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ORIGINAL ARTICLE

Importance of the vaporization margin during CO_2 laser treatment of oral leukoplakia: A survival study

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Abstract

Objectives: The main purpose of this study was to assess the response of oral leukoplakia to CO_2 laser vaporization treatment, as well as determining possible factors that may affect recurrence of lesions.

Materials and methods: A retrospective study was conducted, in which the medical records of patients who had been clinically and histologically diagnosed with oral leukoplakia and treated with CO_2 laser between 1996 and 2019 at the Oral Medicine Teaching Unit of the Faculty of Dentistry of the University of Santiago de Compostela were reviewed.

Results: Fifty-eight patients were included: 36 female and 22 male subjects, with a mean age of 63.7 years old (SD ±13.1). The average follow-up time was 57.5 months (SD ±57.9). A relapse rate of 52.6% was determined. Of all the studied variables, the margin was the only one for which a statistically significant association with recurrence of lesions was demonstrated ($p < 0.05$).

Conclusion: The vaporization of lesions using CO_2 laser with a safety margin of at least 3 mm from the clinical limits of OL is a key factor in preventing recurrence.

KEYWORDS
carbon dioxide lasers, leukoplakia, oral, margins of excision, mouth mucosa

1 | INTRODUCTION

Oral leukoplakia (OL) is one of the most common potentially malignant disorder of the oral cavity (van der Waal, 2009). It was recently defined by a WHO collaborative centre as "white plaque with a questionable risk of malignancy once all other similar clinical lesions that carry no increased risk of cancer have been excluded" (Warnakulasuriya et al., 2021). It has an estimated prevalence of 4.11% (95% CI = 1.98–6.97; Mello et al., 2018); an annual risk of malignant transformation of between approximately 2% and 3% (Carrard & van der Waal, 2018) and the pooled proportion of malignant transformation is 9.8% (95% CI: 7.9–11.7), according to a systematic review covering the last 5 years (Aguirre-Urizar et al., 2021).

When treating OL, it is important to firstly eliminate any possible etiological factors, such as tobacco or alcohol consumption. If the lesion cannot be related to any of the above, or if it persists for longer than 3 months after the aforementioned factors have been eliminated, a biopsy must be taken in order to confirm the diagnosis

and determine the presence of dysplasia or carcinoma (Carrard & van der Waal, 2018).

Given that it is an asymptomatic lesion, the treatment procedure consists of preventing malignant transformation. Several different treatment approaches have been considered, which include safety excision, pharmacological treatment and no intervention. However, there is no evidence to date of any treatment that is effective in preventing the subsequent development of oral cancer. However, there is no evidence to date of any treatment that is effective in preventing the subsequent development of oral cancer (Arduino et al., 2021; Lodi et al., 2016).

Surgery is the most common treatment for OL patients. Findings in the literature have also shown that safety methods such as cold scalpel or CO_2 lasering achieve better results than systemic or topical medication (Mogedas-Vegara et al., 2016).

In particular, CO_2 laser produces minimal pain and inflammation, as well as providing a haemostatic effect, which is especially useful in large, vascularized zones, and which results in a clearer safety field, therefore making it possible to reduce the duration of the safety intervention (López-Jornet & Camacho-Alonso, 2013).

Even though there is no evidence that CO_2 laser treatment could prevent malignant transformation, the recurrence rate may decrease (de Pauli Paglioni et al., 2020). As a result of the foregoing and taking into consideration the fact that laser surgery is associated with low rates of intraoperative and postoperative complications, CO_2 laser surgery is an accepted safety option for the treatment of these lesions (Dong et al., 2019).

Few studies have actually addressed the treatment of OL using CO_2 laser and the factors related to its recurrence. Therefore, the objective of this study was to increase evidence and knowledge on this topic by assessing the response of OL to CO_2 laser vaporization treatment in a group of patients, as well as determining possible factors that may affect recurrence of lesions.

2 | MATERIALS AND METHODS

A retrospective follow-up study was conducted, in which the medical records of patients who had been diagnosed with OL and treated with CO_2 laser between 1996 and 2019 at the Oral Medicine Teaching Unit of the Faculty of Dentistry of the University of Santiago de Compostela were reviewed.

The following inclusion criteria were used: Patients who presented with clinical leukoplakia lesions confirmed by an incisional biopsy (having excluded other known diseases or disorders that carry no increased risk of cancer), who underwent CO_2 laser vaporization, with follow-up for at least one month following the laser treatment, and who presented with non-dysplastic or mild dysplastic lesions. On the contrary, the following exclusion criteria were used: Patients who presented with lesions with a white or predominantly white clinical appearance or histological findings, with a benign disease, such as leukoedema or linea alba buccalis, and with follow-up of less than one month after the laser treatment.

The study design was approved by the Santiago-Lugo Research Ethics Committee on November 19, 2019 (registration code: 2019/407).

The following data were collected: gender, age of diagnosis, tobacco and/or alcohol consumption, information related to the lesions (clinical type, location, number of lesions and degree of dysplasia), and information related to the CO_2 laser treatment (power, mode, margins and complications).

All patients, who were included once their records had been reviewed, had been managed according to the same protocol. Firstly, any possible causal factors were eliminated. If the lesion persisted for more than 3 months, an incisional biopsy was performed in order to confirm the OL diagnosis before commencing CO_2 laser treatment. Patients who presented with non-dysplastic and mild dysplastic OL lesions were considered as candidates for laser treatment. The laser used was LASERSAT 20 (Satelec®) in a continuous or pulsed mode, and the power was set to between 3 and 12 W depending on the operator's criteria. With regards to vaporization margins, differentiation was made between patients treated without safety margins, and those treated using vaporization at a distance of between 2 and 3 mm from the visible lesion margin. Initially, treatment was performed without margins until a new treatment protocol was established in which a margin of between 2 and 3 mm was used, therefore resulting in a shorter follow-up time for these patients. At each examination following vaporization, the evolution of lesions was verified. If the lesion had reappeared at the location that had been treated with laser, this was considered a recurrence, whereas, if no visible changes were observed in the treated area of oral mucosa, it was considered that the lesion had successfully resolved. Patients who presented with lesions in locations other than those that had been treated were not considered as cases of recurrence.

Data were subsequently analysed using SPSS software for Windows, version 20.0 (SPSS Inc). Descriptive analysis of the clinical factors and therapeutic parameters was conducted. Logistic regression analysis was performed to assess the effect of risk.

For the survival analysis, the Kaplan–Meier and log-rank test were used to assess whether the generated survival curves were significantly different. The study time was considered the period from vaporization until recurrence (non-censured observation), or until the end of patient follow-up (censored observation). All *p*-values (P) were bilateral and *p*-values of 0.05 or less were considered significant.

3 | RESULTS

The sample consisted of 58 patients: 36 female subjects (62.1%) and 22 male subjects (37.9%), and the average age at the time of diagnosis was 63.7 years old (34–94) (SD ±13.1).

With regards to their concomitant habits at the time of diagnosis, 15 patients (25.9%) were smokers and 10 were former smokers (17.2%). In addition, 26 (44.8%) stated that they drank at least one alcoholic drink per day.

A total of 78 lesions were included, 41 patients (70.7%) presented with multiple lesions and 23 of those lesions (29.3%) were found in high-risk locations (floor of the mouth, lateral and ventral side of the tongue). The most frequent location was the buccal mucosa (19.2%), followed by the gingiva (16.7%).

In the majority of cases (64.1%), no complications were reported. However, in 22 lesions (28.2%), postoperative pain was reported and granuloma was reported in 6 lesions (7.7%). The average follow-up time was 57.5 months (range 1–214, SD ±57.9).

Of a total of 78 lesions, complete resolution was reported for 37 of the lesions (47.4%), without any recurrences since the date of data collection. On the contrary, 2 patients developed Oral Squamous Cell Carcinoma (OSCC) at the same location where they had previously undergone laser treatment (2.6%) after 174 and 26 months, respectively. The average time to recurrence was 11.6 (SD 26.5) months after laser treatment.

The chi-square test was used to compare the studied qualitative variables to the evolution of the lesions following laser treatment, and a statistically significant relationship with the margins used was observed ($p < 0.5$; Table 1).

A risk of recurrence of 5.4 in vaporized lesions was obtained in cases in which no margin was left from the visible limits of the lesion at the time of treatment ($p < 0.05$; Table 2).

Lastly, a survival analysis was conducted for the total sample population (Figure 1) in order to show the evolution with respect to follow-up time. The disease-free survival (DFS) was 52.9% (SE ±0.061) at 1 year, 41.7% (SE ±0.061) at 3 years, and 26.0% (SE ±0.114) at 15 years.

The survival curves show that in the group of patients treated with margins, no recurrence occurred in the first year, while in the group of patients treated without margins, the disease-free survival (DFS) was 44.3% (SE ±0.065). In the group treated with margins, the DFS at 2 years was 70.0% (SE ±0.182) and without margins this was 37.2% (SE ±0.064). The log-rank test revealed the delimitation of the safety margin as a factor with a statistically significant relationship to recurrence after vaporization ($p = 0.038$; Figure 2).

TABLE 1 Clinical characteristics of the patients taking into account the evolution following CO_2 laser treatment (resolution against recurrence)

	Evolution *n* (%)		
Qualitative variables	**Resolution**	**Recurrence**	***p*-value**
Sex			
Male	10 (17.2%)	12 (20.7%)	0.940
Female	16 (27.6%)	20 (34.5%)	
Age			
≤65 years old	16 (27.6%)	17 (29.3%)	0.520
>65 years old	10 (17.2%)	15 (25.9%)	
Clinical type			
Homogeneous	12 (15.4%)	19 (24.4%)	0.210
Non-homogeneous	25 (32.1%)	22 (28.2%)	
Location			
Low risk	28 (35.9%)	27 (34.6%)	0.342
High risk	9 (11.5%)	14 (17.9%)	
No. of lesions			
Single	11 (14.1%)	6 (7.7%)	0.107
Multiple	26 (33.3%)	35 (39.7%)	
Degree of dysplasia			
None	34 (43.5%)	33 (42.3%)	0.148
Mild dysplasia	3 (3.8%)	8 (10.3%)	
Tobacco consumption			
Non-smoker	22 (28.2%)	26 (33.3%)	0.176
Smoker	5 (6.4%)	10 (12.8%)	
Ex-smoker	10 (12.8%)	5 (6.4%)	
Alcohol consumption			
Yes	14 (17.9%)	18 (23.1%)	0.587
No	23 (29.5%)	23 (29.5%)	
Margins			
Yes	8 (10.3%)	2 (2.6%)	0.027
No	29 (37.2%)	39 (50.0%)	
Mode			
Continuous	32 (41.0%)	36 (46.2%)	0.862
Pulsed	5 (6.4%)	5 (6.4%)	
Power			
≤6 W	15 (19.2%)	25 (34.6%)	0.071
>6 W	22 (28.2%)	16 (17.9%)	
Complications			
Yes	12 (15.4%)	16 (20.5%)	0.544
No	25 (32.1%)	25 (32.1%)	
Tobacco consumption during follow-up			
Yes	4 (5.1%)	8 (10.3%)	0.288
No	33 (42.3%)	33 (42.3%)	

4 | DISCUSSION

The recurrence rate in this study was 52.6% after an average follow-up period of 4.8 years. This percentage is high compared with other studies. In the literature, this rate varies between 3.1% and 40.7% for a follow-up time from 1 to 6.4 years (Mogedas-Vegara et al., 2016).

According to this data, disease-free survival (DFS) was 52.9% during the first year. Pedrosa et al. (2015) reported a DFS of 88% after a year of follow-up; Chandu and Smith (2005) found a DFS of 55.4% at 3 years, which decreased to 33.9% at 5 years, therefore indicating the importance of carrying out regular long-term follow-up in order to detect possible recurrence. Lim et al. (2010) obtained a DFS of 57.5% at 3 years and 35.9% at 5 years, which is similar to the findings of this study (DFS of 38.9% at 5 years).

These differences with other studies may be due to the fact that the majority of patients in the present study were treated without margins, and these patients have a longer follow-up period because they were treated with margins at a later stage.

Independent variables (reference category)	Bivariate mode		
	OR	CI 95%	*p*-value
Margins (yes)	5.379	(1.062–27.247)	0.042
Degree of dysplasia (no dysplasia)	2.747	(0.670–11.261)	0.160
Power (>6 W)	2.292	(0.924–5.682)	0.073
Number of lesions (single)	2.468	(0.808–7.539)	0.113
Tobacco consumption during treatment (no)	2.000	(0.549–7.292)	0.294

TABLE 2 Adjustment of bivariate logistic regression to measure the risk effect, considering the evolution of the lesion as a dependant variable, and the clinical risk factors as independent variables

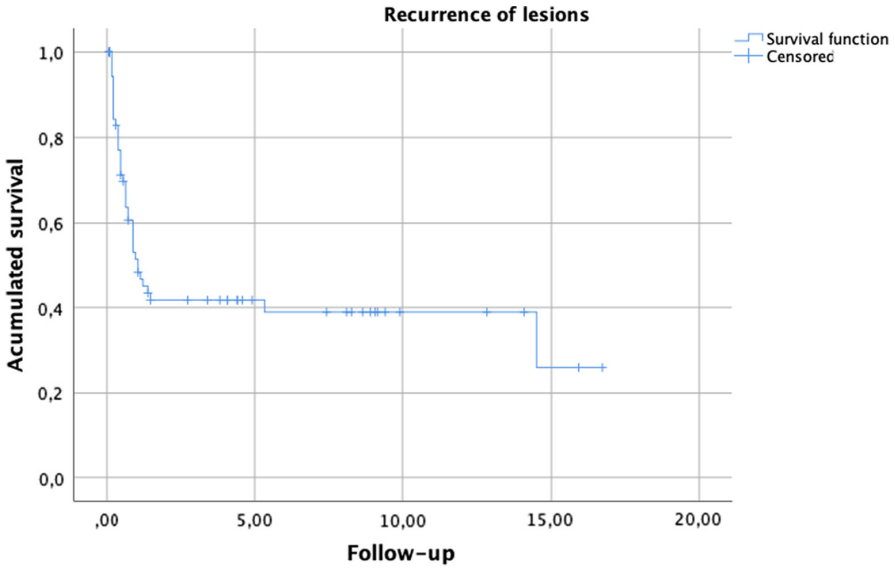

FIGURE 1 Kaplan–Meier curve showing the relapse during the follow-up period (years)

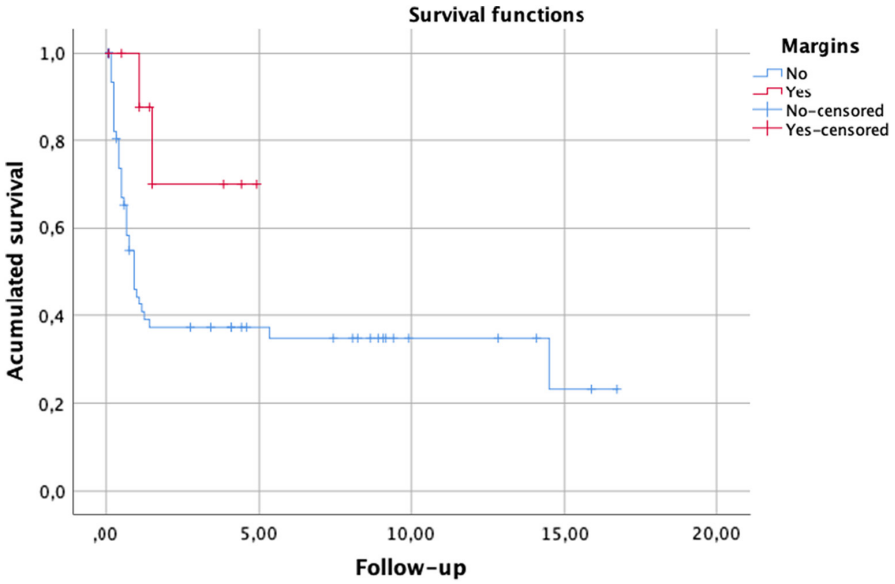

FIGURE 2 Survival curve comparing evolution depending on clearance of margins

By using logistic regression analysis, it was observed that lesions treated without safety margins had a 5 times higher risk of recurrence than those treated with margins. In fact, the recurrence of lesions treated with a margin of at least 3 mm from the visible limits of the lesion was much less than in those treated without any margin ($p < 0.05$), and this was the only significant clinical variable in relation to recurrence in the survival study, once the log-rank test had been used, despite the lower number of cases and shorter follow-up time. These results concur with the clinical trial performed by Romeo et al., in which a 45.5% recurrence in the group treated without margins was obtained, compared with a 36.4% recurrence in the group treated with at least 3 mm of margin, after 6 months of

follow-up (Romeo et al., 2020). Moreover, a study by Chainani-Wu et al. (2015), in which OL lesions were assessed, poor accessibility to the margins of the lesions was noted, with the oral cavity being divided into 3 areas, denoted from best to worse accessibility as an indicator of early OL recurrence, highlighting the importance of the adequate elimination of the OL margins. Additionally, Farah. et al. analysed the molecular differences between autofluorescence and white light in oral potentially malignant disorders excision margins, concluding that autofluorescence determined margins were superior to the white light margin in achieving a clear molecular margin (Farah et al., 2018).

In this study, patients who continued smoking or who started to smoke again during the follow-up period had a risk of recurrence that was twice as high, as patients who ceased smoking. However, this factor was not statistically significant ($p = 0.294$). Other authors such as Romeo et al. (2020) reported similar findings, observing that there was a significant relationship between tobacco consumption and complete resolution of the OL after therapy, with a lower percentage of complete resolution reported in former smokers (42.8%). Yang et al. (2011) also established that continuing to consume tobacco or chewing betel was significantly related to postoperative recurrence. However, many other studies have not shown any association between this factor and recurrence of OL lesions (Chainani-Wu et al., 2015; Del Corso et al., 2015; Mogedas-Vegara et al., 2015; Monteiro et al., 2017; Pedrosa et al., 2015).

The degree of dysplasia is one of the factors that is most commonly linked to recurrence (Pedrosa et al., 2015; Yang et al., 2011; Yang et al., 2021). Pedrosa et al. (2015) linked high-grade dysplasia to a DFS of 25% at 6 months after laser treatment, compared with a DFS of 94% in patients with low-grade dysplasia or no dysplasia. Likewise, a study carried out by Yang et al. (2011) showed that patients who do not cease smoking or betel chewing following the surgical procedure, those with multifocal lesions, those with non-homogeneous forms, and those with a high-grade of dysplasia had a greater tendency for recurrence. Our study did not observe a statistically significant relationship between dysplasia and recurrence; however, we did note a 2.7 times greater risk of recurrence in patients who presented with mild dysplasia. In this context, our data is limited because only patients with mild dysplasia or no dysplasia underwent laser treatment.

In terms of the number of lesions, the data recorded in the literature is somewhat controversial. Mogedas-Vegara et al. (2015) did not determine a statistically significant relationship between multiple lesions and recurrence or malignant transformation. On the contrary, Yang et al. (2011) established that there was a statistically significant relationship between multifocal lesions and recurrence. Our data shows that patients with multiple lesions had a 2.5 times greater risk of recurrence ($p = 0.113$) than patients with a single lesion. PVL is formed initially as a white plaque that evolves into slow-growing multifocal lesions that are resistant to treatment. It has a high rate of recurrence and a tendency for malignant transformation (Capella et al., 2017). The diagnosis of this entity is complex, and it is possible that many multifocal OLs could evolve into PVL, therefore explaining the high tendency for recurrence in our study.

With regards to complications following CO_2 laser treatment, in this study, pain and granuloma formation were observed. Pain is the most frequently reported complication (Chee & Sasaki, 2013; Deppe et al., 2012; Romeo et al., 2020; Tambuwala et al., 2014). Despite this, López-Jornet and Camacho-Alonso (2013) concluded that pain and swelling is more frequent when using a cold scalpel than when using CO_2 laser, and unlike our study, they did not observe granuloma formation. Other less frequent complications that have been reported in the literature include granulomas, bleeding, paraesthesia, sialadenitis, headache, difficulty speaking or swallowing and obstruction of the submandibular gland, among others.

Lastly, very few studies in the literature have actually considered the most suitable laser power and mode for treating OL lesions. Although no differences have been observed in relation to the mode, the data obtained demonstrate that the risk of recurrence was 2.3 times higher ($p = 0.073$) amongst the group in which a laser power of less than 6.8 W was used. With regards to the laser mode, Deppe et al. (2012) found that the lowest statistically significant recurrence rates were obtained when using the defocused continuous laser beam delivery technique, followed by the continuous wave mode plus scanner and super-pulsed mode pulse scanner, and, likewise, it was determined that other techniques with less penetration of the thermal effects, were unable to reach the deeper cells, therefore producing higher rates of recurrence. In relation to the technique used, Nammour et al. (2017) found that the method in which complete superficial vaporization of the lesion was performed in 2 runs had a lower success rate compared with other methods in which excision was performed.

According to the literature, numerous factors can provoke the recurrence of OL after laser treatment (Galletta et al., 2017). In a retrospective study that analysed lingual OL lesions treated with CO_2 laser excision, when performing the multivariate logistic regression study, the only prognostic factor for recurrence was the size of the lesion (Yang et al., 2021). Chandu and Smith (2005) pointed out that alcohol consumption and a previous history of malignant lesions were factors for recurrence. On the contrary, other studies did not find any relationship with any of the analysed factors. This includes the study by Thomson and Wylie (2002), in which tobacco and alcohol consumption, the initial lesion appearance and the histologic diagnosis were not related to recurrence.

5 | CONCLUSION

Despite the fact that an effective treatment for OL is yet to be developed, CO_2 laser vaporization is a valid treatment with a low rate of postoperative complications, although it is not free of recurrence; therefore, it is fundamental that patients undergo regular follow-up examinations in the long term.

CO_2 laser vaporization with a safety margin from the clinical limits of the lesion appears to be an important factor in preventing

recurrence, and a margin of at least 3 mm is advisable, where possible. Nevertheless, further research are needed to support these conclusions. As this topic has not been widely addressed in the existing literature, prospective studies that shed light on the role that wider margins play in the removal of leukoplakia and the prevention of recurrence would be necessary.

AUTHOR CONTRIBUTIONS

Marta Vilar Villanueva: Data curation; formal analysis; investigation; methodology; writing—original draft; writing—review and editing. **Jos Manuel Somoza-Martn:** Project administration; resources; supervision. **Andrs Blanco Carrin:** Project administration; resources; supervision. **Abel Garcia:** Project administration; resources; supervision. **Tamara Garca-Carnicero:** Investigation; resources. **Xabier Marichalar-Menda:** Formal analysis; methodology; software. **Mercedes Gallas-Torreira:** Resources; supervision. **Pilar Gandara Vila:** Conceptualization; investigation; project administration; resources; supervision; validation; writing—review and editing.

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CONFLICT OF INTEREST

None to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

PEER REVIEW

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