

Treatment of oral leukoplakia with CO₂ laser (10,600 nm): analysis of 37 cases

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Abstract: Oral leukoplakia is a potentially malignant disorder, defined as a white plaque that cannot be diagnosed as another known disease or disorder, and has an increased risk of malignancy. The aim of the present study was to evaluate the results of CO₂ laser treatment in a well-defined cohort of patients with oral leukoplakia in order to identify the occurrence of clinical outcomes of relapse, resolution, or malignancy after treatment. The study group comprised 37 patients. Before treatment, clinical photographs and incisional biopsies were obtained in all cases. In addition, the post-treatment results were documented using photographs. Evaluation of treatment results was performed by an independent researcher who had not performed the surgery. The minimum, maximum, and mean values of continuous variables were calculated. Statistically significant relationships were tested using the Cox regression analysis. A survival curve was constructed according to the Kaplan–Meier method to analyze the malignant transformation and recurrence of oral leukoplakia. The clinical outcomes analyzed were resolution, recurrence, and malignancy. The mean follow-up period was 36 months (range, 6–239 months). In 13/37 patients, leukoplakia recurred between 6 and 93 months (mean, 38.2 months). In 8/37 patients, a malignant transformation occurred (mean, 50.6 months). In 16/37 patients, lesion resolution occurred. No risk factor was statistically significant for malignancy or recurrence of lesions. The treatment of the lesions by CO₂ laser was efficient in the removal of the lesions; however, it did not avoid the clinical outcomes of recurrence or malignancy.

Keywords: Leukoplakia; Leukoplakia, Oral; Lasers; Lasers, Gas.

Introduction

Leukoplakia is a relatively common oral lesion that may precede the development of squamous cell carcinoma, although most lesions are asymptomatic.¹ The clinical location and presence of epithelial dysplasia are factors that may increase the incidence of malignant transformations.² Treatment of oral leukoplakia consists of conventional surgical excision, topical and systemic medication, laser surgery, and even conservative approaches.³

Many types of lasers have been described for laser surgery, such as Nd:YAG, diode, and carbon dioxide (CO₂)⁴ lasers. Since the 70s, studies have shown that CO₂ laser is an effective instrument for the treatment of



lesions of the oral mucosa. Soft tissues can be removed by superficial ablation with minimal thermal damage to adjacent tissues, resulting in minimal scarring and little postoperative pain and edema.⁵

In the treatment of leukoplakias with CO₂ laser, studies have shown recurrence rates ranging from 5.3% to 40.7% and malignant transformation rates ranging from 0 to 10.2%.⁶⁻⁹ Thus, it presents a wide range of results.

To date, there is still no evidence that treatment with oral leukoplakia prevents malignant transformation.¹

The present study aimed to evaluate the treatment results of CO₂ lasers for the treatment of patients with oral leukoplakias.

Methodology

In this retrospective study, 37 patients treated with CO₂ laser were included between 2000 and 2019, with definitive clinical and histopathological diagnosis of oral leukoplakia, with a minimum follow-up of 6 months after treatment. Proliferative verrucous leukoplakia cases were excluded from the study because they behave differently.

Oral leukoplakia location, presence/degree of epithelial dysplasia, age, sex, alcohol consumption, tobacco habits, clinical aspects (homogeneous or non-homogeneous), and lesion size were analyzed. Alcohol consumption and tobacco habits were registered as users or non-users in a simplified manner. Lesions were classified according to Axéll et al.¹⁰ as homogeneous leukoplakia using the following criteria: presence of a predominantly white lesion, with a flat, thin surface, which may show superficial cracks with a smooth, wrinkled or corrugated aspect, and consistent texture. Non-homogeneous leukoplakia was classified using the following criteria: presence of a predominantly white or reddish-white lesion, which may have an irregular, nodular, or exophytic surface. Lesion size was recorded in mm², multiplying the length by the width of the lesions, as proposed by Holmstrup et al.¹¹

Evaluation of treatment results was performed by an independent researcher who had not performed the surgery. The resolution, recurrence, and malignant transformation were analyzed for clinical outcomes.

Recurrence was defined as an oral leukoplakia that appeared within the limits of the treated area, regardless of size and time interval; for malignant transformation, it was defined as a carcinoma that appeared within the limits of the treated area.

Clinical photographs were taken from all patients of the primary lesions as well as any recurrence or malignancies.

The protocol for this study was submitted and approved by the Research Ethics Committee (3.239.256). All volunteers signed an informed consent form.

The UM-L30 (Union Medical Engineering Co, Incheon, South Korea; 10,600 nm, 5–10 W in continuous mode) CO₂ laser system was used in this study. The treatment was performed under local anesthesia. A margin of 4–5 mm around the lesion, as described by Vedtofte et al.,¹² was taken. After treatment, patients were evaluated for follow-up after 1 week and then monthly. They were instructed to return in advance if they noticed any changes (Figure 1).

The minimum, maximum, and mean values of the continuous variables were calculated. Statistically significant relationships were tested using the Cox regression analysis. Age, sex, alcohol consumption, tobacco habits, lesion homogeneity, lesion size, and the presence or degree of epithelial dysplasia were analyzed. Results were considered statistically significant at $p < 0.05$. A survival curve was constructed according to the Kaplan–Meier method to analyze the malignant transformation and recurrence of oral leukoplakia.

Results

The sample of 37 patients consisted of 23 women (mean age, 64.69 years; range, 35–88 years) and 14 men (mean age, 58.35 years; range, 18–80 years).

The follow-up period ranged from 6 to 239 months (mean, 36 months). No complications were reported in treated patients. The period for complete surgical wound repair by re-epithelialization after surgical treatment was between 4 and 5 weeks.

Habitual tobacco users included 13 patients (35%, 7 men and 6 women), while alcohol consumption was reported by nine patients (24%, 5 men and 4 women). There were six patients that both smoked and consumed alcohol (16.2%).

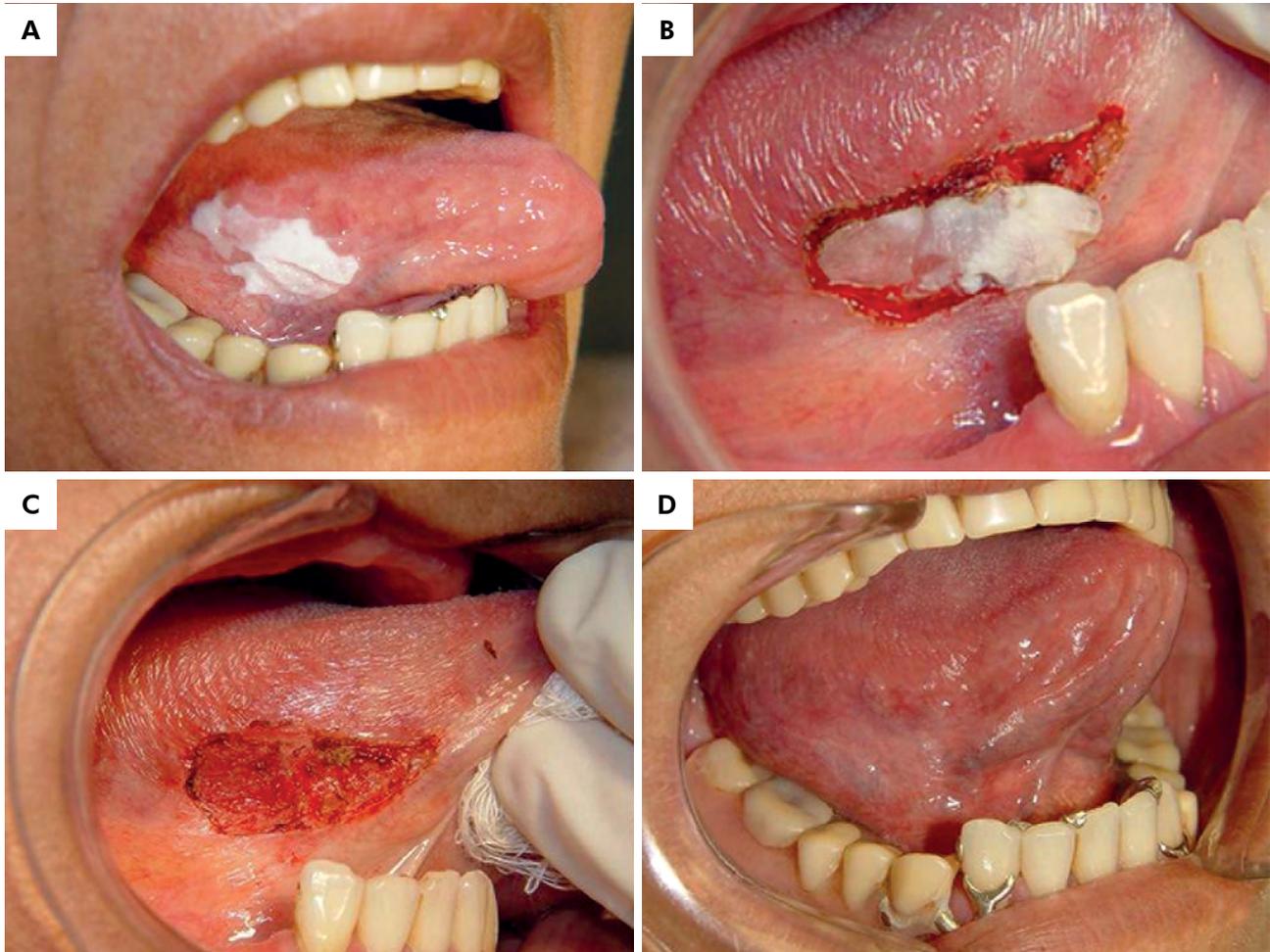


Figure 1. CO₂ laser technique. a) Leukoplakia on the lateral border of the tongue. b) Demarcation of the lesion. c) Complete excision of the lesion. d) Complete healing after 30 days.

Most of the oral leukoplakias were non-homogeneous (22/37; 59.45%), most of the lesions were larger than 200 mm² (26/37; 70.27%), and the most frequently

affected locations were the lateral border of the tongue (10/37; 27.02%), buccal mucosa (7/37; 18.91%), and other sites (7/37; 18.91%, Table 1).

Table 1. Clinical characteristics and locations of oral leukoplakias (n = 37)

Location	Clinical feature		> 200 mm ²	
	Homogeneous	Non- homogeneous	No	Yes
Floor of mouth	1	2	0	3
Lateral border of tongue	4	6	1	9
Dorsal tongue	1	1	1	1
Buccal mucosa	4	3	4	3
Multiple sites	2	4	1	5
Hard palate	1	0	1	0
Soft palate	0	1	0	1
Lower alveolus and gingiva	1	3	1	3
Upper alveolus and gingiva	1	2	2	1
Subtotal	15	22	11	26

The initial histopathological analysis of biopsies performed on oral leukoplakias indicated the presence of epithelial dysplasia in 29/37 patients (78.37%), mild dysplasia in 10 patients (27%), moderate dysplasia in 8 patients (21.6%), and severe dysplasia in 11 patients (29.7%, Table 2).

Eight patients experienced a malignant transformation (21.6%); recurrence outcomes occurred in 13 patients (35.1%), and lesion resolution occurred in 16 patients (43.2%). Malignant transformations occurred at a mean of 50.6 months (range, 6–144 months) after treatment of the initial lesion.

Table 2. Details of clinical and histopathological characteristics of patients diagnosed with oral leukoplakia and treated with CO₂ laser, with their respective clinical outcomes.

Dysplasia	Sex*	Race	Age	Location	Follow-up (months)	Outcome
Moderate	F	Black	41	Floor of mouth	6	Resolution
No dysplasia	F	Black	60	Lower alveolus and gingiva	6	Resolution
No dysplasia	F	Black	72	Multiple sites	6	Malignancy
Moderate	F	Black	72	Multiple sites	6	Recurrence
Severe	F	Black	76	Multiple sites	6	Resolution
Mild	M	White	57	Buccal mucosa	6	Resolution
Mild	F	White	65	Upper alveolus and gingiva	6	Resolution
Mild	F	White	77	Lateral border of tongue	6	Resolution
Moderate	M	White	80	Dorsal tongue	6	Resolution
Mild	M	White	84	Soft palate	6	Resolution
No dysplasia	F	White	84	Buccal mucosa	7	Recurrence
Mild	F	White	45	Lateral border of tongue	8	Resolution
Severe	F	White	35	Lateral border of tongue	9	Malignancy
No dysplasia	F	White	65	Hard palate	9	Resolution
Moderate	M	White	63	Lower alveolus and gingiva	12	Resolution
Severe	F	Asian	56	Lateral border of tongue	14	Resolution
Severe	M	Black	52	Lateral border of tongue	14	Malignancy
Severe	F	Asian	57	Lateral border of tongue	15	Recurrence
Mild	M	White	18	Dorsal tongue	16	Recurrence
Mild	F	White	42	Buccal mucosa	16	Resolution
No dysplasia	F	White	77	Upper alveolus and gingiva	20	Recurrence
Severe	M	White	64	Buccal mucosa	24	Malignancy
Moderate	F	White	78	Buccal mucosa	25	Recurrence
No dysplasia	F	White	88	Upper alveolus and gingiva	26	Recurrence
No dysplasia	F	White	60	Multiple sites	28	Resolution
Moderate	M	White	66	Lower alveolus and gingiva	30	Recurrence
Severe	F	Asian	66	Multiple sites	37	Recurrence
Severe	M	White	71	Lateral border of tongue	52	Malignancy
No dysplasia	F	White	52	Lower alveolus and gingiva	59	Recurrence
Severe	M	White	52	Lateral border of tongue	64	Malignancy
Mild	M	White	57	Floor of mouth	75	Resolution
Mild	F	White	58	Buccal mucosa	78	Recurrence
Severe	F	White	80	Lateral border of tongue	85	Recurrence
Moderate	F	White	82	Multiple sites	92	Malignancy
Moderate	M	White	54	Lateral border of tongue	93	Recurrence
Severe	M	White	58	Floor of mouth	144	Malignancy
Mild	M	White	65	Buccal mucosa	239	Resolution

*F: female; M: male.

The probability of recurrence after 50 months was approximately 76% (Figure 2), and the probability of malignancy free status after 50 months of follow-up was 87% (Figure 3). The Cox regression analysis (Table 3) for the factors analyzed (age, sex, alcohol consumption, tobacco habits, lesion homogeneity, lesion size, and presence/degree of epithelial dysplasia) did not show any statistical significance for the occurrence of recurrence or malignancy ($p > 0.05$).

Discussion

Of the studied sample, 23 patients were female (62%) and 14 patients were male (38%), a proportion of 1.64 to 1, with a mean age of 62.94 years (range, 18–88 years). White races were the most affected by oral leukoplakia (29/37; 75.6%). In the Brazilian population, a study¹³ evaluated 52 patients: 26 male patients (50%),

23 female patients (44%), and 3 without identification (6%); 77% were white, and the seventh decade of life was the most affected. In another study¹⁴ of 106 patients, 66 were male (62.3%) and 40 were female (37.7%); 66.7% were white, with a mean age of 56.09 years.

In this study, 9/37 patients reported using alcohol (24%), and 9/37 reported tobacco use (35%). Holmstrup et al.¹¹ studied 236 patients with oral leukoplakias and found that lesions were associated with smoking in 73% of the patients. In another study, 45.3% of patients were smokers and 33% used alcohol ($n = 106$)¹⁴.

In the present study, the most affected sites were the lateral border of the tongue (10/37; 27.02%), buccal mucosa (7/37; 18.91%), and other sites (6/37; 16.21%). The lesions located on the lateral border of the tongue, buccal mucosa, and floor of the mouth had a more rigorous clinical follow-up, likely because they are sites of greater risk for malignant transformation.

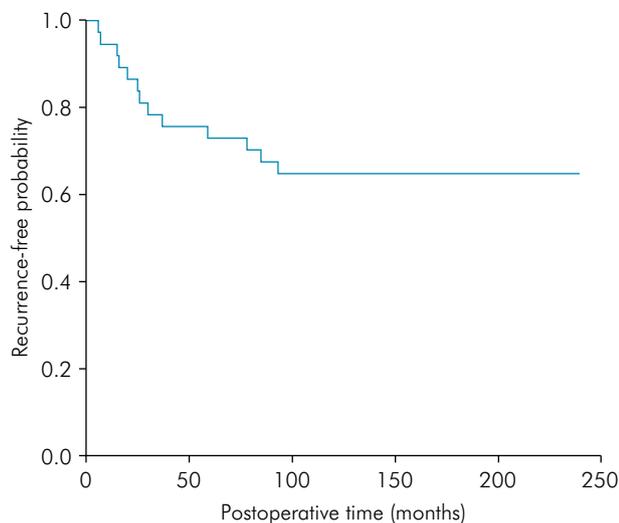


Figure 2. Kaplan–Meier curve for recurrence outcomes

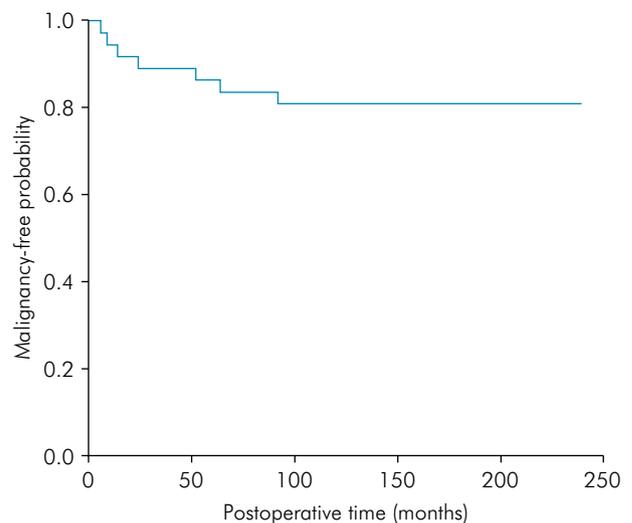


Figure 3. Kaplan–Meier curve for malignancy outcomes

Table 3. Cox regression analysis for the occurrence of clinical outcomes (recurrence and malignancy).

Variables	Risk rate	p-value	IC 95%
Age	0.987	0.4868	0.9513–1.0241
Sex	0.339	0.1061	0.0913–1.2590
Alcohol consumption	0.2914	0.1255	0.0602–1.4112
Tobacco habits	26.572	0.1409	0.7235–9.7584
Lesion homogeneity*	22.984	0.1591	0.7217–7.3200
Lesion size**	0.5081	0.2997	0.1413–1.8265
Degree of epithelial dysplasia***	11.134	0.6339	0.7156–1.7322

*Homogeneous or non-homogeneous; ** > 200 mm²; *** None, mild, moderate, or severe

When analyzing the clinical characteristics of the lesions, non-homogeneous lesions were the most prevalent (22/37; 59.45%), and a large proportion of lesions were greater than 200 mm² (26/37; 70.27%). Both characteristics are risk indicators of statistical significance for lesion malignancy of a lesion.¹¹ Most lesions were single/localized (22/37; 59.45%), a lower risk factor for malignant transformation.¹¹

Brouns et al.¹⁵ treated 35 oral leukoplakia patients with CO₂ laser; the only complication was temporary paresthesia of the mental nerve. In another study, 65 patients were treated and five had complaints of postoperative pain that was controlled with non-steroidal anti-inflammatory drugs.⁴ In this study, no trans- or postoperative complications were reported, demonstrating that the CO₂ laser technique is extremely safe. However, it is important that high-power lasers be used only by trained professionals.

In one study, the initial biopsy showed mild/moderate dysplasia in almost half of the patients (29, 44.6%) and hyperplasia without dysplasia in approximately one-third of the patients (21, 32.3%).⁴ In another study, 282 oral leukoplakias were analyzed; 152 lesions had no dysplasia (62.8%) and mild/moderate dysplasia was found in 75 lesions (31%).¹⁶ In the present study, the initial biopsy revealed epithelial dysplasia in 29 of 37 patients: 10 with mild dysplasia (27%), 8 with moderate dysplasia (21.6%), and 11 with severe dysplasia (29.7%).

Despite the benefits of treating oral leukoplakia with a CO₂ laser, many patients experience recurrences.¹⁷ Recurrence rates vary between 9.9% and 40%.^{4,15,16} In this study, recurrence outcomes were observed in 13 patients (35.1%).

Patients who did not stop chewing betel or smoking cigarettes were 19.8 or 9.7 times, respectively, more likely to develop recurrences of oral leukoplakia after treatment than those who stopped; continuous smoking after surgical treatment and multiple/generalized lesions are the prognostic indicators of recurrence after CO₂ laser surgery.¹⁸ In this study, 13 patients had recurrences of the lesion; of these, 3 continued smoking (23%) after treatment with the CO₂ laser, and 6 had multiple lesions (46.15%).

Lesion resolution occurred in 16 patients (43.2%) in this study, with a mean follow-up of 36.5 months. In a

study of 65 patients, the lesion resolved in 33 patients (50.76%), with a mean follow-up of 15 months.⁴ In another study involving 35 patients, the lesion resolved in 16 patients (45.71%), with a mean follow-up of 61.9 months¹⁵. In another study of 282 patients, the lesions resolved in 251 (89%) patients, with a mean follow-up period of 52 months.¹⁶ In the present study, malignant transformation occurred in eight patients (21.6%), with a mean of 50.6 months after CO₂ laser treatment. Of the 8 patients, only 2 smoked and consumed alcohol, while the other 5 did not smoke or drink alcohol. Other studies reported malignancy in 3 patients among 282 treated (1.1%),¹⁶ malignancy in 5 patients among 35 (14%)¹⁵, and malignancy in 10 patients among 65 treated (15.4%).⁴

In this study, of the 8 patients who had a malignancy, 6 had severe dysplasia at the initial biopsy (75%). For some authors, the greater the degree of dysplasia, the greater the risk of malignancy,¹⁹ while others consider that the relationship between the degree of dysplasia and the risk of malignancy is not statistically significant.¹¹ The available data do not allow for a subgroup analysis of lesions with or without dysplasia; therefore, it is not possible to establish whether any specific treatment can be more indicated in the presence of dysplasia of different degrees.¹ Many molecular biomarkers have been proposed, but no marker seems predictive enough to be implemented during clinical care.¹ However, although the number of patients treated in this study was limited, our findings corroborate the hypothesis that the greater the degree of dysplasia, the greater the risk of malignancy of oral leukoplakia.

The available evidence on the treatment of patients with oral leukoplakia is limited. Regarding the treatments available for oral leukoplakias, a wide range of options were trial-tested: retinoids/vitamin A, anti-inflammatory drugs, herbal extracts, bleomycin, carotenoids, and surgical interventions, including scalpel blade, laser surgery, and cryotherapy.¹ Although treatments with vitamin A and beta carotenes may be effective in the management of oral leukoplakias, relapses and side effects are common.¹ Surgical treatment of oral leukoplakia has not been evaluated in a randomized clinical trial that includes a comparison without treatment or with placebo (control group),

as well as with the cessation of risk factors such as smoking.¹ In our opinion, the difficulty in delineating a study as detailed above is in acquiring patients to be a part of the control group, as well as the virtual impossibility of carrying out a placebo group. In our experience, all patients opt for the surgical procedure with the CO₂ laser as opposed to conventional surgery or follow-up only.

In a recent systematic review,²⁰ authors analyzed 36 studies totaling 5.051 oral leukoplakias lesions that were treated by multiple laser systems. Most studies (67.5%) used a CO₂ laser. Overall recurrence and incidence of malignant transformation for oral leukoplakias occurred in 16.5% and 5.2% of subjects, respectively. They concluded that surgical laser excision of oral leukoplakia may decrease recurrence rates when compared with scalpel blade excision.

In addition to the effectiveness of treating oral leukoplakias using a CO₂ laser, it is necessary to analyze the cost of treatment. In countries like Brazil, which in many situations lack basic supplies for the clinical treatment of patients, the cost of the equipment is prohibitive for its use on a large scale.

Analysis of the Kaplan–Meier curve (survival analysis) revealed that the probability of treated patients not having any clinical outcome (malignancy or recurrence) after 50 months postoperatively was approximately 62%; the probability of no recurrence after 50 months was 76%, and the probability of no malignant transformation after 50 months was 87% (Figure 3). Authors performing the same analysis had an approximately 56% chance of being free of recurrences after 50 months and an approximately 80% chance of being free of malignancies after 50 months.¹⁵

Less than half (33% to 42%) of people with oral leukoplakia who undergo malignancy suffer from it within two years after diagnosis.^{21,22} However, in patients treated with CO₂ laser, as in this study or in the study by Brouns et al.,¹⁵ 87% and 80% of patients,

respectively, tended to be free of malignancy after 50 months of postoperative follow-up. It is possible that the treatment of oral leukoplakia with CO₂ laser delayed the occurrence of malignancy in these lesions.

In the Cox regression analysis (Table 3), the factors analyzed were age, sex, alcohol consumption, tobacco habits, lesion homogeneity, lesion size, and the presence or degree of epithelial dysplasia. We did not find any statistical significance for any of the predictive values as risk factors. The absence of statistical significance for the factors analyzed may be due to the small number of patients in this study.

Lesions that initially have an indolent clinical feature without dysplasia can develop malignant transformation, especially if time as a factor is considered; this makes it evident that these patients should be monitored throughout their lives.

Conclusions

The treatment of the lesions by CO₂ laser was efficient in the removal of the lesions, and clinical resolution occurred in 16 patients (43.2%); however, it did not avoid clinical outcomes of recurrence in 13 patients (35.1%) or malignancy in 8 patients (21.6%).

No risk factor was statistically significant for malignancy or recurrence of lesions. Most lesions with malignant transformation had severe dysplasia at the initial biopsy and were located on the lateral border of the tongue. The longer the postoperative time, the greater the likelihood of malignancy or recurrence; therefore, follow-up is necessary.

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