (Pinto et al., 2020).

Non-homogeneous leukoplakia carries a higher risk of malignant transformation than homogeneous leukoplakia, and it is not uncommon for non-homogeneous leukoplakia to show severe dysplasia or even superficially invasive SCC on biopsy at baseline (Paglioni et al., 2022; Warnakulasuriya et al., 2021) The grade of dysplasia influenced, among other patient factors, the risk of transformation with non-homogeneous appearance of the lesion, increasing clinical suspicion and leading to the prescription of a more aggressive

treatment approach by surgical excision (Warnakulasuriya & Ariyawardana, 2016; Ho et al., 2012).

However, according to Narayan & Shilpashree, (2016), habit association and histopathological grade of dysplasia have the least significance as tobacco history, no habit, no dysplasia, mild, moderate and severe are all associated with more or less similar degree of transformation.

Although tobacco use is a well-established risk factor for the development of OL, the increased risk in non-smokers suggests that an underlying genetic predisposition may also be involved in at least a proportion of cases (Ho et al., 2012; Paglioni et al., 2022).Therefore, it is imperative that clinicians have more evidence-based information to make informed decisions in the clinical management of OL. For the reasons discussed above, more studies with clear case definitions are needed (Warnakulasuriya & Ariyawardana, 2016).

From a clinician's perspective, our goals in managing patients with OPMDs are to prevent the development of cancer, reduce mortality/improve survival, reduce morbidity (i.e. improve our patients' quality of life and reduce anxiety), and reduce the burden of healthcare costs (Kerr & Lodi, 2021).

As leukoplakia is a provisional clinical diagnosis, a tissue biopsy of the observed white patch should be performed and a representative sample of the specimen sent for histopathological analysis. The reasons for biopsy are (1) to exclude other pathologies (including carcinoma) that may be responsible for the white patch, and (2) to assess the presence and degree of epithelial dysplasia within the patch. An additional reason is to assess for any candidal colonisation within the epithelium. The grade of dysplasia as reported by a pathologist remains our best tool for assessing the risk of malignant transformation of OPMDs, despite controversy over interpretation (Warnakulasuriya, 2018).

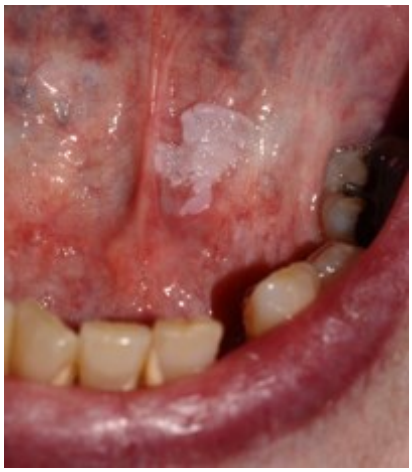


Figure 5-Oral leukoplakia (image provided by António Mano Azul and Pedro Trancoso)

1.8. Treatment

Management of OPMDs includes establishing the correct diagnosis, risk assessment, counselling on risk factors and selection of an appropriate intervention. Most cases require regular follow-up by an oral health professional (Warnakulasuriya, 2020).

Treatment modalities include ongoing surveillance, tobacco/alcohol cessation, pharmacological treatment and surgery using scalpel, laser or cryosurgery. Surgical excision, if possible, and surveillance are considered the gold standard for the management of OL (Sundberg et al., 2019).

All patients diagnosed with OPMD should be counseled on the individual risk factors noted in their social history and all contributing factors should first be eliminated with the aim of reducing their future risk of malignancy through tobacco cessation, alcohol moderation and, for Asian patients, betel quid (areca nut) cessation. For tobacco cessation there are good learning resources and guidelines and the practitioner should improve his/her skills to provide brief interventions in clinical practice. There is sufficient evidence to stress the significance of tobacco cessation to aid reversal of oral leukoplakia. Of course, it is recognised that complete regression may take much longer. (Mohammed & Fairozekhan, 2023; van der Waal, 2009; Warnakulasuriya, 2020).

Surgery, either cold knife or laser, is the recommended treatment modality and oral cancer requires immediate referral to a tertiary care centre. It is also essential to rule out other mucosal conditions masquerading as oral leukoplakia and to assess their risk of malignant transformation (Birur et al, 2022).

The purpose of a biopsy is to diagnose and characterize lesions. Incisional biopsy can be recommended, with the following specific indications: the biopsy should be taken from the most suspicious areas of the lesion, such as red patches, areas with surface thickening, or symptomatic regions, without the need to extend into healthy tissue for an accurate pathological report; in cases of multifocal or widespread leukoplakia, multiple biopsies (field mapping) may be necessary; for non-homogeneous leukoplakia, a single incisional biopsy may not be representative, so multiple biopsies should be considered, if the leukoplakia is smaller than 2 cm, an excisional biopsy may be performed, but the surgical team should be capable of conducting further procedures if the biopsy report reveals high-grade dysplasia or invasive carcinoma (Birur et al., 2022).

Surgical excision remains the first-line treatment for oral cancer and the most common intervention for dysplastic OL. The rationale is that removal of the OL reduces the risk of cancer development. Surgically accessible, homogeneous and well-demarcated unifocal OL <2cm in diameter are often indicated for surgical excision for diagnostic purposes. Similar to the argument made earlier for medical treatments, surgical excision of the visible abnormalities does not always correspond to histologically or molecularly disease-free margins. Field effects and diseased margins are important factors predicting local recurrence after surgical excision for OL. Surgical excision is preferred because unlike laser ablation that destroys lesional tissue, surgical excision allows for histologic study of the specimen in order to assess for variations in the grade of dysplasia and the presence of OSCC.A meta-analysis of interventional studies suggest that excision of oral leukoplakias may reduce the risk of transformation .Based on this evidence it is now recommended that high risk lesions such as erythroplakias, erythroleukoplakias or leukoplakias with moderate or severe dysplasia should be excised in the absence of any surgical contraindications (Jones & Jordan, 2015; Kerr & Lodi, 2021; Warnakulasuriya, 2020).

Apart from surgical excision, various treatment modalities are available such as cryosurgery, laser surgery (including evaporation), administration of retinoids, either topically or systemically, mouthwash therapy containing an attenuated adenovirus and photodynamic therapy (van der Waal, 2009).

The management and treatment of leukoplakia remains challenging, particularly for large lesions and PVLs. Patients with multifocal non-contiguous lesions (PVL) often present with a histopathological diagnosis of "hyperkeratosis without dysplasia", yet 70%-100% will develop cancer over time. Current strategies for oral leukoplakia include surgery, watchful waiting and medical management (Villa & Sonis, 2018).
In patients with multifocal or widespread leukoplakia multiple biopsies (“field mapping”), if needed using general anesthesia, should be considered. Particularly in case of a non-homogeneous leukoplakia an incisional biopsy may not be representative (van der Waal, 2009).

As cancer may arise during the natural history of an OPMD it is recommended to undertake patient follow up at appropriate intervals. The follow up intervals should be decided based on the individual's risk assessment and considering patient compliance (Warnakulasuriya, 2020).

In general, lifelong follow-up visits are advised both in treated and untreated patients. The recommended time interval as reported in the literature varies from several months up to 1 year. However, there are no studies that show the effectiveness of such follow-up protocol with regard to a better survival in case of malignant transformation, compared with a protocol in which patients refer themselves in case of symptoms, being the main indication of unfavorable changes (van der Waal, 2019).

1.9. Recurrence

Recurrence is the reappearance of OPMD after treatment and is a common problem following excision of any OL. Despite optimal surgery, recurrence rates are estimated at 30% (de Pauli Paglioni et al., 2020; Pinto et al., 2020; Sundberg et al., 2019).

Epithelial dysplasia is a factor that has been used as a potential microscopic predictor of the risk of OPMD progression to cancer and OPMD recurrence after treatment. However, conflicting recent studies have demonstrated the subjectivity and variability of epithelial dysplasia grading, highlighting that it is not a definitive factor in determining the risk of malignant progression or recurrence (Pinto et al., 2020; Sundberg et al., 2019).Some studies using surgical intervention have found that the degree of epithelial dysplasia does not correlate with the clinical course of the lesions. Similarly, no association has been found between the severity of dysplasia and recurrence. It is important to note that no single molecular pathway has been identified as a primary risk factor for recurrence or malignant transformation of oral leukoplakia (Kuribayashi et al., 2012)

The relationship between appearance and OL recurrence is another controversial determinant. However, recent studies have observed a significant association between the clinical presentation of OL and the rate of recurrence after treatment with non-homogeneous OL lesions showing an increased likelihood of recurrence after treatment compared to homogeneous lesions. This finding supports previous research suggesting that even after surgical removal, the risk of cancer transformation remains. (Paglioni et al., 2022; Sundberg et al., 2019)

Recurrence of oral leukoplakia is also more likely in cases with positive margins, where epithelial abnormalities are present at the resection margins, than in cases with negative margins. This suggests that surgical resection is curative only if all areas of epithelial abnormality are identified and adequately removed. Furthermore, maintaining an adequate resection margin may help to reduce the risk of recurrence. Although the most common site of recurrence after surgical resection hasn't been identified, studies suggest that the retromolar/mandibular alveolus, floor of the mouth, lateral border of the tongue and buccal mucosa have the highest incidence of recurrence or development of further oral lesions after laser surgery (Kuribayashi et al., 2012).

Although lesions with high-grade dysplasia are usually resected with wide margins, many lesions with low-grade or no dysplasia are resected with minimal or even no margins. However, the high recurrence rate (10%-35%) observed in some studies suggests that these minimal margins are inadequate, regardless of the severity of the dysplasia. Many recurrent lesions are found to have been resected with margins less than 3mm. Therefore, surgical margins less than 3 mm may be a valuable predictor of recurrence in patients

with surgically resected oral leukoplakia, regardless of epithelial dysplasia (Jones & Jordan, 2015; Kuribayashi et al., 2012).

Smoking cessation is an important management strategy that has been shown to reduce both the rate of recurrence and the risk of transformation to OSCC. Some studies have even shown that smoking cessation can lead to a reduction or complete regression of OL lesions over time(Jones & Jordan, 2015; van der Waal, 2019).

If there is no clinical evidence of obvious pathogenesis and the lesion has sharply demarcated margins, it should be followed closely, re-evaluated periodically by biopsy, or excised or ablated, depending on the clinical context. Lesions larger than 200 mm2 should be reassessed every 3 months and re-evaluated by biopsy every 6 to 12 months; patients with lesions smaller than 200 mm2 should be reassessed every 3 months with periodic biopsy, as appropriate (Villa & Woo, 2017).

II. MATERIALS AND METHODS

2.1. Study population

All the clinical histories of patients who attended oral medicine appointments at the Clínica Integrada de Medicina Oral, located at Rua da Beneficência 227, 1600-185 Lisbon, and had a diagnosis of oral leukoplakia were consulted..

33 cases met the inclusion criteria and were considered valid for the study.

2.2. Criteria

2.2.1. Inclusion criteria:

Diagnosis of a lesion with a diagnosis of oral leukoplakia at the oral medicine clinic.

Informed consent.

2.2.2. Exclusion criteria:

No diagnosis of an oral leukoplakia lesion in the oral medicine consultation.

No informed consent.

2.3. Data collection and processing

The following data was collected from each clinical history and sent to a Microsoft Office Excel database:

- Gender
- Date of birth
- Localization of the lesion
- Lesion focus
- Size of the lesion
- Clinical diagnosis
- Date of clinical diagnosis
- If biopsy performed and result
- Result of histological diagnosis when present

- Degree of dysplasia
- Treatment carried out.
- Presence of malignant transformation
- Time until malignant transformation
- Systemic pathologies
- Habits (smoker)
- Presence of leukoplakia recurrence
- Time until recurrence
- Total number of recurrences

There were cases in which data such as date of birth, date of clinical diagnosis or whether a biopsy was performed was not recorded,

. In cases where the date of birth was missing (one), relevant to the valid percentage of diagnosis, it was omitted from the percentage relating to age group.

As for the diagnosis, cases in which the histological and clinical diagnosis coincided were counted as positive. When the histological diagnosis did not coincide with the clinical diagnosis, the histological diagnosis was taken as a certainty.

As for the time until recurrence, the time interval between the removal of the leukoplakia lesion and the next diagnosis of the reappearance of the same lesion was counted in number of days.

2.4. Statistical method

The descriptive statistical analysis and the creation of the associated graphs were performed using the SPSS software (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp). To compare the data from the groups with and without recurrence, Student's t-test was applied for continuous variables and the chi-square test for categorical variables.

Firth logistic regression, performed in RStudio through the *logistf* package, allowed to reduce bias in the adjusted logistic models, using the selection of variables by steps based on the significance of the predictive variables, evaluated by the Wald test. This penalized

logistic regression approach is particularly effective to overcome the limitations of traditional logistic regression in small datasets, especially in situations characterized by the occurrence of rare events. The results were presented in the form of *odds ratios* (odds ratio/OR) and the significance values associated with the predictive variables in relation to the binary dependent variable of recurrence or not of leukoplakia.

Cox regression for multiple events (multiple recurrences of leukoplakia) was implemented in RStudio, using the *survival* package, using an approach based on *frailty models*. The overall significance of the model was evaluated and optimized through the likelihood ratio test (*Likelihood Ratio Test*), the Wald test and the logrank test (*Score Test*).

III. RESULTS

3.1. Selection of cases

From a sample of 33 cases, 0 cases (0%) had no gender information, 1 (3%) had no date of birth, and 22 (66,7%) cases had a histological diagnosis, that was compatible with the clinical diagnosis of oral leukoplakia.

3.2. Study population

A total of 33 patients were diagnosed with oral leukoplakia. Recurrence was observed in 12 (36.4%).

Also, in the present study, only one case of malignant transformation of oral leukoplakia into squamous cell carcinoma was observed, resulting in a malignant transformation rate of 3.0%.

The sample comprised 15 women (45.5%) and 18 men (54.5%), with a mean age of 59.11 years (of the 32 cases), ranging from a minimum of 40 to a maximum of 95 years. In the 12 cases where recurrence was present the mean age was 66.02.

The mean length of the leukoplakia lesions analysed was 14 mm.

	Valid N	Mean	Standard Deviation
Age sample	32	59.11	14.45
Age of recurrence	12	66.02	12.68
Lenght	24	14	8

Table 2- Distribution of the population by patient age, lesion length

Number of recurrences	Count	% of total patients
0 (No recurrence)	21	63.6%
1 Recurrence	5	15.2%
2 Recurrences	4	12.1%
3 Recurrences	2	6.1%
5 Recurrences	1	3.0%
Total	33	100%

Table 3- Distribution of patients according to the number of recurrences of oral leukoplakia.

Table 3 shows the distribution of patients according to the number of recurrences of oral leukoplakia. In total, 33 cases were analysed, of which 63.6% (21 cases) showed no recurrence, while 36.4% (12 cases) showed recurrence.

On the other hand, of the patients with recurrence, the following distribution was observed:15.2% (5 cases) had 1 recurrence; 12.1% (4 cases) had 2 recurrences; 6.1% (2 cases) had 3 recurrences; 3.0% (1 case) had 5 recurrences.

Multiple recurrences				
	Coeficiente	odds ratio(OR)	95% confidence interval	Significance *p*
Age	0.063	1.065	1,021 to 1,112	0,004

Table 4-The influence of age in the risk of multiple recurrences of oral leukoplakia in patients

Table 4 refers to the study of the influence of age in cases where there are multiple recurrences. Age is a weak risk factor for multiple recurrences, associated with an increased risk of around 6.5%.

For the ‘age’ variable, the coefficient is 0.063. This means that, keeping all the other variables constant, for every one-unit increase in age, the logarithm of the risk of an event (multiple recurrences of oral leukoplakia) increases by 1.065 units.

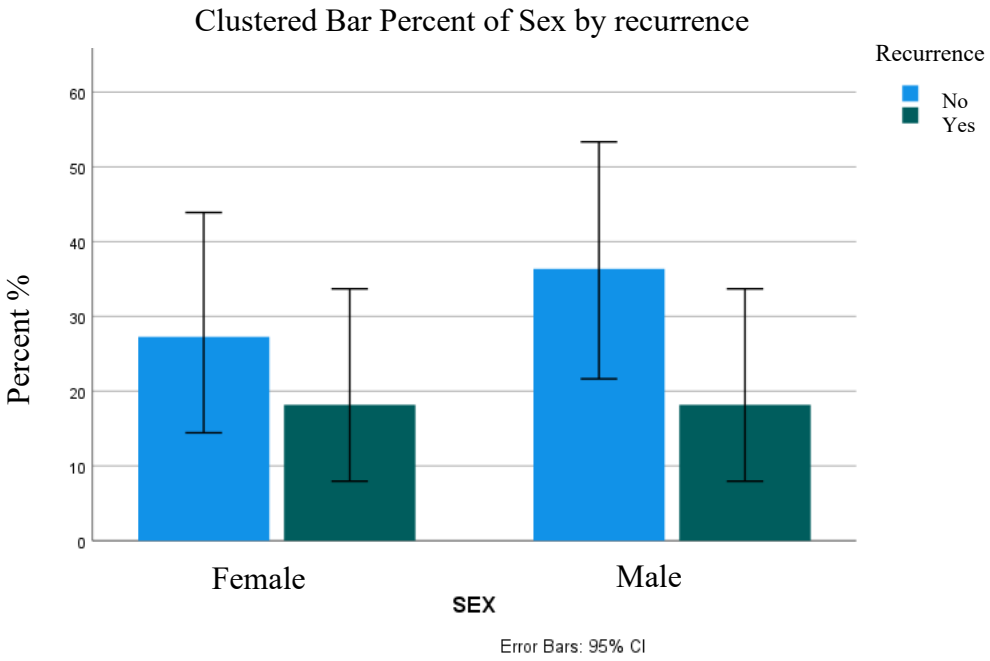
The p-value for the variable 'age' is low (0,004), indicating a high level of statistical significance. Furthermore, an exponential coefficient greater than one indicates an increase in event risk, whereas a value less than one indicates a reduction in risk. To illustrate, for the variable 'age', the exponential coefficient is 1.065. This indicates that, when all other variables are held constant, the event risk (multiple recurrences of oral leukoplakia) increases by approximately 6,5% for every one-unit increase in age, meaning that for patients with the same characteristics, every 1 year older increases the risk of multiple recurrence by 6.5%.

3.3. Gender of the population

The study sample comprised 45.40 per cent women (n=15) and 54.50 per cent men (n=18). Regarding the cases of recurrence, the data indicates that 50% (6) occurred in women and 50% (6) in men. In cases where no recurrence occurred, 42.90% (9) were women and 57.10% (12) were men. Consequently, recurrence was distributed equally between genders, with no significant difference. This is evidenced by the p-value of 0.692, which suggests that there is no statistically significant association between gender and recurrence in the analysed sample.

Recurrence					
		Total %	No%	Yes%	Significance p
Gender	Female	45,4%	42,9%	50,00%	0,692
	Male	54,5%	57,1%	50,00%	

Table 5-Distribution of the sample by recurrence and gender



Graph 1- Distribution of the sample by gender

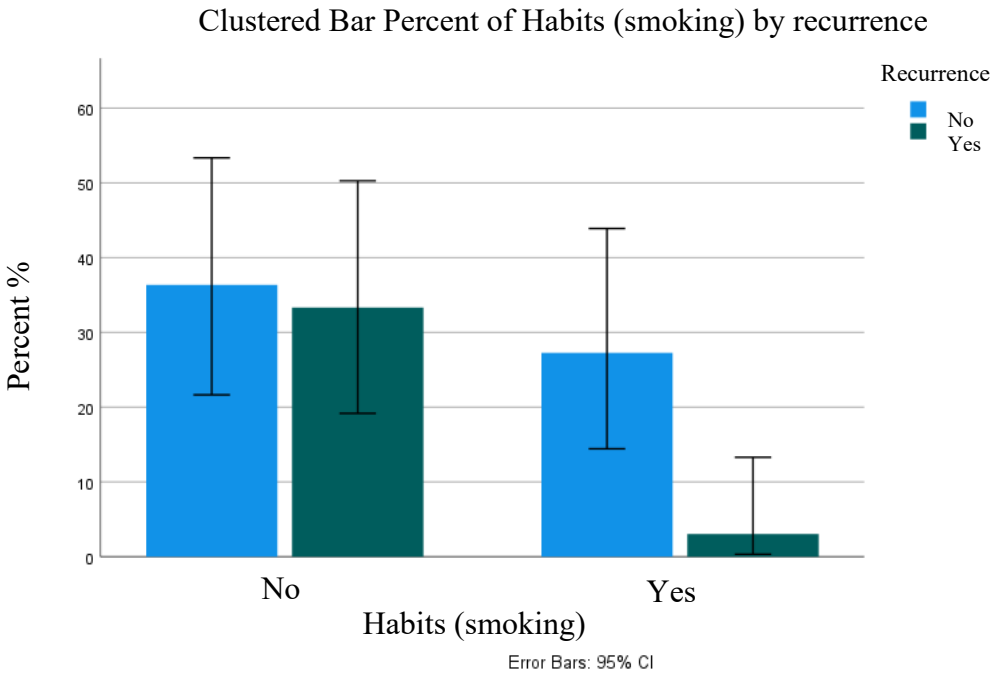
3.4. Smoking habits

The sample included 23 (69.70%) non-smokers and 10 (30.30%) smokers. Regarding the cases in which there was no recurrence, 57.10% (12) were non-smokers and 42.90% (9) were smokers. In the cases of recurrence, 91.70% (11) were non-smokers and 8.30% (1) were smokers.

Thus, most cases of recurrence occurred in non-smokers (91.70%), while smokers accounted for only 8.30% of cases of recurrence. This indicates a possible association between smoking and the absence of recurrence in the sample analysed. This difference was statistically significant ($p = 0.038$), indicating a possible association between smoking and the absence of recurrence in the sample analysed.

Recurrence					
		Total %	No%	Yes%	Significance p
Smokers	No	69,70%	57,10%	91,70%	0,038
	Yes	30,30%	42,90%	8,30%	

Table 6-Distribution of the sample according to smoking habit and recurrence of oral leukoplakia



Graph 2- Distribution of smoking habits by recurrence

3.5. Systemic diseases

A comprehensive analysis of the patients' medical histories was conducted to investigate the interrelationships between various systemic pathologies, including cardiovascular, renal, nervous, gastric, immunological, endocrine, hepatic, dermatological, vascular, autoimmune, oral, lymphatic, respiratory, and the presence of chemotherapy in the patient's history.

Of the aforementioned variables, only the presence of respiratory and immunological pathologies was found to be statistically significant.

3.5.1 Respiratory diseases

Multiple recurrences				
	Coeficiente	odds ratio(OR)	95% confidence interval	Significance *p*
Respiratory diseases	2,539	12,665	2,801 to 57,263	<,001

Table 7-The influence of respiratory diseases in the risk of multiple recurrences of oral leukoplakia in patients

Table 7 refers to the study of the influence of respiratory diseases in cases where there are multiple recurrences. The presence of respiratory diseases is a strong risk factor for multiple recurrences, with an increased risk of around 12.7 times when this type of diseases is present.

The variable respiratory pathologies has a coefficient of 2.539, suggesting that the presence of these conditions considerably increases the chances of the event occurring (multiple recurrences of oral leukoplakia). The p-value is less than 0.001, indicating a highly significant association. The OR of 12.665 shows that the presence of respiratory pathologies multiplies the chance of the event happening by around 12.7 times. The 95% confidence interval ranges from 2.801 to 57.263, showing that although the interval is wide, the association is robust, since the value 1 is not included.

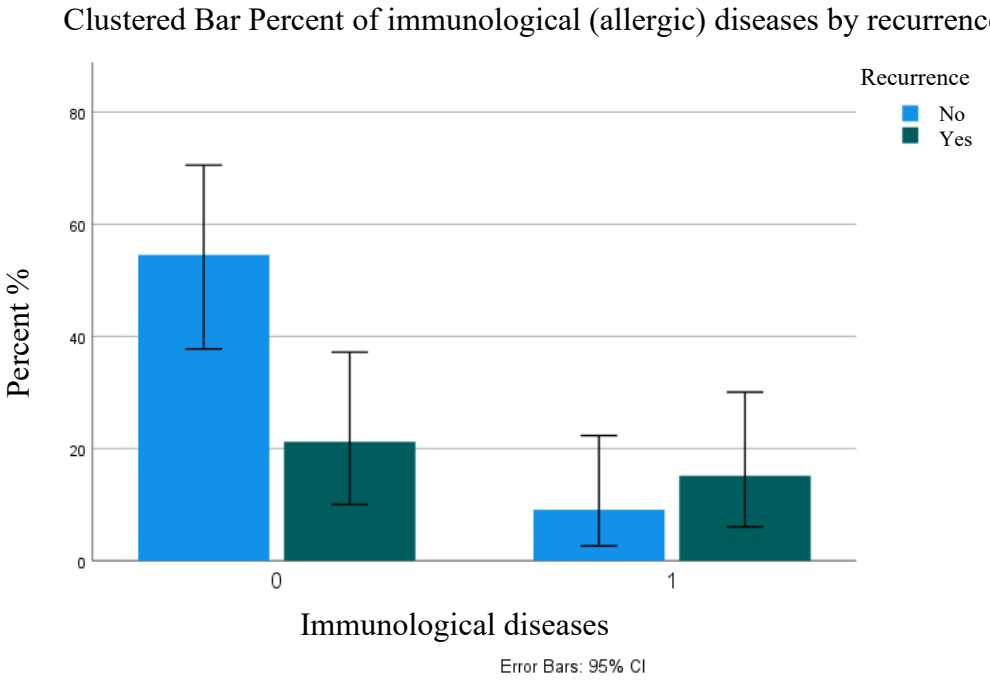
3.5.2 Immunological diseases

The table studied included 25 (75.80%) individuals without immunological pathologies (allergies) and 8 (24.20%) with immunological pathologies. Regarding the cases in which there was no recurrence, 85.70% (18) of the individuals had no immunological pathologies, while 14.30% (3) had immunological pathologies. In cases of recurrence, 58.30% (7) of the individuals were without immunological pathologies, while 41.70% (5) had immunological pathologies.

Thus, the majority of non-recurrence cases occurred among individuals without immunological pathologies (85.70%), while recurrence cases were more distributed among individuals with or without immunological pathologies, with 41.70% of recurrences having these pathologies. This may suggest a possible relationship between the presence of immunological pathologies and the higher recurrence rate.

Recurrence					
		Total %	No%	Yes%	Significance p
Immunological diseases	No	75,80%	85,70%	58,30%	0,077
	Yes	24,20%	14,30%	41,70%	

Table 8-Distribution of the sample according to immunological diseases and recurrence of oral leukoplakia



Graph 3- Distribution of immunological diseases by recurrence

Presence/absence of recurrence.				
	Coeficiente	odds ratio(OR)	95% confidence interval	Significance p
Intercept	-1.088	.337	.034 to 3.336	.352
No Immunological diseases	-2,234	,107	,011 to 1,073	.057
No smoking	2,813	16,652	1,109 to 249,965	.042

Table 9- Impact of immunological pathologies (allergies) and habits (such as smoking and alcohol consumption) on the likelihood of oral leukoplakia lesions recurring

Immunological pathologies (allergies):

The parameter for the absence of immunological diseases (no immunological diseases) is -2.234. The Wald test shows a value of p = 0.057, which suggests almost statistical significance (tending towards significance). The value of OR= 0.107 suggests that the absence of immunological pathologies is associated with a reduced chance of recurrence (approximately 89% per cent lower)

Furthermore, the risk of leukoplakia recurrence is reduced by approximately 89% in individuals without allergies, compared to approximately 10.7 % in those with allergies. The OR for leukoplakia recurrence in individuals without allergies is 0.107, indicating that those with allergies are at an elevated risk of recurrence. Consequently, the average risk of leukoplakia recurrence is 9.35 times higher in individuals with allergies than in those without.

Habits (smoking):

The parameter for the absence of risk habits (No smoking) is 2.813, with a significant p-value (p = 0.042). The value of OR = 16.652 indicates that the absence of risk habits is associated with a significant increase in the chance of recurrence, with an odds ratio 16 times higher.

With regard to ‘Habits’, those who didn't have any showed an average increase in the risk of recurrence of around 16.6 times.

In summary, the model suggests a significant influence of smoking on the recurrence of lesions, while the relationship with immunological pathologies is more uncertain, requiring more data or additional analyses to confirm any significant impact.

3.6. Lesion focus

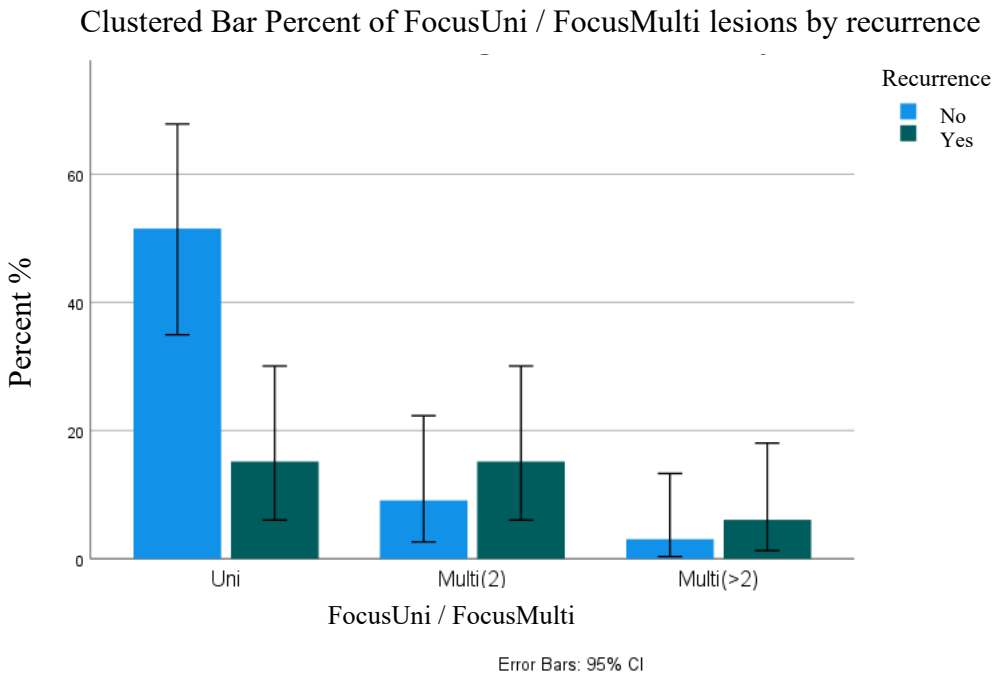
The table studied included 22 individuals (66.70%) with unifocal lesions, 8 (24.20%) with multifocal lesions in two areas, and 3 (9.10%) with multifocal lesions in more than two areas.

In cases where recurrence was not observed, 81.00% (17) of individuals presented with unifocal lesions, 14.30% (3) had multifocal lesions in two areas, and 4.80% (1) had multifocal lesions in more than two areas.
In cases of recurrence, 41.70% (5) of the individuals had unifocal lesions, 41.70% (5) had multifocal lesions in two areas, and 16.70% (2) had multifocal lesions in more than two areas.

Consequently, the majority of cases of non-recurrence were observed in individuals with unifocal lesions (81.00%). However, cases of recurrence were distributed more evenly among individuals with unifocal and multifocal lesions in two areas, each accounting for 41.70% of recurrence cases. Furthermore, individuals with multifocal lesions in more than two areas exhibited a higher recurrence rate (16.70%), indicating a potential correlation between the number of affected areas and the probability of recurrence.

Recurrence					
		Total%	No%	Yes%	Significance p
Uni/Multi	Uni	66,7%	81,0%	41,70%	0,070
	Multi (2)	24,2%	14,30%	41,70%	
	Multi(>2)	9,1%	4,80%	16,70%	

Table 10- Distribution of the sample by lesion focus and recurrence of oral leukoplakia



Graph 4-Distribution of pathology focus by recurrence

3.7 Site of lesion

Among the population studied, 36.4% (12) of the lesions were located on the tongue, 24.2% (8) on the floor of the mouth, 9.1% (3) on the palate, and 6.1% (2) on the alveolar ridge. Additional lesions were found at the lateral border of the tongue, on the gingiva, multilocally, and at the retromolar trigone, each comprising 3.0% (1) of the cases.

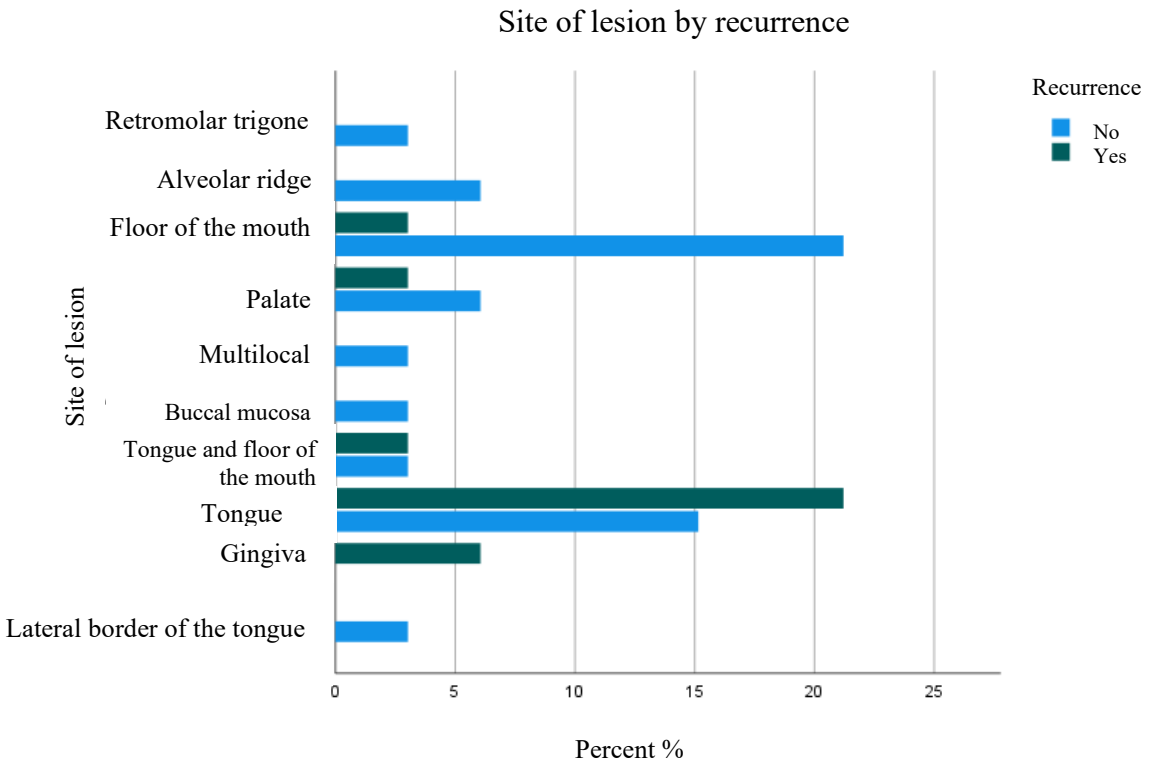
In cases where no recurrence was observed, 33.3% (7) of the lesions were located on the floor of the mouth, 23.8% (5) on the tongue, and 9.5% (2) on the palate and alveolar ridge. The remaining cases with no recurrence included 4.8% (1) at the lateral border of the tongue, as well as multilocal and jugal mucosa locations, each contributing 3.0% (1) to the total.

Among the cases that exhibited recurrence, 58.3% (7) of the lesions were located on the tongue, 16.7% (2) on the gingiva, and 8.3% (1) each on the floor of the mouth and at the tongue and floor junction. The statistical analysis yielded a p-value of 0.238, indicating

that there was no statistically significant correlation between the location of the lesion and recurrence in the evaluated sample.

Recurrence					
Site of lesion		Total%	No%	Yes%	Significance p
	Lateral border of the tongue	3,0%	4,8%	0%	0,238
	Gingiva	6,1%	0%	16,7%	
	Tongue	36,4%	23,8%	58,3%	
	Tongue and floor of the mouth	6,1%	4,8%	8,3%	
	Buccal mucosa	3,0%	4,8%	0%	
	Multilocal	3,0%	4,8%	0%	
	Palate	9,1%	9,5%	8,3%	
	Floor of the mouth	24,2%	33,3%	8,3%	
	Alveolar ridge	6,1%	9,5%	0%	
	Retromolar trigone	3,0%	4,8%	0%	

Table 11- Distribution of the sample by site of the lesion and recurrence of oral leukoplakia



Graph 5- Distribution of recurrence according to the site of the lesion

3.8. Dysplasia

The sample included 11 (33.30%) patients with no dysplasia, 5 (15.20%) with mild dysplasia, 4 (12.10%) with moderate dysplasia, and 1 (3.00%) with severe dysplasia.

Among the cases with no recurrence, 33.30% (7) had no dysplasia, 4.80% (1) had mild dysplasia, 9.50% (2) had moderate dysplasia, and none (0%) had severe dysplasia.

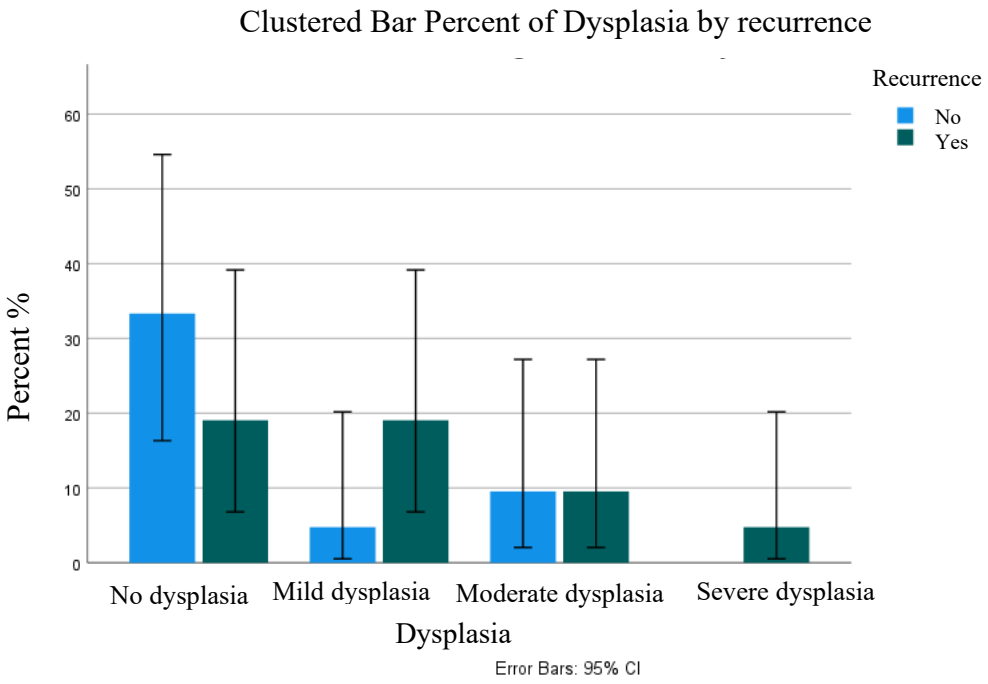
In the cases of recurrence, 33.30% (4) had no dysplasia, 33.30% (4) had light dysplasia, 16.70% (2) had moderate dysplasia, and 8.30% (1) had severe dysplasia.

Thus, recurrence occurred at similar rates (33.30%) in patients with no dysplasia and mild dysplasia. A higher percentage of recurrence was observed in patients with mild dysplasia (33.30%) compared to non-recurrent cases (4.80%). However, the difference in dysplasia

categories was not statistically significant (p = 0.311), suggesting no strong association between the degree of dysplasia and recurrence in the sample analysed.

Recurrence					
Dysplasia		Total%	No%	Yes%	Significance p
	Not present	33,3%	33,3%	33,3%	0,311
	Mild	15,2%	4,8%	33,3%	
	Moderate	12,1%	9,5%	16,7%	
	Severe	3,0%	0%	8,3%	

Table 12- Distribution of the sample by level of lesion dysplasia and recurrence of oral leukoplakia



Graph 6-Distribution of the degree of lesion dysplasia by recurrence

3.9. Clinical diagnosis

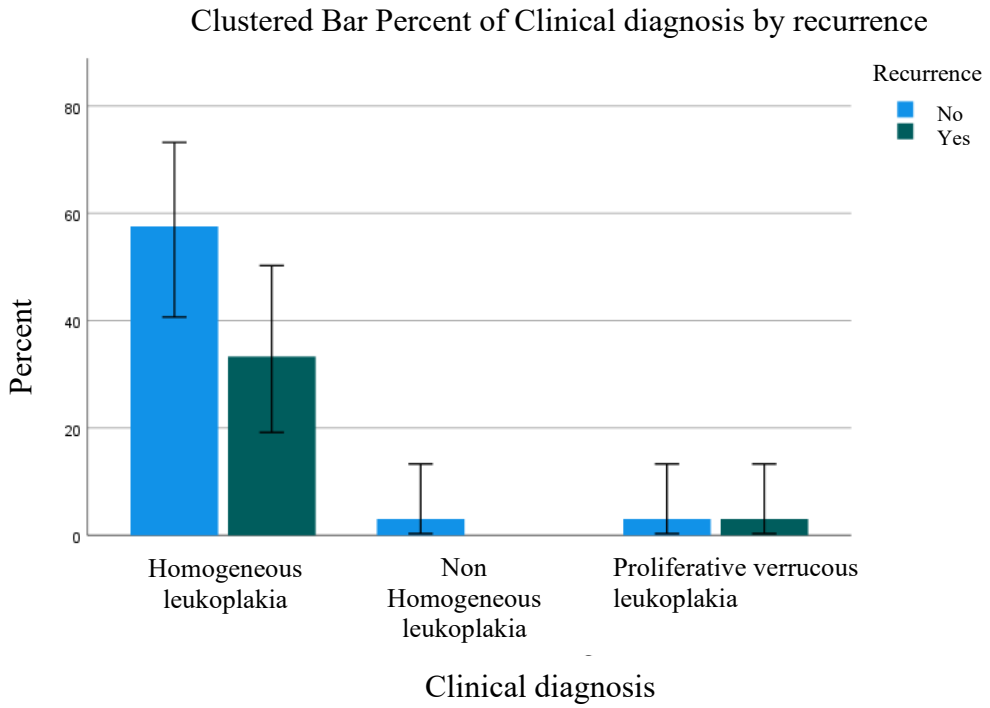
The lesions were classified according to clinical diagnosis into three main categories: homogeneous leukoplakia, non-homogeneous leukoplakia and proliferative verrucous leukoplakia.

Of the population under study, 90.9% (30) of the lesions were classified as homogeneous leukoplakia, with 19 cases (90.5%) showing no recurrence and 11 cases (91.7%) exhibiting recurrence. In contrast, non-homogeneous leukoplakia accounted for 3.0% (1) of the lesions, with 1 case (4.8%) reported without recurrence and none with recurrence. Finally, proliferative verrucous leukoplakia represented 6.1% (2) of the lesions, with 1 case (4.8%) showing no recurrence and 1 case (8.3%) exhibiting recurrence.

The statistical analysis of these findings suggests that the majority of lesions observed were of the homogeneous leukoplakia type, indicating a potentially lower risk of recurrence compared to other forms.

Recurrence					
Clinical diagnosis		Total%	No%	Yes%	Significance p
	Non-homogeneous leukoplakia	3,00%	4,80%	0,00%	0,693
	Homogeneous leukoplakia	90,90%	90,50%	91,70%	
	Proliferative verrucous leukoplakia	6,10%	4,80%	8,30%	

Table 13- Distribution of the sample according to clinical diagnosis and recurrence of oral leukoplakia



Graph 7-Distribution of the clinical diagnosis of the lesion by recurrence of oral leukoplakia

3.10. Histological diagnosis

Of the population studied, a total of 66.7% (22) lesions were classified under the "yes" category in the histological diagnosis group, meaning these lesions underwent histological evaluation (compatible with oral leukoplakia). Among these cases, 47.6% (10) showed no recurrence, while all (100.0%) of the recurrence cases (12) were also in this category.

Recurrence				
		Total %	No%	Yes%
Histological diagnosis	Yes	66,70%	47,60%	100,00%

Table 14- Distribution of the sample according to histological diagnosis and recurrence of oral leukoplakia

3.11. Treatment

The sample included 23 (69.70%) patients who underwent surgery and 7 (21.20%) who received topical retinoid treatment.

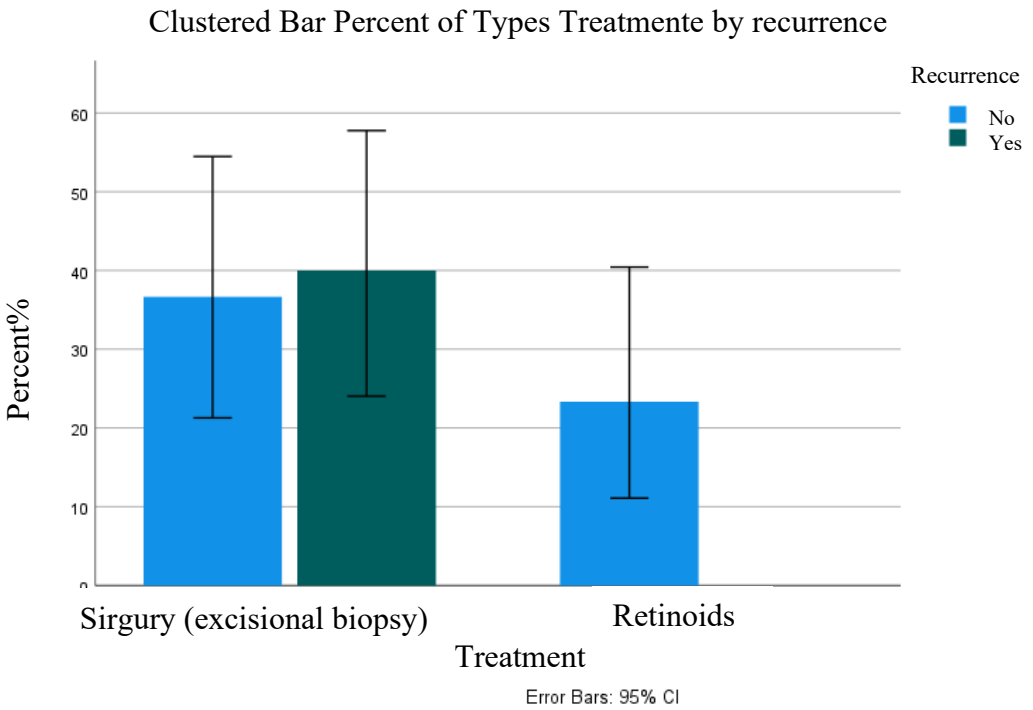
Among the cases with no recurrence, 47.80% (11) were treated with surgery, and 100.00% (7) were treated with topical retinoids.

In the cases of recurrence, 52.20% (12) were treated with surgery, while none (0.00%) of the patients treated with topical retinoids experienced recurrence.

Thus, all cases of recurrence occurred in the surgery group, while no patients treated with retinoids had a recurrence. This difference was statistically significant ($p = 0.014$), indicating a possible association between retinoid treatment and the absence of recurrence in the sample analysed.

		Recurrence			
		Total%	No%	Yes%	Significance p
Treatment	Surgery	69,7%	47,80%	52,20%	0,014
	Retinoids	21,2%	100,00%	0,00%	

Table 15- Distribution of the sample according to the type of treatment employed for the lesion and recurrence of oral leukoplakia



Graph 8- Distribution of lesion treatment by recurrence

IV. DISCUSSION

4.1. Prevalence

The recurrence rate of oral leukoplakia in our study was 36.4%, with 12 of the 33 patients exhibiting recurrence of the lesion. This figure is higher than that reported in other studies, such as those by Holmstrup et al. (2006) with 13.5% and Pandey et al. (2001) with 17.09%, which examined recurrence rates following surgical resection. Nevertheless, our findings align with the postoperative recurrence rates reported by Sundberg et al., 2019 which range from 13% to 42%. This evidence suggests that the recurrence rate can vary considerably depending on the sample and the clinical context. The reason for this is unknown, and the recurrence patterns of OL have been found to be independent of the intervention procedure (Sundberg et al., 2019).

It is notable that in our sample, as the number of recurrences increased, the frequency of patients decreased. Consequently, the majority of cases of recurrence were observed in patients with a single recurrence (15.2%), while cases of multiple recurrences (2 or more) were less common. The maximum number of recurrences observed was five, present in only one case (3.0% of cases with recurrence).

A consistent pattern emerges from these studies: while recurrence is a significant issue, particularly after surgical intervention or other treatments for oral leukoplakia, the incidence of multiple recurrences remains lower. The results of our study, as well as those of Holmstrup et al., (2006) and Georgaki et al.(2021) , indicate that the majority of recurrent cases involve one or two recurrences, with three or more recurrences being relatively uncommon. This indicates that close monitoring and prompt intervention following the initial recurrence may assist in preventing subsequent recurrences, emphasising the significance of meticulous clinical management in such cases.

4.1.2. Malignant transformation rate

In the present study, only one case of malignant transformation of oral leukoplakia into squamous cell carcinoma was observed, resulting in a malignant transformation rate of 3.03%.

This figure is in close alignment with the global estimate of malignant transformation for oral leukoplakia (OL) of 3.5%, as reported by Warnakulasuriya & Ariyawardana (2016). The authors indicate a considerable range, from 0.13% to 34%. In annual terms, the estimated OL transformation rate is between 1.0% and 2.6%, which is slightly lower than the observed rate in the sample. The increased risk of malignant transformation is associated with several factors, including the clinical type (non-homogeneous), female gender, lesion size and the presence of epithelial dysplasia. These elements should also be considered when analyzing the risk for patients (Sundberg et al., 2019).

4.2. Gender

The data indicated a prevalence of 45.4% (15) in female OL cases and 54.5% (18) in male cases. In the female population, 50% of oral leukoplakia lesions exhibited recurrence, a figure mirrored by the male population, where 50% of lesions also demonstrated recurrence.

With regard to the estimated prevalence grouped by gender, a higher percentage of lesions is observed in men than in women, with statistically significant differences in clinical studies. Nevertheless, other studies indicate that although men are more affected in some countries, this discrepancy is not as pronounced in the Western world (Zhang et al., 2023).

Nevertheless, with regard to the recurrence rate of oral leukoplakia, no significant correlations were observed between age and gender and the recurrence of OL (Sundberg et al., 2019).

4.3. Age

In consideration of the age of the subjects at the time of lesion diagnosis, the mean age of the sample was found to be 59.11 years.

The term 'incidence' is used to describe the number of new diagnoses of a disease, whereas the term 'prevalence' is used to describe the number of existing cases. It can thus be inferred that the incidence of the disease tends to increase with age, reaching a peak at approximately 85 years of age and subsequently declining. Given that oral leukoplakia represents the most common potentially malignant lesion in the elderly, future studies

quantifying the incidence and risk factors for this condition are warranted (Ramesh et al., 2023).

It can be concluded that the diagnosis of potentially malignant lesions (oral leukoplakia) was significantly more prevalent in younger senior groups (aged 60-70 years), which is in accordance with the findings of this study (Radwan-Oczko et al., 2022).

The observed results may be attributed to an impaired capacity for DNA repair and carcinogen metabolism, as well as a reduction in immunological reactivity. Furthermore, older individuals have significantly less access to dental services than other age groups, largely due to physical and financial constraints (Feng et al., 2015).

Our study also revealed that when all other variables are held constant, the risk of multiple recurrences of oral leukoplakia increases by approximately 6.5% for each one-unit increase in age, meaning that for patients with the same characteristics, every 1 year older increases the risk of multiple recurrence by 6.5%.

Nevertheless, numerous studies have demonstrated that age is not a statistically significant predictor of recurrence in OL (Paglioni et al., 2022; Sundberg et al., 2019).

In our study the mean interval between surgical removal of the lesion and recurrence was 48 months, which is markedly longer than that reported in previous studies.

For example, in a previous study, the median duration between surgery and recurrence was 17 months, with a range between 2 and 40 months. This considerable discrepancy can be attributed to a number of factors, including differences in patient follow-up, variations in treatment, and the characteristics of the sample under investigation (Kuribayashi et al., 2012).

4.4. Risk factors

In the population studied, the majority of patients (69.7%) were non-smokers, while 30.3% were smokers. A recurrence of oral leukoplakia was observed in 91.70% of non-smoker patients and in only 8.30% of smokers. In contrast, among cases where no

recurrence was observed, 57.10% of patients were non-smokers and 42.90% were smokers.

This distribution suggests that recurrence of oral leukoplakia was more common among non-smokers, which may appear to be an unexpected finding given that smoking is a known risk factor for this condition. With regard to 'Habits', those who didn't have any showed an average increase in the risk of recurrence of around 16.6 times.

This may indicate that, for this sample, smoking was not the primary factor associated with recurrence, suggesting that other factors, such as genetic predispositions, dietary habits or treatments received, may have played a more significant role in cases of recurrence.

The history of tobacco use, including smoking and the use of snuff, did not demonstrate a statistically significant correlation with the frequency of recurrence of OL (Sundberg et al., 2019)

The majority of lesions are frequently associated with deleterious habits, such as smoking, which had an impact on the oral mucosa, leading to the development of various lesions, including smoker's melanosis (Ramesh et al., 2023).

The current body of literature does not yet establish a definitive consensus regarding the role of tobacco in the recurrence of OL. While some studies have identified tobacco use as a significant factor in the recurrence of the pathology, others have not found any association between tobacco use and recurrence (Chandu & Smith, 2005; Kuribayashi et al., 2012; Monteiro et al., 2017; Sundberg et al., 2019; Yang et al., 2011, 2021).

The impact of oral habits on the progression of malignant alterations in OL has yielded inconclusive findings, with some studies indicating a notable influence and others failing to detect a significant association (Yang et al., 2021).

4.5. Patients' systemic diseases

The aetiology of alterations to the oral mucosa is diverse, encompassing infections, physical and thermal factors, immunological alterations, systemic diseases, neoplasms

and trauma. It is evident that the presence of more than one lesion/condition at the same time in a single patient is prevalent in the elderly population, attributable to a multitude of factors including the natural ageing process, metabolic alterations, systemic diseases, nutritional factors, the use of prostheses, medication, psychobiological habits, as well as alcohol and tobacco consumption. Furthermore, a range of pathological conditions, including neoplasms, infections, immunological, haematological and systemic disorders, are frequently observed in the elderly, resulting in oral pain and discomfort (Ramesh et al., 2023).

In a separate study, a history of head and neck cancer was identified as a significant factor and an independent prognostic indicator associated with postoperative recurrence and malignant transformation. Further research is required to gain a deeper understanding of this issue (Yang et al., 2021).

The findings indicate a correlation immunological condition (allergies) and an elevated risk of leukoplakia recurrence, those with allergies having an average 9.35 times higher risk of leukoplakia recurrence compared to those without allergies. However, this relationship did not reach a clear statistical significance ($p = 0.057$), although it is marginally relevant and deserves to be investigated as it has not been identified in other studies.

With specific regard to the risk of multiple recurrences of oral leukoplakia, the data we analysed indicates that the presence of respiratory diseases is a strong risk factor for multiple recurrences, with an odds ratio (OR) of 12.665. This figure suggests that the presence of respiratory diseases increases the chance of the event occurring by 12.7 times. The association is highly significant, with a p-value of less than 0.001.

Giudice et al. (2020) propose that dyslipidaemia and asthma may serve as independent predictors of the presence of oral leukoplakia (OL). Although the study suggests a relationship between respiratory comorbidities (such as asthma) and oral leukoplakia, it does not present a specific odds ratio value comparable to that presented here. Furthermore, the authors emphasise the necessity for additional longitudinal studies to ascertain the temporal relationship between OL and chronic diseases. They suggest an

association between the two, however, their findings lack the same statistical clarity as our analysis.

In summary, both studies suggest a significant relationship between respiratory pathologies and health problems (multiple recurrences and oral leukoplakia), but our study provides more robust and clear statistical evidence of the magnitude of the association (OR of 12.7), while the study by Giudice et al. (2020). proposes a possible association, especially with asthma, which still requires further investigation to be fully confirmed.

4.6. Multifocal/Uni

The findings of this study indicate that recurrence was more frequent in patients with multifocal lesions, especially those with two or more than two lesions (totaling 58.40%), compared to those with unifocal lesions (41.70%). However, the difference in recurrence between unifocal and multifocal cases was not statistically significant ($p = 0.070$), suggesting no strong association between the number of lesions and recurrence in the sample analysed.

The presence of extensive leukoplakia, multiple leukoplakia in different anatomical locations, and sizable potentially malignant confluent lesions extending across multiple anatomical sites were identified as critical determinants of the risk of transformation into OSCC. Furthermore, the size or area of the leukoplakia on the tongue was identified as a significant factor related to postoperative recurrence, malignant transformation and an independent prognostic factor for recurrence. Patients with larger OL also exhibited diminished quality of life scores. It is therefore recommended that doctors pay closer attention to the treatment of extensive leukoplakia on the tongue and adopt more sophisticated and rigorous strategies in the follow-up of patients who have undergone surgery (Yang et al., 2021).

Nevertheless, numerous studies have demonstrated that there is no statistically significant correlation between the number of lesion sites and the recurrence of OL. This indicates

that the presence of multiple lesions does not serve as a reliable clinical predictor of OL recurrence (Sundberg et al., 2019).

4.7. Site of lesion

A comparison of our study with other studies in the literature reveals both similarities and differences in the location of oral leukoplakia (OL) and its recurrence.

In our study, 36.4% (12) of the lesions were located on the tongue, which was the most common site. A higher frequency of recurrence was observed in lesions located on the tongue, with 58.3% (7) of recurrence cases occurring in this area. Other sites included the 16.7% (2) on the gingiva, and 8.3% (1) each on the floor of the mouth and at the tongue and floor junction. However, the statistical analysis revealed no significant correlation between lesion location and recurrence ($p = 0.238$), a finding that aligns with the observations made in the study by Sundberg et al. (2019), where lesion location also demonstrated no statistically significant correlation with recurrence ($p = 0.34$).

In contrast, Sundberg et al., (2019) observed that 50% of lesions on the tongue and 50% of lesions on the floor of the mouth exhibited recurrence. These findings are comparable to our own, as the tongue was also identified as the site with the highest recurrence rate in our study. However, the study by Sundberg et al. (2019) reported a recurrence rate of 42% in gingival lesions, whereas our study found a recurrence rate of 16.7%. This discrepancy suggests that there may be variation in the results between studies.

Furthermore, the concern about the location of leukoplakia on the tongue, particularly in the ventral and lateral areas, as emphasised by Yang et al. (2021), is also reflected in our findings, as lesions on the tongue were more prone to recurrence. This similarity serves to reinforce the importance of paying special attention to lesions in this area, given that previous studies have associated the tongue with a higher risk of malignant transformation.

Based on the evidence, it can be concluded that while the location of the lesion, particularly on the tongue, appears to be a significant factor influencing the recurrence and risk of malignant transformation, statistical analyses do not consistently demonstrate

a statistically significant correlation between these factors. This suggests that the relationship between the location of leukoplakia and its recurrence or malignant transformation may be contingent on other factors, such as histological or genetic characteristics.

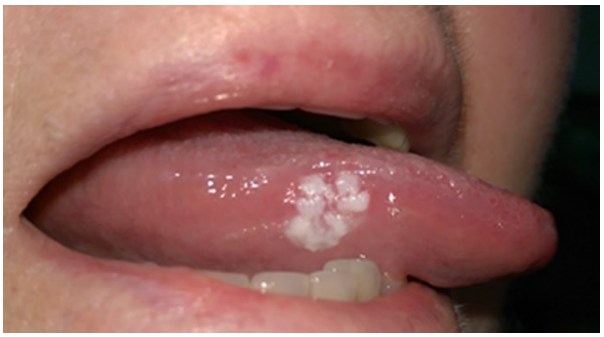


Figure 6-Oral leukoplakia affecting the tongue (image provided by António Mano Azul and Pedro Trancoso)

4.8. Dysplasia

The findings of our study indicate that the presence and degree of dysplasia were not statistically significant factors for the recurrence of oral leukoplakia lesions. The data analysis revealed that 11 (33.30%) of the lesions did not exhibit dysplasia, and 33.30% (7) of the cases without recurrence did not display dysplasia. However, 33.30% (4) of cases with recurrence also exhibited no dysplasia, indicating that the absence of dysplasia is not a determining factor for recurrence.

With regard to mild dysplasia ,15.20% of the lesions exhibited this degree, with a higher proportion of recurrences , 33.30% (4) compared to cases without recurrence ,4.80% (1). The lesions exhibiting moderate dysplasia, observed in 12.10%(4 cases) of the sample, demonstrated minimal differences between cases with and without recurrence (16.70% and 9.50%, respectively). Conversely, lesions exhibiting severe dysplasia, present in 3% of the lesions, were more frequently associated with recurrence (8.30%) and were not

observed in cases without recurrence. Nevertheless, the p-value (0.311) indicates that there is no statistically significant correlation between dysplasia and recurrence.

A comparison with other studies reveals a divergence in the literature on this topic. Monteiro et al. (2017) highlighted that dysplasia, in conjunction with clinical type and gender, was associated with elevated rates of malignant transformation, particularly in cases of severe dysplasia. This study lends further support to the view that the severity of dysplasia is a reliable predictor of malignant transformation. However, Paglioni et al. (2022).contend that although epithelial dysplasia is a potential predictor of recurrence or malignant transformation, there are subjective variations in its assessment, which may compromise its accuracy as a risk indicator.

Yang et al. (2021) dysplasia as an important risk factor, particularly moderate to severe dysplasia, associating it with a significant risk of recurrence and malignant transformation. They recommended complete excision of lesions with any degree of dysplasia. This finding is at odds with the results of our study, which revealed no statistically significant correlation between the presence or degree of dysplasia and the recurrence of lesions. Our findings suggest that, in our sample, dysplasia was not as reliable a predictor of recurrence as previously indicated in other studies.

In conclusion, although our study did not identify a significant correlation between dysplasia and recurrence, other research indicates that dysplasia, particularly in moderate to severe cases, may serve as a pertinent predictor of recurrence and malignant transformation. This emphasises the necessity for further research to resolve the discrepancies in the literature and enhance comprehension of the function of dysplasia in oral leukoplakia.

4.9. Clinical diagnosis

Oral white lesions are typically straightforward to diagnose clinically; however, in numerous instances, histopathological confirmation is imperative for various reasons. One such lesion is leukoplakia, which is one of the most common lesions and is potentially malignant. In 5-25% of cases, leukoplakia can develop into squamous cell carcinoma. Furthermore, some white lesions with entirely distinct pathological

aetiologies may manifest analogous clinical characteristics when observed with the naked eye (Coimbra et al., 2013).

The present study classified white oral lesions into three principal categories: non-homogeneous leukoplakia, homogeneous leukoplakia, and proliferative verrucous leukoplakia. The majority of cases were diagnosed as homogeneous leukoplakia (90.90%). Among these cases, 90.50% exhibited no recurrence, while 91.70% of recurrent cases were also classified as homogeneous.

Non-homogeneous leukoplakia constituted 3.00% of cases, with 4.80% of cases without recurrence falling into this category. Notably, there were no recurrent cases classified as non-homogeneous leukoplakia. Proliferative verrucous leukoplakia was diagnosed in 6.10% of cases, with 4.80% of these cases being non-recurrent and 8.30% with recurrence.

The statistical analysis of the study data yielded a p-value of 0.693, indicating that there was no statistically significant correlation between the clinical diagnosis and the recurrence of the lesions. This result suggests that, despite the observed differences in lesion types, the statistical analysis did not yield a clear association between clinical diagnosis and recurrence.

In comparison to other studies, such as that conducted by Sundberg et al. (2019), which identified a more pronounced correlation between non-homogeneous leukoplakia and an elevated risk of recurrence following surgical intervention, which contradicts our findings. Conversely, we state that there is a correlation between homogenous leukoplakia and an elevated risk of recurrence. Similarly, the study by Yang et al. (2021) corroborates the assertion that non-homogeneous leukoplakia is often associated with a higher rate of malignant transformation and recurrence after treatment.

Additionally, the study by Paglioni et al. (2022) reached a significant conclusion regarding the correlation between the non-homogeneous type of leukoplakia and an elevated risk of malignant transformation.

However, the study conducted by Ho et al. (2012) indicates that the relationship between the clinical presentation of leukoplakia and the risk of malignant transformation or recurrence remains unclear and varies according to the specific study in question.

In light of these findings, our study makes a valuable contribution to the understanding of oral leukoplakia. It highlights the importance of histopathological confirmation and indicates that, although there is a trend towards a higher risk associated with non-homogeneous leukoplakia, further investigation is required to reach definitive conclusions regarding the statistical correlation between clinical type and recurrence.

4.10. Histological diagnosis

The diagnosis of oral white lesions is typically straightforward at the clinical level. It is important to note that the diagnosis of leukoplakia is primarily clinical in nature. Histopathology is employed to eliminate other potential diagnoses and to ascertain the presence or absence of dysplasia, which is not exclusive to leukoplakia. Nevertheless, there are numerous instances in which the necessity for histopathological evidence arises for various reasons. In light of the high prevalence of erroneous clinical diagnoses of white lesions, it is recommended that histological examinations be conducted as a matter of course (Coimbra et al., 2013).

In this study, there was only 22 of the cases underwent histological (and it was compatible with oral leukoplakia). Among these cases, 47.6% (10) showed no recurrence, while all (100.0%) of the recurrence cases (12) were also in this category.

The role of histopathological grading of dysplasia in managing leukoplakia remains a topic of debate, as the relationship between malignant transformation and various risk factors is still unclear, and large cohort studies have yet to validate reliable biomarkers, with dysplasia grading often being regarded as important due to its link with recurrence and malignancy risk, many experts argue that it should not be the sole determining factor for treatment transformation (Yang et al., 2021). Given that even leukoplakia without dysplasia carries a risk of malignant transformation, there is growing consensus that surgical removal of all leukoplakias remains the true gold standard (Mohammed & Fairozekhan, 2023) .

4.11. Treatment

The present study offers significant insights into the treatment of oral leukoplakia (OL) and the recurrence of lesions. A comparison of our findings with those of the other related studies reveals both similarities and divergences.

Treatment methods were classified into two categories: surgery and topical retinoid therapy. The majority of patients were treated with surgery (69.7%). Among these cases, 47.80% exhibited no recurrence, while 52.20% of recurrent cases were treated with surgery.

Topical retinoid therapy was used in 21.2% of cases, with 100% of these patients showing no recurrence, and no recurrent cases were observed in patients treated with retinoids.

The statistical analysis of the study data yielded a p-value of 0.014, indicating a statistically significant correlation between the type of treatment and recurrence. This result suggests that topical retinoid therapy may be associated with a lower risk of recurrence compared to surgery in this sample.

The study by Mogedas-Vegara et al. (2015) indicates that incisional biopsy may result in an underestimation of dysplastic lesions compared to excisional biopsy. This suggests that up to 28% of dysplastic lesions may be underdiagnosed, and that 9% of squamous cell carcinoma (OSCC) cases may remain undetected. In our study, the majority of cases were treated surgically, and we found that surgical treatment was associated with a higher percentage of recurrence.

The study by Kuribayashi et al. (2012) discusses the use of different surgical techniques (scalpel, laser and cryosurgery) and the lack of consensus on the most appropriate treatment for OL. It is emphasised that recurrence and malignant transformation can occur irrespective of the surgical method employed. This finding is consistent with our own, as we also observed considerable recurrence rates among patients who had undergone surgical treatment (52.2% of operated patients experienced recurrence). However, our study did not directly investigate the different types of surgical techniques, focusing instead on conventional surgery, which limits direct comparison with methods such as laser and cryosurgery.

With regard to malignant transformation, Yang et al. (2020) report that surgery can be effective in reducing this risk, but the results vary between studies. They emphasise the importance of post-operative monitoring due to the possibility of recurrence and malignant transformation, a point we also highlighted in our analysis.

The study by de Pauli Paglioni et al. (2020) on the use of lasers for the treatment of OL demonstrated a significantly lower recurrence rate (16.5 per cent) in comparison to conventional treatments, including excision with a scalpel, electrosurgery and cryosurgery, where the recurrence rate can reach 49 per cent after five years. Although the present study focused on conventional surgical procedures, with a high recurrence rate (52.2 per cent) observed, the data provided by Pauli Paglioni et al. (2020) suggests that the use of lasers could be a promising alternative for reducing recurrence in patients with OL.

In conclusion, our study corroborates the finding that, despite the widespread use of excisional surgery, it does not necessarily lead to the complete elimination of lesion recurrence. In comparison with other studies it is evident that there is a multitude of approaches with disparate outcomes, yet no definitive consensus has been reached. Despite the potential benefits of surgical intervention, the risks of recurrence and malignant transformation necessitate careful consideration. Additionally, there is a need to explore alternative techniques, such as laser therapy, which may offer more favourable long-term outcomes in terms of reducing recurrence. A comparison with these studies reinforces the importance of a meticulous assessment of the specific treatment modality, as each approach has inherent limitations and benefits. Furthermore, it underscores the necessity for rigorous patient monitoring to detect and address potential recurrences and avert malignant transformation.

4.12. Limitations

It must be acknowledged that this study is not without its limitations. Firstly, the sample was not randomly selected and was instead chosen for convenience, which may compromise the representativeness of the results in relation to the general population. Furthermore, the sample size is relatively small, and the geographical scope is limited, which constrains the ability to generalize the findings to the national population.

Furthermore, the retrospective nature of the study may have resulted in the omission of certain variables, potentially impacting the overall completeness of the analyses. It is also important to consider the limitations imposed by the small number of patients and the short follow-up period in some cases.

A further pertinent issue pertains to the evaluation of risk factors. In this study, the distinction between smokers and non-smokers was considered without taking into account the frequency or number of cigarettes consumed. Furthermore, other potential risk factors, such as alcohol consumption and diet, which can significantly influence the results, were not assessed. Furthermore, the age of smokers, which can impact the immune response and, in turn, the recurrence of lesions, was not sufficiently taken into account.

In light of these limitations, the data must be interpreted with caution, particularly in the context of a retrospective study and with due consideration of variables that were not fully representative of reality. It is recommended that future studies be conducted on a larger scale, with multiple centers and a prospective design, to gain a more comprehensive and representative understanding of the disease and its risk factors.

V. CONCLUSION

The study revealed an oral leukoplakia (OL) recurrence rate of 36.36 per cent, with 12 out of 33 patients showing recurrence, a relatively high figure compared to other studies. Furthermore, the majority of cases involved one or two recurrences, with a maximum of five instances observed in a single patient. Our findings indicate that while recurrence is a significant concern in patients with oral leukoplakia, particularly following surgical intervention, multiple recurrences are relatively uncommon. This emphasises the necessity for close monitoring and prompt intervention to prevent further recurrences, thereby underscoring the importance of proactive clinical management strategies.

The rate of malignant transformation was 3.03 per cent, with only one case progressing to squamous cell carcinoma within a period of 2464 days between the initial diagnosis/excision and the subsequent malignant transformation. This is in line with the global rate of malignant transformation of OL, which has been reported to vary between 1.0 and 2.6 per cent per year. These findings underscore the variability in recurrence and malignant transformation rates, indicating that a complex interplay of factors shapes the clinical outcome.

With regard to gender, the data demonstrated a balanced distribution between men and women, with comparable recurrence rates for both groups (50% in each). Nevertheless, the incidence of OL was marginally higher in males (54.5%). Despite the absence of a statistically significant correlation between gender and recurrence, existing literature indicates that in certain regions, men may be more susceptible to leukoplakia, potentially due to cultural practices such as tobacco and alcohol consumption.

The impact of age on the risk of multiple recurrence has been a subject of investigation. The findings indicate that the risk increases with age, with age being a weak risk factor for multiple recurrences, associated with an increased risk of around 6.5%. Nevertheless, alternative research indicates that age may not be a statistically significant predictor in isolation. Oral leukoplakia is more prevalent in the elderly, necessitating greater attention due to their diminished DNA repair capacity and restricted access to healthcare services.

Another pertinent risk factor that was subjected to examination was tobacco consumption. It is noteworthy that the majority of patients who presented with recurrence (91.7 per cent) were non-smokers, which suggests that, for this specific sample, smoking may not

have been the primary trigger for recurrence. This finding gives rise to the hypothesis that genetic, dietary or treatment-related factors may have played a more significant role in this cohort of patients.

In addition, the analysis of oral habits revealed that those who did not have any harmful habits had an average increase of around 16.6 times in the risk of recurrence, which may indicate that, in this sample, factors other than tobacco, such as immunological conditions or the response to treatment, may have contributed more strongly to the reappearance of the lesions, highlighting the importance of considering multiple variables when analysing the behaviour of the disease.

Regarding patients' systemic diseases the data indicates that, while a statistically significant correlation between immunological conditions (allergies) and the risk of leukoplakia recurrence could not be demonstrated, a potential association exists. Individuals with allergies exhibited a 9.35 increased risk of recurrence. This indicates that immunological elements may influence the progression of oral lesions, although further investigation is required to substantiate this hypothesis.

The findings of our study indicate that respiratory diseases represent a significant risk factor for the multiple recurrences of oral leukoplakia. Our analysis revealed an odds ratio (OR) of 12.665, which suggests that the presence of these conditions increases the likelihood of the multiple recurrences by 12.7 times. The association is highly significant, with a p-value of less than 0.001, providing clear and robust statistical evidence of the magnitude of the relationship between respiratory diseases and multiple recurrences of oral leukoplakia. However, the lack of literature on this topic indicates a need for further research.

The study acknowledges several limitations, including the non-randomized, convenience-based sample selection, a small sample size, and a geographically limited study population, which limits generalizability. The study calls for larger, multi-center prospective research to provide a more comprehensive understanding of OL risk factors and recurrence.

In essence, the study indicates that oral leukoplakia is a multifactorial condition, with the risk of recurrence and malignant transformation contingent upon a combination of clinical

and histopathological factors. This emphasizes the necessity of meticulous clinical follow-up and the utilization of histopathological diagnoses to inform patient management strategies.

VI. BIBLIOGRAPHICAL REFERENCES

Aldagistani, A. (2022). *Lesões leucoplásicas nos utentes da clinica dentária universitária:um estudo retrospetivode 17 anos*. https://repositorio.ucp.pt/bitstream/10400.14/38564/1/203050711.pdf

Axell, T., Holmstrup, P., Kramer, I. R. H., Pindborg, J. J., & Shear, M. (1984). International seminar on oral leukoplakia and associated lesions related to tobacco habits. *Community Dentistry and Oral Epidemiology*, *12*(3), 145–154. https://doi.org/10.1111/j.1600-0528.1984.tb01428.x

Axéll, T., Pindborg, J. J., Smith, C. J., & van der Waal, I. (1996). Oral white lesions with special reference to precancerous and tobacco-related lesions: conclusions of an international symposium held in Uppsala, Sweden, May 18–21 1994. *Journal of Oral Pathology & Medicine*, *25*(2), 49–54. https://doi.org/10.1111/j.1600-0714.1996.tb00191.x

Bhargava, A., Shakeel, M., Srivastava, A. N., Raza, T., Rizvi, S., & Varshney, P. (2016). Role of human papilloma virus in oral leukoplakia. *Indian Journal of Cancer*, *53*(1), 206. https://doi.org/10.4103/0019-509x.180812

Birur, P., Patrick, S., Warnakulasuriya, S., Gurushanth, K., Raghavan, S., Rath, G., Chaturvedi, P., Chandru, V., Mathew, B., Prabhash, K., Gurudath, S., Mukhia, N., Sunny, S., Mehrotra, R., Vivek, V., Patil, S., Kumar, Gs., Fasalkar, S., Pratima, R., & Kuriakose, M. (2022). Consensus guidelines on management of oral potentially malignant disorders. *Indian Journal of Cancer*, *0*(0), 0. https://doi.org/10.4103/ijc.IJC_128_21

Carrard, V. C., & Van Der Waal, I. (2018). A clinical diagnosis of oral leukoplakia; A guide for dentists. *Medicina Oral Patologia Oral y Cirugia Bucal*, *23*(1), e59–e64. https://doi.org/10.4317/medoral.22292

Chandu, A., & Smith, A. C. H. (2005). The use of CO2 laser in the treatment of oral white patches: outcomes and factors affecting recurrence. *International Journal of Oral and Maxillofacial Surgery*, *34*(4), 396–400. https://doi.org/10.1016/j.ijom.2004.10.003

Coimbra, F., Nunes, I., Pereira-Lopes, O., & Felino, A. (2013). Correlação entre diagnóstico clínico e patológico das lesões brancas da cavidade oral. *Revista*

Portuguesa de Estomatologia, Medicina Dentária e Cirurgia Maxilofacial, *54*(3), 156–160. https://doi.org/10.1016/j.rpemd.2013.04.002

de Almeida, C. G., Freitas, F., Francisco, H., Marques, J. A., & Caramês, J. (2022). Oral biopsies in a Portuguese population: A 20-year clinicopathological study in a university clinic. *Journal of Clinical and Experimental Dentistry*, *14*(12), e1024–e1031. https://doi.org/10.4317/jced.59688

de Pauli Paglioni, M., Migliorati, C. A., Schausltz Pereira Faustino, I., Linhares Almeida Mariz, B. A., Oliveira Corrêa Roza, A. L., Agustin Vargas, P., Franco Paes Leme, A., Bianca Brandão, T., Prado Ribeiro, A. C., Ajudarte Lopes, M., & Santos-Silva, A. R. (2020). Laser excision of oral leukoplakia: Does it affect recurrence and malignant transformation? A systematic review and meta-analysis. In *Oral Oncology* (Vol. 109). Elsevier Ltd. https://doi.org/10.1016/j.oraloncology.2020.104850

Farooq, I., & Bugshan, A. (2020). Oral squamous cell carcinoma: Metastasis, potentially associated malignant disorders, etiology and recent advancements in diagnosis. *F1000Research*, *9*. https://doi.org/10.12688/f1000research.22941.1

Feng, J., Zhou, Z., Shen, X., Wang, Y., Shi, L., Wang, Y., Hu, Y., Sun, H., & Liu, W. (2015). Prevalence and distribution of oral mucosal lesions: a cross-sectional study in Shanghai, China. *Journal of Oral Pathology & Medicine*, *44*(7), 490–494. https://doi.org/10.1111/jop.12264

Flores-Hidalgo, A., Lim, S. O., Curran, A. E., Padilla, R. J., & Murrah, V. (2018). Considerations in the diagnosis of oral hairy leukoplakia—an institutional experience. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, *125*(3), 232–235. https://doi.org/10.1016/j.oooo.2017.10.017

Georgaki, M., Avgoustidis, D., Theofilou, V. I., Piperi, E., Pettas, E., Kalyvas, D. G., Vlachodimitropoulos, D., Perisanidis, C., Lazaris, A. C., & Nikitakis, N. G. (2021). Recurrence in Oral Premalignancy: Clinicopathologic and Immunohistochemical Analysis. *Diagnostics*, *11*(5), 872. https://doi.org/10.3390/diagnostics11050872

Giudice, L. W., Graff, E. A., Haripersad, Y., Frydrych, A. M., Parsons, R., Kujan, O., & Farah, C. S. (2020). Chronic disease comorbidity in patients with oral leukoplakia: A matched case–control study. *Oral Diseases*, *26*(5), 894–902. https://doi.org/10.1111/odi.13315

Guimarães, L. M., Diniz, M. G., Rogatto, S. R., Gomez, R. S., & Gomes, C. C. (2020). The genetic basis of oral leukoplakia and its key role in understanding oral

carcinogenesis. *Journal of Oral Pathology & Medicine*, *50*(7), 632–638. https://doi.org/10.1111/jop.13140

Hashibe, M., Sankaranarayanan, R., Thomas, G., Kuruvilla, B., Mathew, B., Somanathan, T., Parkin, D. M., & Zhang, Z.-F. (2000). Alcohol drinking, body mass index and the risk of oral leukoplakia in an Indian population. *International Journal of Cancer*, *88*(1), 129–134. https://doi.org/10.1002/1097-0215(20001001)88:1<129::aid-ijc20>3.0.co;2-u

Ho, M. W., Risk, J. M., Woolgar, J. A., Field, E. A., Field, J. K., Steele, J. C., Rajlawat, B. P., Triantafyllou, A., Rogers, S. N., Lowe, D., & Shaw, R. J. (2012). The clinical determinants of malignant transformation in oral epithelial dysplasia. *Oral Oncology*, *48*(10), 969–976. https://doi.org/10.1016/j.oraloncology.2012.04.002

Holmstrup, P., Vedtofte, P., Reibel, J., & Stoltze, K. (2006). Long-term treatment outcome of oral premalignant lesions. *Oral Oncology*, *42*(5), 461–474. https://doi.org/10.1016/j.oraloncology.2005.08.011

Jones, K., & Jordan, R. (2015). White lesions in the oral cavity: Clinical presentation, diagnosis, and treatment. *Seminars in Cutaneous Medicine and Surgery*, *34*(4), 161–170. https://doi.org/10.12788/j.sder.2015.0180

Kerr, A. R., & Lodi, G. (2021). Management of oral potentially malignant disorders. *Oral Diseases*, *27*(8), 2008–2025. https://doi.org/10.1111/odi.13980

Kumari, P., Debta, P., & Dixit, A. (2022). Oral Potentially Malignant Disorders: Etiology, Pathogenesis, and Transformation Into Oral Cancer. In *Frontiers in Pharmacology* (Vol. 13). Frontiers Media S.A. https://doi.org/10.3389/fphar.2022.825266

Kuribayashi, Y., Tsushima, F., Sato, M., Morita, K., & Omura, K. (2012). Recurrence patterns of oral leukoplakia after curative surgical resection: important factors that predict the risk of recurrence and malignancy. *Journal of Oral Pathology & Medicine*, *41*(9), 682–688. https://doi.org/10.1111/j.1600-0714.2012.01167.x

Mogedas-Vegara, A., Hueto-Madrid, J.-A., Chimenos-Küstner, E., & Bescós-Atín, C. (2015). The treatment of oral leukoplakia with the CO2 laser: A retrospective study of 65 patients. *Journal of Cranio-Maxillofacial Surgery*, *43*(5), 677–681. https://doi.org/10.1016/j.jcms.2015.03.011

Mohammed, F., & Fairozekhan, A. T. (2023). *Oral Leukoplakia*. StatPearls Publishing, Treasure Island (FL). http://europepmc.org/books/NBK442013

Monteiro, L., Barbieri, C., Warnakulasuriya, S., Martins, M., Salazar, F., Pacheco, J., Vescovi, P., & Meleti, M. (2017). Type of surgical treatment and recurrence of oral

leukoplakia: A retrospective clinical study. *Medicina Oral Patología Oral y Cirugia Bucal*, 0–0. https://doi.org/10.4317/medoral.21645

Monteiro, L. S., Salazar, F., Pacheco, J. J., Martins, M., & Warnakulasuriya, S. (2014). Outcomes of invitational and opportunistic oral cancer screening initiatives in Oporto, Portugal. *Journal of Oral Pathology & Medicine*, *44*(2), 145–152. https://doi.org/10.1111/jop.12216

Narayan, T., & Shilpashree, S. (2016). Meta-analysis on clinicopathologic risk factors of leukoplakias undergoing malignant transformation. *Journal of Oral and Maxillofacial Pathology*, *20*(3), 354. https://doi.org/10.4103/0973-029X.190900

Paglioni, M. de P., Khurram, S. A., Ruiz, B. I. I., Lauby-Secretan, B., Normando, A. G., Ribeiro, A. C. P., Brandão, T. B., Palmier, N. R., Lopes, M. A., da Silva Guerra, E. N., Meleti, M., Migliorati, C. A., Carvalho, A. L., de Matos, L. L., Kowalski, L. P., & Santos-Silva, A. R. (2022a). Clinical predictors of malignant transformation and recurrence in oral potentially malignant disorders: A systematic review and meta-analysis. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, *134*(5), 573–587. https://doi.org/10.1016/j.oooo.2022.07.006

Paglioni, M. de P., Khurram, S. A., Ruiz, B. I. I., Lauby-Secretan, B., Normando, A. G., Ribeiro, A. C. P., Brandão, T. B., Palmier, N. R., Lopes, M. A., da Silva Guerra, E. N., Meleti, M., Migliorati, C. A., Carvalho, A. L., de Matos, L. L., Kowalski, L. P., & Santos-Silva, A. R. (2022b). Clinical predictors of malignant transformation and recurrence in oral potentially malignant disorders: A systematic review and meta-analysis. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, *134*(5), 573–587. https://doi.org/10.1016/j.oooo.2022.07.006

Pandey, M., Thomas, G., Somanathan, T., Sankaranarayanan, R., Abraham, E. K., Jacob, B. J., & Mathew, B. (2001). Evaluation of surgical excision of non-homogeneous oral leukoplakia in a screening intervention trial, Kerala, India. *Oral Oncology*, *37*(1), 103–109. https://doi.org/10.1016/S1368-8375(00)00070-1

Pinto, A. C., Caramês, J., Francisco, H., Chen, A., Azul, A. M., & Marques, D. (2020). Malignant transformation rate of oral leukoplakia—systematic review. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, *129*(6), 600-611.e2. https://doi.org/10.1016/j.oooo.2020.02.017

Radwan-Oczko, M., Bandosz, K., Rojek, Z., & Owczarek-Drabińska, J. E. (2022). Clinical Study of Oral Mucosal Lesions in the Elderly—Prevalence and Distribution.

International Journal of Environmental Research and Public Health, *19*(5), 2853. https://doi.org/10.3390/ijerph19052853

Ramesh, M. V, Sri, K. B., Supriya, A. N., Manyam, R., Pasupuleti, S., & Ramesh, T. (2023). Prevalence of Oral Mucosal Lesions among Geriatric Patients: A Cross-sectional Study. *World Journal of Dentistry*, *14*(4), 340–345. https://doi.org/10.5005/jp-journals-10015-2214

Sundberg, J., Korytowska, M., Holmberg, E., Bratel, J., Wallström, M., Kjellström, E., Blomgren, J., Kovács, A., Öhman, J., Sand, L., Hirsch, J.-M., Giglio, D., Kjeller, G., & Hasséus, B. (2019). Recurrence rates after surgical removal of oral leukoplakia—A prospective longitudinal multi-centre study. *PLOS ONE*, *14*(12), e0225682. https://doi.org/10.1371/journal.pone.0225682

Thomas, G., Hashibe, M., Jacob, B. J., Ramadas, K., Mathew, B., Sankaranarayanan, R., & Zhang, Z.-F. (2003). Risk factors for multiple oral premalignant lesions. *International Journal of Cancer*, *107*(2), 285–291. https://doi.org/10.1002/ijc.11383

van der Waal, I. (2009). Potentially malignant disorders of the oral and oropharyngeal mucosa; terminology, classification and present concepts of management. *Oral Oncology*, *45*(4–5), 317–323. https://doi.org/10.1016/j.oraloncology.2008.05.016

van der Waal, I. (2015). Oral leukoplakia, the ongoing discussion on definition and terminology. *Medicina Oral, Patologia Oral y Cirugia Bucal*, *20*(6), e685–e692. https://doi.org/10.4317/medoral.21007

van der Waal, I. (2019). Oral Leukoplakia: Present Views on Diagnosis, Management, Communication with Patients, and Research. In *Current Oral Health Reports* (Vol. 6, Issue 1, pp. 9–13). Springer Science and Business Media B.V. https://doi.org/10.1007/s40496-019-0204-8

van der Waal, I., & Axéll, T. (2002). Oral leukoplakia: a proposal for uniform reporting. *Oral Oncology*, *38*(6), 521–526. https://doi.org/10.1016/S1368-8375(01)00125-7

Villa, A., & Sonis, S. (2018). Oral leukoplakia remains a challenging condition. *Oral Diseases*, *24*(1–2), 179–183. https://doi.org/10.1111/odi.12781

Villa, A., & Woo, S. Bin. (2017). Leukoplakia—A Diagnostic and Management Algorithm. *Journal of Oral and Maxillofacial Surgery*, *75*(4), 723–734. https://doi.org/10.1016/j.joms.2016.10.012

Warnakulasuriya, S. (2018). Clinical features and presentation of oral potentially malignant disorders. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, *125*(6), 582–590. https://doi.org/10.1016/j.oooo.2018.03.011

Warnakulasuriya, S. (2019). White, red, and mixed lesions of oral mucosa: A clinicopathologic approach to diagnosis. *Periodontology 2000*, *80*(1), 89–104. https://doi.org/10.1111/prd.12276

Warnakulasuriya, S. (2020). Oral potentially malignant disorders: A comprehensive review on clinical aspects and management. *Oral Oncology*, *102*, 104550. https://doi.org/10.1016/j.oraloncology.2019.104550

Warnakulasuriya, S., & Ariyawardana, A. (2016). Malignant transformation of oral leukoplakia: a systematic review of observational studies. *Journal of Oral Pathology & Medicine*, *45*(3), 155–166. https://doi.org/10.1111/jop.12339

Warnakulasuriya, S., Dietrich, T., Bornstein, M. M., Casals Peidró, E., Preshaw, P. M., Walter, C., Wennström, J. L., & Bergström, J. (2010). Oral health risks of tobacco use and effects of cessation. *International Dental Journal*, *60*(1), 7–30. https://pubmed.ncbi.nlm.nih.gov/20361572/

Warnakulasuriya, S., Johnson, Newell. W., & Van Der Waal, I. (2007). Nomenclature and classification of potentially malignant disorders of the oral mucosa. *Journal of Oral Pathology & Medicine*, *36*(10), 575–580. https://doi.org/10.1111/j.1600-0714.2007.00582.x

Warnakulasuriya, S., Kujan, O., Aguirre-Urizar, J. M., Bagan, J. V., González-Moles, M. Á., Kerr, A. R., Lodi, G., Mello, F. W., Monteiro, L., Ogden, G. R., Sloan, P., & Johnson, N. W. (2021). Oral potentially malignant disorders: A consensus report from an international seminar on nomenclature and classification, convened by the WHO Collaborating Centre for Oral Cancer. *Oral Diseases*, *27*(8), 1862–1880. https://doi.org/10.1111/odi.13704

Warnakulasuriya, S., Kujan, O., Aguirre-Urizar, J. M., Bagan, J. V., González-Moles, M. Á., Kerr, A. R., Lodi, G., Mello, F. W., Monteiro, L., Ogden, G. R., Sloan, P., & Johnson, N. W. (2021). Oral potentially malignant disorders: A consensus report from an international seminar on nomenclature and classification, convened by the WHO Collaborating Centre for Oral Cancer. In *Oral Diseases* (Vol. 27, Issue 8, pp. 1862–1880). John Wiley and Sons Inc. https://doi.org/10.1111/odi.13704

Yang, L.-Q., Xiao, X., Li, C.-X., Wu, W.-Y., Shen, X.-M., Zhou, Z.-T., Fan, Y., & Shi, L.-J. (2019). Human papillomavirus genotypes and p16 expression in oral leukoplakia and squamous cell carcinoma. *International Journal of Clinical and Experimental Pathology*, *12*(3), 1022–1028. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6945145/

Yang, S., Lee, Y., Chang, L., Hwang, C., & Chen, T. (2020). Clincopathological characteristics and treatment outcomes of oral leukoplakia by carbon dioxide laser excision in the elderly patients. *Head & Neck*, *42*(5), 1014–1023. https://doi.org/10.1002/hed.26074

Yang, S.-W., Lee, Y.-S., Chang, L.-C., Yang, C.-H., Luo, C.-M., & Wu, P.-W. (2021). Oral tongue leukoplakia: analysis of clinicopathological characteristics, treatment outcomes, and factors related to recurrence and malignant transformation. *Clinical Oral Investigations*, *25*(6), 4045–4058. https://doi.org/10.1007/s00784-020-03735-1

Yang, S.-W., Tsai, C.-N., Lee, Y.-S., & Chen, T.-A. (2011). Treatment Outcome of Dysplastic Oral Leukoplakia with Carbon Dioxide Laser—Emphasis on the Factors Affecting Recurrence. *Journal of Oral and Maxillofacial Surgery*, *69*(6), e78–e87. https://doi.org/10.1016/j.joms.2010.11.029

Zhang, C., Li, B., Zeng, X., Hu, X., & Hua, H. (2023). The global prevalence of oral leukoplakia: a systematic review and meta-analysis from 1996 to 2022. *BMC Oral Health*, *23*(1). https://doi.org/10.1186/s12903-023-03342-y