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The treatment of oral leukoplakia with the CO_2 laser: A retrospective study of 65 patients

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ABSTRACT

The use of CO_2 laser has become a routine procedure for the treatment of oral leukoplakia. In this retrospective study, we evaluated 65 patients with oral leukoplakia treated with CO_2 laser vaporization. The main location was the tongue (n = 21/65, 32.3%). The initial biopsy showed mild/moderate dysplasia in almost half the patients (n = 29, 44.6%) and hyperplasia without dysplasia in around a third of the patients (n = 21, 32.3%). The recurrence and malignant transformation rates were 33.8% (n = 22) and 15.4% (n = 10), respectively. The follow-up mean (standard deviation) was 15.0 (10.6) months. The procedure-related complications rate was 7.7% (n = 5). The Kaplan–Meier curves for time to recurrence showed differences only for gingiva lesions compared to tongue lesions (log rank, p = 0.032). Malignant leukoplakia transformation is independent of treatment, although it seems advisable to treat leukoplakia with or without dysplasia.

1. Introduction

The World Health Organization (WHO) first defined oral leukoplakia as a white patch or plaque that could not be characterized clinically or pathologically as any other disease (Axell et al., 1996). At a workshop coordinated by the WHO in 2005, "potentially malignant disorder" was the preferred terms, with the working group agreeing that the term leukoplakia should be used to recognize "white plaques of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer" (Warnakulasuriya et al., 2007). Prevalence of oral leukoplakia is reported to be approximately 2% (Petti, 2003; Brouns et al., 2013a, 2013b) and the annual malignant transformation rate is estimated to be between 0.13% and 17.5% (Deppe et al., 2012; Kumar et al., 2013; Brouns et al., 2014). Leukoplakia is considered to be the most common premalignant lesion of the oral cavity; its occurrence is related to smoking, with alcohol as an independent factor. The role played by human papilloma virus is currently unknown (Van der Waal, 2009). Risk factors associated with malignant leukoplakia transformation are: female gender, longer duration, non-smokers, location on the tongue, size >200 mm^2, nonhomogeneous type and presence of *Candida albicans*, or epithelial dysplasia (Van der Waal, 2009, Ho et al., 2013). Head and neck cancers are the sixth most common cancer worldwide and are considered an important public health problem because of the poor prognosis and associated high morbidity and mortality (Jerjes et al., 2011).

Incisional biopsy and histopathological examination are the gold standard in diagnosis. Early detection of oral lesions increases survival rates; hence, early and minimally invasive treatment would be indicated for those patients who would be expected to have low recurrence rates (Deppe et al., 2012; Brouns et al., 2013a; Kumar et al., 2013). Several treatments have been suggested in the literature, including surgery, electrosurgery, cryosurgery, topical agents (bleomycin, vitamin A), systemic agents (β-carotene, lycopene, retinoids), CO_2 laser and photodynamic treatment, although surgery and CO_2 laser are most frequently used. There is still no evidence that treatment prevents malignant transformation, although it seems advisable to treat oral leukoplakia with or without dysplasia (Horch et al., 1986; Chandu and Smith, 2005; Van der Waal, 2009; Santos et al., 2010; Yang et al., 2011; Song and Franco, 2011; Brouns et al., 2014).

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New technologies and improvements in oral and maxillofacial surgery and especially in laser surgery prove less invasive and more comfortable for patients. The use of CO_2 laser is becoming increasingly common in the treatment of oral leukoplakia and malignant tumours, with outcomes, advantages and disadvantages fully reported in the literature (Chandu and Smith, 2005; Escribano-Bermejos and Bascones-Martínez, 2009; Yang et al., 2011; Deppe et al., 2012; Goodson et al., 2012). CO_2 laser can be used for both excision and vaporization. For vaporization, preferred for large lesions, a prior biopsy is necessary (Chandu and Smith, 2005; Santos et al., 2010; Deppe et al., 2012; Brouns et al., 2013a, 2014). Vaporization has also been used to resect small (T1/T2) oral squamous cell carcinoma (OSCC), with results comparable to those of surgery (Jerjes et al., 2011).

We retrospectively reviewed the results for a sample of patients with oral leukoplakia treated with CO_2 laser. Our main objective was to evaluate treatment results, and our secondary objectives were to determine the recurrence and malignant transformation rates, to quantify complications associated with the procedure, and to suggest a follow-up protocol.

2. Material and methods

A total of 65 patients were treated with CO_2 laser vaporization between January 2010 and April 2013. Medical records were reviewed to evaluate demographic data, history of OSCC, location of the lesion, histological malignancy grade, complications, recurrences, and malignant transformation.

A histopathological diagnosis of leukoplakia was obtained prior to surgery on the basis of an incisional biopsy. All surgical procedures were performed under local anesthesia via local tissue infiltration with articaine hydrochloride (72.0 mg) and epinephrine (0.018 mg). A Lumenis CO_2 laser (10.6-μm wavelength) set up in superpulse focused mode was used for vaporization (15 W). The mucosa–handpiece distance was 15–20 mm, handpiece focus length was 125 mm, laser exposure was 20 s, spot diameter was 0.3 mm, and fluence energy was 4,244 J/cm^2. Depending on the location of the lesion, buccal mucosa, lip, or tongue were separated using gauze. The laser was tested on a moist gauze prior to each surgery, and the mandatory special mask and glasses were worn. A high-potency vacuum device was used to aspirate the laser plume. Clinical pictures of the oral leukoplakia were taken in the operation room and during follow-up. Prescribed for postoperative care were 0.12% chlorhexidine gel and 600 mg of ibuprofen every 8 h. Follow-up examinations were performed according to our protocol on day 7 after surgery, every 3 months in the first year, every 6 months in the second year, and annually thereafter.

2.1. Statistical analysis

Demographic and clinical variables were analyzed descriptively, and categorical variables were reported as frequencies and percentages. The Shapiro–Wilks statistic was used to test the distribution of continuous variables, described as mean (standard deviation) if they followed a normal distribution or as median (interquartile range) otherwise. Kaplan–Meier curves with log-rank tests were used to assess time to recurrence and malignant transformation according to the different clinical characteristics of interest. Univariate Cox regression was used to identify risk factors for recurrence and malignant transformation, calculating the hazard ratio (HR) and establishing a 95% confidence interval (95% CI). A p value of less than 0.05 in these tests was considered to indicate statistical significance. SPSS 18.0 for Windows (SPSS Inc, Chicago, IL, USA) was used for all statistical analyses.

3. Results

The study cohort consisted of 65 patients who underwent vaporization at our center between January 2010 and April 2013. The median follow-up was 15.0 (0.3–38.7) months. Demographic and clinical characteristics of the patients are summarized in Table 1. Just under half the patients were male (n = 32, 49.2%), patient mean age at surgery was 66.2 (13.1) years, and 15 patients (23.1%) had a history of OSCC. Primary sites were mainly identified in the tongue (n = 21, 32.3%) and the gingiva (n = 19, 29.2%). The initial biopsy showed mild/moderate dysplasia in almost half the patients (n = 29, 44.6%) and hyperplasia without dysplasia in around a third of patients (n = 21, 32.3%). Half the gingiva lesions presented no dysplasia (n = 10/19, 52.6%). The procedure-related complications rate was 7.7% (n = 5), with all complications associated with postoperative pain that required nonsteroidal anti-inflammatory drug treatment.

During follow-up, 22 patients (33.8%) had a recurrence, representing an annual rate of 35.3% (95% CI = 22.1–53.4). The main characteristics of this group and potential risk factors for recurrence are summarized in Table 2. No differences were observed by gender, smoking and alcohol consumption, number of lesions, histological grade, or previous history of OSCC. Lesion location in the gingiva as opposed to the tongue was found to be a risk factor. Kaplan–Meier curves for time to recurrence (Fig. 1) showed differences only for lesion location in the gingiva compared to the tongue (log rank, p = 0.032).

During follow-up, 10 patients (15.4%) presented with malignant transformation, representing an annual rate of 12.3% (95% CI = 6.0–22.7). The main characteristics of this group and potential risk factors for malignant transformation are summarized in Table 3. No differences were observed by gender, smoking and alcohol consumption, number of lesions, or histological grade. Lesion location in the gingiva as opposed to the tongue a history of OSCC showed a tendency to be risk factors for malignant transformation.

4. Discussion

Early detection of premalignant and malignant intraoral lesions improves long-term survival rates and minimizes treatment

Table 1
Demographic and clinical data.

	Total n (%) (n = 65)	Recurrence n (%) (n = 22)	Malignant transformation n (%) (n = 10)
Mean age (y)	66.2	66.6	66.6
Male	32 (49.2)	9 (40.9)	5 (50)
Smokers	36 (55.4)	13 (59.1)	4 (40)
Alcohol consumers	25 (38.5)	9 (40.9)	5 (50)
Leukoplakia location			
Tongue	21 (32.3)	7 (31.8)	4 (40)
Gingiva	19 (29.2)	10 (45.5)	3 (30)
Lip	5 (7.7)	2 (9.1)	–
Buccal mucosa	10 (15.4)	1 (4.5)	2 (20)
Floor of mouth	4 (6.2)	1 (4.5)	1 (10)
Retromolar trigone	3 (4.6)	1 (4.5)	–
Palate	3 (4.6)	0	–
Multiple sites	15 (23.1)	7 (31.8)	2 (20)
Dysplasia grade			
0	21 (32.3)	7 (31.8)	2 (20)
1	29 (44.6)	12 (54.5)	4 (40)
2	8 (12.3)	2 (9.1)	2 (20)
3	7 (10.8)	1 (4.5)	2 (20)
OSCC history	15 (23.1)	7 (31.8)	6 (60)
Complications	5 (7.7)	3 (13.6)	2 (20)
Re-vaporization	20 (30.8)	20 (90.9)	–
Malignant transformation	10 (15.4)	5 (22.7)	–

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Table 2
Recurrence group characteristics.

Characteristic	n (%)	HR (95% CI)
Gender		
Male	9/32 (28.1)	1.00
Female	13/33 (39.4)	1.24 (0.53–2.91)
Tobacco		
Nonuse	9/29 (31.0)	1.00
Use	13/36 (36.1)	1.37 (0.59–3.21)
Alcohol		
Nonuse	13/40 (32.5)	1.00
Use	9/25 (36.0)	1.17 (0.50–2.73)
Leukoplakia location		
Other	5/25 (20.0)	–
Tongue	7/21 (33.3)	1.00
Gingiva	10/19 (52.6)	2.84 (1.07–7.54)
Multiple locations		
No	15/50 (30.0)	1.00
Yes	7/15 (46.7)	1.34 (0.54–3.29)
Dysplasia grade		
0	7/21 (33.3)	2.84 (0.73–11.01)
1	12/29 (41.4)	44.44 (0.69–8.65)
≥2	3/15 (20.0)	1.00
OSCC history		
No	15/50 (30)	1.00
Yes	7/15 (16.7)	0.74 (0.30–1.83)

CI, confidence interval; HR, hazard ratio.

Table 3
Malignant transformation group characteristics.

Characteristic	n (%)	HR (95% CI)
Gender		
Male	5/32 (15.6)	1.00
Female	5/33 (15.1)	1.52 (0.40–5.71)
Tobacco		
Nonuse	6/29 (20.6)	1.00
Use	4/36 (11.1)	0.42 (0.11–1.52)
Alcohol		
Nonuse	5/40 (12.5)	1.00
Use	5/25 (20.0)	1.77 (0.47–6.63)
Leukoplakia location		
Other	3/25 (12.0)	–
Tongue	4/21 (19.0)	1.00
Gingiva	3/19 (15.7)	1.61 (0.35–7.44)
Multiple locations		
No	8/50 (16.0)	1.00
Yes	2/15 (13.3)	0.27 (0.34–2.22)
Dysplasia grade		
0	2/21 (9.5)	0.30 (0.05–1.81)
1	4/29 (13.7)	0.33(0.78–1.4)
≥2	4/15 (26.6)	1.00
OSCC history		
No	4/50 (8)	1.00
Yes	6/15 (40%)	2.25 (0.62–8.10)

CI, confidence interval; HR, hazard ratio.

requirements (Deppe et al., 2012; Ho et al., 2013). Diagnoses of leukoplakia can be classified according to levels of certainty (C-factor), in clinical terms (C1–C2) or in pathological terms (C3–C4). In this study we used a C3 factor, based on evidence obtained by the elimination of suspected etiologic factors during a follow-up period of 2–4 weeks and the absence of any suspected etiological factors, complemented by incisional biopsy (Van der Waal, 2009). Although the histopathological diagnosis was made by incisional biopsy, a recent study has shown that there may be discrepancies between the results for incisional biopsy compared to excisional biopsy, producing a potential underdiagnosis of dysplastic lesions by 28% and masking an OSCC diagnosis in 9% of cases (Goodson et al., 2012; Brouns et al., 2014). Differential diagnoses for white lesions of the oral cavity are candidiasis, lupus erythematosus, lichen planus,

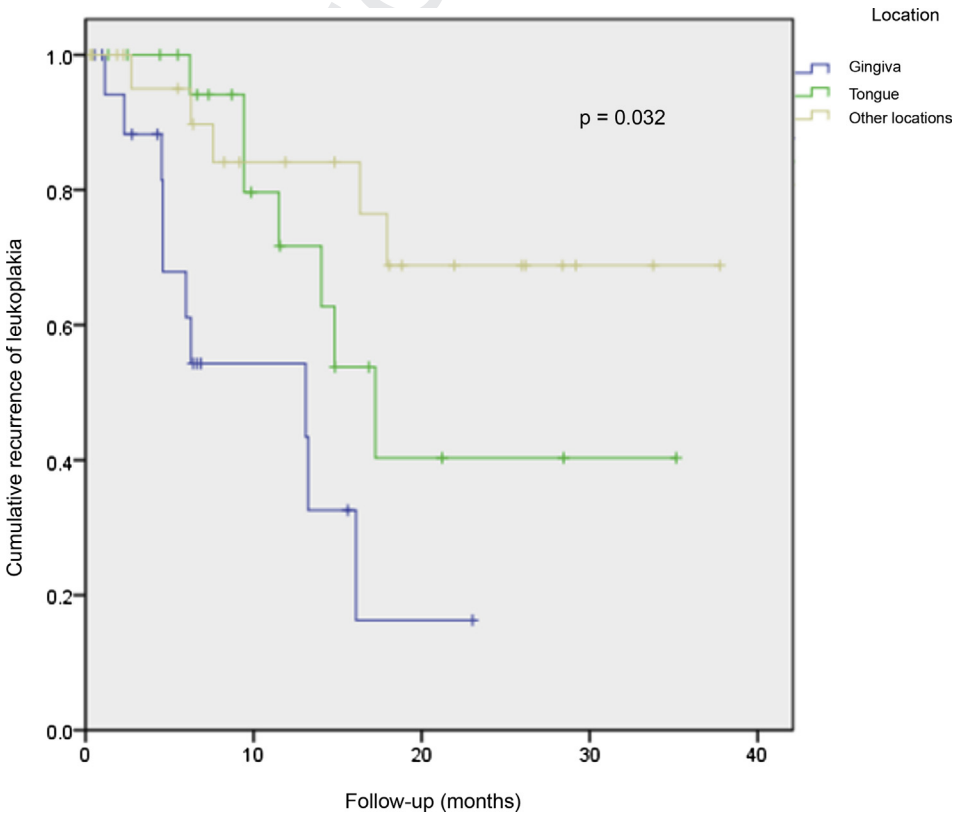

Fig. 1. Kaplan–Meier curves for time to recurrence showed differences only for the location of the lesion in the gingiva compared to the location on the tongue (log rank p = 0.032).

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Table 4
Recurrence and malignant transformation rates.

First author, year	Patients (n)	Lesions	Recurrence	Malignant transformation	Follow-up
Brouns 2013	35	35	40%	14%	61.5 mo
Jerjes 2012	77	123	19.5%	10.4%	6.4 y
Deppe 2012	119	120	23.3%	0.83%	75 mo
Yang 2011	114	114	17.5%	11.4%	3.4 y
Van der Hem 2005	200	282	9.9%	1.1%	52 mo
Chandu 2005	43	73	28.9%	7.3%	47.2 mo
Thomson & Wylie 2002	57	55	24%	7%	4 y
Schoelch 1999	55	55	38.18%	9.09%	32 mo
Chiesa 1993	167	167	34.73%	3%	5 y
Horch 1986	50	50	22%	NA	37 mo

traumatic irritative lesions, aspirin-induced necrosis, syphilis, papilloma, hereditary white lesions and geographic tongue (Escribano-Bermejos and Bascones-Martínez, 2009; Brouns et al., 2013b). The most commonly reported location of leukoplakia is the lateral border of the tongue (Escribano-Bermejos and Bascones-Martínez, 2009; Brouns et al., 2013a, 2014). In our cohort, the tongue was also the most frequent location (n = 21, 32.3%).

Although there is no scientific evidence that any treatment prevents the onset of OSCC, it is safe to treat and successively follow up leukoplakia whether or not dysplasia is present (Chandu and Smith, 2005; Van der Waal, 2009; Santos et al., 2010; Jerjes et al., 2011; Yang et al., 2011; Goodson et al., 2012; Ho et al., 2013). Dysplasia severity is the most common risk factor associated with malignant transformation (Chandu and Smith, 2005; Goodson et al., 2012); however, we could not demonstrate this fact in our sample. No randomized trials are reported in the literature that compare surgery with CO_2 laser in terms of local recurrence and malignant transformation (Brouns et al., 2013a). The recurrence and malignant transformation rates for our sample were 33.8% and 15.4%, respectively, comparable with those found in literature (7.7%–40% for recurrences and 0.83%–14% for malignant transformation; Table 4) (Chiesa et al., 1993; Schoelch et al., 1999; Thomson, 2002; Thomson and Wylie, 2002; Chandu and Smith, 2005; Van der Hem et al., 2005; Yang et al., 2011; Deppe et al., 2012; Jerjes et al., 2012; Brouns et al., 2013a, 2014). It is currently unknown whether resection margin width is a factor in recurrence, and no molecular marker currently exists that determines this risk. No uniform criteria are available, although it is recommended to respect a few millimeters to the margin; nonetheless, it has been shown that there may be changes in the cell nucleus beyond where the leukoplakia is visible (Van der Waal, 2009; Brouns et al., 2014). Slaughter et al. first used the term "field of cancerization" in 1953 (Slaughter et al., 1953), on realizing that patients with OSCC frequently presented with premalignant lesions and often had multiple primary tumors in the upper aerodigestive tract (UADT), and hypothesized that the UADT epithelium showed a higher proportion of premalignant lesions than other tissues because of multiple genetic abnormalities in the whole tissue region (Thomson, 2002; Thomson and Wylie, 2002; Feller and Lemmer, 2011).

In our sample of 65 patients, of 15 (23.1%) with a history of OSCC, 7 had recurrences and 6 presented with malignant transformation. For patients with a previous history of OSCC, no statistically significant differences were observed with the occurrence of recurrences, whereas a trend was evident for the case of malignant transformation (2.25 [0.62–8.10]).

Malignant transformation of leukoplakia is independent of treatment, and it seems that areas with molecular preneoplastic changes may lead to multiple lesions (Yang et al., 2011; Ho et al., 2013; Kumar et al., 2013; López-Jornet and Camacho-Alonso, 2013). Despite advances in molecular biology, there are currently no markers to predict malignant transformation of oral leukoplakia; hence, several authors recommend excision of any leukoplakia whether or not dysplasia is present (van der Waal., 2009; Ho et al., 2013; Kumar et al., 2013; Brouns et al., 2014).

Although different laser types have been used in the treatment of oral leukoplakia, including neodymium:yttrium-aluminium garnet (Nd:YAG), potassium-titanyl-phosphate (KTP) and argon lasers, the CO_2 laser is the most frequently used (Novakovic et al., 2011).

Nd:YAG lasers (wavelength 1,064 nm) are the second most popular lasers for leukoplakia vaporization and intraoral tumor excision after the CO_2 lasers. They are recommended for patients with hemorrhage risk due to their higher potency and deep penetration, but higher postoperative pain rates have been reported for Nd:YAG lasers compared with CO_2 lasers (Ishii et al., 2003). Vivek et al. (2008) reported recurrence and a malignant transformation rate of 10.71% after 3 years of follow-up of a group of 28 patients treated with Nd:YAG laser. White et al. reported a recurrence rate of 27.2% (6/22) for the YAG laser and 23.5% (4/17) for the CO_2 laser (White et al., 1998).

KTP laser penetrates deeper into the tissue (wavelength 532 nm) and is frequently used to coagulate vascular lesions. Lim et al. compared KTP laser and CO_2 laser for leukoplakia ablation, reporting recurrence rate of 25% and 39.5%, respectively, and malignant transformation rates of 13.3% and 6.6%, respectively (Ishii et al., 2003; Lim et al., 2010).

Currently there is no evidence about the possible value of follow-up. However, due to the high recurrence rate, we recommend follow-up every 3 months in the first year, every 6 months in the second year, and annually for life thereafter (Van der Waal, 2009). Clinical examination and photographs are essential to observe the evolution of lesions. New biopsies are mandatory if changes are detected on inspection or palpation (López-Jornet and Camacho-Alonso, 2013).

5. Conclusion

The use of CO_2 laser for the treatment of oral leukoplakia is a reliable, reproducible technique associated with a very low complications rate. Recurrence and malignancy rates for our cohort (33.8% and 15.4%, respectively) were similar to rates (7.7% and 40% for recurrences and 0.83% and 14% for malignancies) reported for other studies (Chiesa et al., 1993; Schoelch et al., 1999; Thomson, 2002; Thomson and Wylie, 2002; Chandu and Smith, 2005; Van der Hem et al., 2005; Yang et al., 2011; Deppe et al., 2012; Jerjes et al., 2012; Brouns et al., 2013a, 2014). We would recommend close lifelong follow-up with photographs, along with new biopsies when changes are detected. Future development of molecular markers may help to determine the risk of malignant leukoplakia transformation and to choose the best treatment. Q2

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