Outcome of CO₂ laser vaporization for oral potentially malignant disorders treatment

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Abstract
Background: Oral cancer is a public health issue worldwide. Oral potentially malignant disorders (OMPDs) are lesions of the oral mucosa that are predisposed to malignant transformation. The mainstay of OMPDs treatment around the world is now the carbon dioxide (CO₂) laser but the reported recurrence and malignant transformation rates vary widely in the literature. We aimed to estimate the recurrence and the malignant transformation rates of OMPDs treated with CO₂ laser at the University Hospital of Bordeaux, in France, from 2010 to 2014, and to identify associated factors with recurrence or malignant transformation.

Material and Methods: We conducted a retrospective study in patients with a minimum follow-up of 12 months. Collected variables included characteristics of the patients (gender, age, alcohol and tobacco consumption, previous diagnosis of graft-versus-host disease, previous treatments for OPM and or upper aerodigestive tract cancers and human immunodeficiency virus infection), characteristics of the lesions (form, colour, size, location, degree of dysplasia), laser treatment outcome (complications, recurrence, malignant transformation).

Results: Twenty-five patients were included. Mean follow-up was 28.9 months. Recurrence was observed in 11 patients (44%). Annual recurrence rate was 18.3% and annual malignant transformation rate was 1.7%. Hyperplasia without dysplasia was the only factor found to be statistically associated with recurrence.

Conclusions: Our results suggest that OMPDs treated by CO₂ laser vaporization have high recurrence rates, particularly those presenting hyperplasia. A standardized definition of recurrence would be necessary for inter-study comparisons. Long-term follow-up is recommended in order to detect and treat squamous cell carcinoma in its early stages.

Key words: CO₂ lasers, precancerous conditions, malignant transformation, oral cancer, recurrence.
Introduction
Cancer is becoming the first cause of premature deaths among noncommunicable diseases according the World Health Organization (WHO). An estimated 300 373 new cases of cancers of the lip and oral cavity occurred worldwide in 2012, with 145 353 deaths (WHO). Most oral cancers are oral squamous cell carcinoma. The main risk factors for oral cancer are tobacco smoking and chewing and alcohol consumption. Prognosis of the oral cancer decreases with advanced disease at presentation. The five-years survival rates are approximately 80% for stage I cancers, and 20% for advanced diseases (stages III/IV) (1). The treatment of oral cancer of early stage permits to improve survival and to reduce morbidity in patients (2). Unfortunately worldwide the half of patients present with a late stage of disease (1). Management of oral potentially malignant disorders (OPMDs) to prevent malignant transformation (primary prevention, not evidence-based to date (3)) or to detect very early cancer (secondary prevention) is worthy of consideration (2).

OPMDs are lesions of the oral mucosa that are predisposed to malignant transformation. The most common OPMD in France include leukoplakia (homogeneous leukoplakia, nonhomogeneous leukoplakia and proliferative verrucous leukoplakia (PVL)), lichen planus, lichenoid dysplasia and actinic cheilitis (Table 1) (4-10). Standard care of these lesions are surgical removal of the lesion (cold-knife, laser excision and vaporization, cryosurgery, photodynamic therapy), medical treatment (topical or systemic), cessation of risk activities (smoking and alcohol) and surveillance (3). Carbon dioxide (CO₂) laser is now the mainstay of treatment of OPMD around the world (11), it has been previously reported to be a safe and an effective tool (12-15). The reported recurrence and malignant transformation rates vary widely after treatment of OPMDs because of differences in terms of lesions treated, treatment, follow-up time and definition of recurrence, which leads to difficulties in informing patients (9-11,13,14,16-18).

The objective of the present study was to estimate the recurrence and the malignant transformation rates of OPMDs treated with CO₂ laser at the University Hospital of Bordeaux, in France, from 2010 to 2014, and to identify associated factors with recurrence or malignant transformation.

Material and Methods
- Study design
This retrospective study included all patients treated with CO₂ laser for oral potentially malignant disorders (OPMD) at the University Hospital of Bordeaux from 2010 to 2014 with a minimum follow-up of 12 months. Follow-up started from the date of first laser treatment and ended on the date of the last visit to the hospital in 2014 or on the date of malignant transformation. Written informed consent was obtained from each patient. The study was approved by the French ethics committee Comité de Protection des Personnes Sud-Ouest et Outre Mer III.

- Laser treatment
All included OPMDs were treated with laser vaporization after incisional biopsies. Lesions with severe dysplasia were not included because they were surgical excised to allow histological examination of the whole lesion. The CO₂ laser system was a Lumenis ® 40C (Lumenis Inc., CA, USA). Laser wavelength was 10966 nm, the beam was used at focal spot 4, power from 10 to 20W, in a noncontact application. The same surgeon treated all patients. Treatment was performed under local anaesthesia (articaine with epinephrine 1:100000). Lesions were delimited with a surgical marker with a 2-3 mm margin when feasible. Paracetamol, alone or combined with codeine, was prescribed for pain control after treatment.

- Data collection
• Patients: The characteristics of the patients treated with laser vaporization included the demographic characteristics (gender, age), the risk factors (alcohol and tobacco consumption (user, non-user, or former user), previous diagnosis of graft-versus-host disease, previous treatments for OPMD or for upper aerodigestive tract cancers and human immunodeficiency virus infection (5)) and the follow-up (number of medical appointments and laser sessions).
• Oral potentially malignant disorders: The OPMD included were homogeneous leukoplakia, nonhomogeneous leukoplakia, proliferative verrucous leukoplakia (PVL), lichen planus, lichenoid dysplasia and actinic cheilitis (Table 1). The lesions were described according to their form (unifocal, multiple sites, symmetric multiple sites), colour (white, red, black), size of greatest dimension (under 2 cm, from 2 to 4 cm, over 4 cm), and location (tongue, upper lip, lower lip, oral commissures, upper alveolus and gingiva, lower alveolus and gingiva, floor of mouth, buccal mucosa, hard palate and soft palate). The degree of dysplasia was classified as hyperplasia without dysplasia, or with dysplasia (mild, moderate).
• Laser treatment outcome:
  ◦ Complications: All complications after laser treatment such as necrosis of the treated area, granuloma onset were taken into account.
  ◦ Recurrence: Local recurrence was defined as an OPMD arising within the borders of the treated area after complete remission. Small white lesions arising between laser sessions were not considered as recurrence. Recurrence time was the period in months from the first laser session until the appearance of a recurrent OPMD.
  ◦ Annual recurrence rate was calculated as (15,16):

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\text{Annual recurrence rate} = \left( \frac{\text{total number of recurrences}}{\text{total number of lesions included in the study}} \right) \times 100
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Table 1. Literature review on the most common oral potentially malignant disorders (OPMDs) in France.

| OMP                  | Definition                                      | Aetiology                                                                 | Epidemiology | Diagnosis                                                                 | Main differential diagnosis                                                                 | Clinical presentation                                                                 | Histology                                                                 | Treatment                                                                 | Annual malignant transformation |
|----------------------|-------------------------------------------------|---------------------------------------------------------------------------|--------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|-------------------------------|
| Leukoplakia          | 'a with plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk of cancer' (5). | Tobacco and areca nut use, or idiosyncratic (4).                          | The most prevalent OPMD – 2% worldwide (5). | It is a diagnosis of exclusion (4). A biopsy is mandatory.                  | Other known with lesions of the oral mucosa including white sponge nevus, frictional keratosis, candidiasis, lichen planus, lichenoid reaction, hairy leukoplakia, leukokeratoosis nicotina palate (4). | 3 clinical types: (a) homogeneous leukoplakia (uniformly flat, thin and exhibit shallow cracks of the surface keratin (4), (b) non-homogeneous leukoplakia (have subtypes: speckled (white-and-red lesion), nodular, verrucous (4) & (c) proliferative verrucous leukoplakia (PVL) (widespread, multifocal leukoplakia involving more than 2 oral sub-sites of least 3 cm and a period of progression of at least 5 years with ≥1 recurrence(s) after treatment (6). | Histology is not specific (4). Leukoplakia can be atrophic or hyperplastic and with or without dysplasia. | Tobacco use-cessation may results in regression or disappearance of the leukoplakia (7). Other treatments are surgical (incl. laser), non-surgical, chemoprevention, follow-up (4). | Annual malignant transformation ranges from 2% to 3% for all clinical subtypes together (7). Homogeneous leukoplakia have relatively low risk for malignant transformation (4), inhomogenous leukoplakia have a higher risk for malignant transformation and PVL probably nearly always transforms into carcinoma (5). |
| Oral lichen planus and lichenoid dysplasia | OLP is a chronic mucocutaneous immunological inflammatory condition (WHO). | Unknown (4).                                                             | Prevalence 1% (7). | Biopsy is mandatory to confirm the clinical diagnosis (4).              | 6 types of OLP, papular, reticular, plaque-like, atrophic, erosive and bullous (WHO). Atrophic and erosive form can be symptomatic (6). | OLP is characterized by a dense and well-defined infiltrate of lymphocytes in the superficial lamina propria (WHO). Generally, the presence of epithelial dysplasia is not accepted into the OLP diagnosis (7). Lichenoid dysplasia is an histopathological term. It is a subtype of dysplasia, characterized by a band-like lymphocytic infiltrate underneath dysplastic epithelium (5). | Treatment are essentially symptomatic. The drugs of first choice are topical and systemic steroids, alternative treatments are various (including imiquimod, intralesional steroids, CO2 laser vaporization, retinoids, PUVA...) (8-10). | Annual malignant transformation rate of OLP is less than 0.5% (7). | |
| Actinic cheilitis     | OPMD of the lip (4).                             | Actinic radiation (WHO).                                                  | Mainly seen in the lower lip of elderly men (5). | The clinical diagnosis should be confirmed by biopsy (4).               | Lichen planus.                                                                           | Ukerative or crusted lesions of the vermilion border of the lip (5). The epithelium of the lip vermilion may be hyperplastic or atrophic and shows disordered maturation, varying degrees of keratinization, cytopathic atypia and increased mitotic activity. The underlying connective tissue usually shows basophilic degeneration of collagen and elastosis (WHO). | Limiting sun exposure and promoting sun protection. Treatment by superficial surgical excision or CO2 laser vaporization (5). | Limiting sun exposure and promoting sun protection. Treatment by superficial surgical excision or CO2 laser vaporization (5). | Unknown (lack of follow-studies of untreated lesions) (5). |
Malignant transformation: Malignant transformation was defined as the development of oral squamous cell carcinoma or carcinoma in situ at the site of a previously treated OPMD. Malignant transformation time was the period in months from the first laser session until the development of oral squamous cell carcinoma or carcinoma in situ. Annual malignant transformation rate was calculated with the same formula using the total number of malignant transformations instead of the total number of recurrences.

Clinical outcome categories: At the time of data extraction, patients were assigned to one of the 4 clinical outcome categories: complete remission (the absence of OPMD), under treatment or scheduled for treatment (achieving treatment or additional treatment required), stable on surveillance (OPMD persisting despite treatment) and malignant transformation (confirmed histologically).

Data extraction: Data were extracted from medical records. Patients with missing risk factor data were contacted and asked by phone. When available, photographs were used to check the clinical characteristics of the lesions reported on medical records.

Data analysis

Frequencies and percentages were calculated for qualitative variables. Mean, standard deviation (SD), and minimum (min) and maximum (max) were calculated for quantitative variables. The log-rank test and Kaplan-Meier survival curves were used to compare the 2 groups of patients (with recurrence or malignant transformation and without recurrence or malignant transformation) regarding the potential risk factors for recurrence: gender, age (in 2 categories, under 65 and 65 or over), tobacco and alcohol use, previous treatment, graft-versus-host disease and human immunodeficiency virus infection, lesion shape, colour, size, location, clinical and pathological diagnosis (mild and moderate dysplasia cases were grouped together). Tests were considered statistically significant if the p-value was <0.05.

RStudio 0.98.1062 (RStudio, Inc.) was used for tests and description of variables.

Results

1/ Patients

Of 46 patients examined for an OMPD and treated with laser vaporization from 2010 to 2014 at the University Hospital of Bordeaux, 21 were excluded because they did not have at least 12 months of follow-up at the time of data extraction (September 2014) (15,16). The remaining 25 patients were included: 14 men and 11 women, mean age 66.4 years (SD 11.1, min 49, max 90) (Table 2). Seventeen patients (68.0%) reported a tobacco use (user and former user), 10 (43.5%) an alcohol use, and 3 (14.3%) a tobacco and alcohol use. Previous treatments for OPMD or for upper aerodigestive tract cancers were found in 5 cases (20.0%), GVH and HIV in 2 cases (8.0%). Follow-up ranged from 12.3 to 50.7 months (mean 28.9, SD 12.6). The mean number of medical appointments per patient was 8.3 (SD 3.5, min 2, max 17). The mean number of laser sessions was 4 (SD 2.2, min 1, max 9).

2/ Oral potentially malignant disorders

These 25 patients presented 25 OMPDs. Lesions were mainly unifocal (n=15, 60.0%), white (n=18, 75.0%), from 2 to 4 cm (n=9, 40.9%), at multiple site (n=10, 40%). 6 clinical diagnosis were encountered: homogeneous leukoplakia (n=11, 44.0%), nonhomogeneous leukoplakia (n=3, 12.0%), proliferative verrucous leukoplakia (PVL) (n=5, 20.0%), actinic cheilitis (n=1, 4.0%), lichen planus (n=3, 12.0%) and lichenoid dysplasia (n=2, 8.0%) (Table 3).

3/ Laser treatment outcome

Complications: Nine patients had minor complications (36%), 5 had granulomas (20.0%), 2 had small bone necrosis which resolved spontaneously (8.0%), 1 had delayed wound healing (4.0%) and 1 had a sclerotic scar (4.0%).

Recurrence: Recurrence after laser treatment was observed in 11 of the 25 patients (44.0%). All recurrences appeared between 5.4 and 39.7 months after the first laser session (mean 19.7, SD 11.1; Fig. 1). Annual recurrence rate was 18.3%. Table 3 shows that most recurrent lesions were unifocal, 70.0% were white, 44.4% were 2-4 cm in size, 45.5% were located at multiple sites, and 54.5% were homogeneous leukoplakias. More than half of recurrent lesions initially had no dysplasia. Recurrence was managed by surveillance in 5 cases and by CO2 laser excision or vaporization in 6.

Malignant transformation: In 1 of 25 treated patients (4%), malignant transformation occurred during the 48th month after the first laser treatment session. Annual malignant transformation rate was 1.7%. The patient with an initial diagnosis of actinic cheilitis and moderate dysplasia was later diagnosed with carcinoma in situ and was referred to the oncology department, where he is currently undergoing treatment

Clinical outcome categories: Excluding the lesion with malignant transformation, at the time of time of data extraction, 13 lesions (52%), including 4 that recurred, reached complete remissions (Fig. 2), 7 (28%) were stable on surveillance and 4 (16%) were under treatment or scheduled for treatment.

4/ Factors associated with recurrence or malignant transformation

Hyperplasia without dysplasia was the only factor found to be statistically associated with recurrence (p-value=0.02; Table 3). No other factor/characteristic was found to be statistically associated with recurrence/malignant transformation (Tables 2 and 3).
### Table 2. Characteristics of patients diagnosed with oral potentially malignant disorders (OPMDs), recurrent OPMDs and oral squamous cell carcinoma (OSCC). Centre Hospitalier Universitaire de Bordeaux, France, 2010-2014.

| Variables                  | OMPDs (n=25) | Recurrence (n=11) | Non-recurrence (n=14) | OSCC (n=1) | p-value (Log-rank test) |
|----------------------------|--------------|-------------------|-----------------------|-----------|-------------------------|
| Gender                     | N (%)        | N (%)             | N (%)                 | N         |                         |
| Male                       | 14 56.0      | 6 54.5            | 8 57.1                | 1         | 0.87                    |
| Female                     | 11 44.0      | 5 45.5            | 6 42.9                | 0         |                         |
| Age (years)                |              |                   |                       |           | 0.42                    |
| < 65                       | 12 48.0      | 3 27.0            | 9 64.0                | 0         |                         |
| ≥ 65                       | 13 52.0      | 8 73.0            | 5 36.0                | 1         |                         |
| Average [SD]               | 66.4 [11.1]  | 69.8 [11.9]       | 63.7 [10.0]           | 82.6      |                         |
| Median                     | 65.0         | 68.0              | 61.5                  | -         |                         |
| Quartile range             | 56.0 – 75.0  | 65.5 – 77.0       | 56.0 – 65.7           | -         |                         |
| Min – Max                  | 49.0 – 90.0  | 49.0 – 90.0       | 55.0 – 88.0           | -         |                         |
| Tobacco consumption        |              |                   |                       |           | 0.75                    |
| User                       | 8 32.0       | 2 18.2            | 6 42.9                | 0         |                         |
| Former user                | 9 36.0       | 4 36.4            | 5 35.7                | 0         |                         |
| Non-user                   | 8 32.0       | 5 45.5            | 3 21.4                | 1         |                         |
| Alcohol consumption        |              |                   |                       |           | 0.33                    |
| User                       | 9 39.1       | 5 45.5            | 4 33.3                | 0         |                         |
| Former user                | 1 4.3        | 0 0               | 1 8.3                 | 0         |                         |
| Non-user                   | 13 56.5      | 6 54.5            | 7 58.3                | 0         |                         |
| Unknown                    | 2 -          | -                 | 2 -                   | 1         |                         |
| Tobacco and Alcohol        |              |                   |                       |           | 0.57                    |
| consumption                |              |                   |                       |           |                         |
| User                       | 3 14.3       | 1 11.1            | 2 16.7                | 0         |                         |
| Former user                | 0 0          | 0 0               | 0 0                   | 0         |                         |
| Non-user                   | 18 85.7      | 8 88.9            | 10 83.3               | 1         |                         |
| Unknown                    | 4 -          | 2 -               | 2 -                   | 0         |                         |
| GVH                        |              |                   |                       |           | 0.71                    |
| Yes                        | 2 8.0        | 1 9.1             | 1 7.1                 | 0         |                         |
| Previous treatment*        |              |                   |                       |           | 0.14                    |
| Yes                        | 5 20.0       | 1 9.1             | 4 28.6                | 0         |                         |
| HIV                        |              |                   |                       |           | 0.11                    |
| Yes                        | 2 8.0        | 0 0               | 2 14.3                | 0         |                         |

*Previous treatments for OPMD or for upper aerodigestive tract cancers
GVH: Graft Versus Host disease
HIV: Human Immunodeficiency Virus
Table 3. Characteristics of oral potentially malignant disorders (OPMDs), recurrences and oral squamous cell carcinomas (OSCC) diagnosed and treated among 25 patients. Centre Hospitalier Universitaire de Bordeaux, France, 2010-2014.

| Variables                                | OPMDs (n=25) | Recurrence (n=11) | Non-recurrence (n=14) | OSCC (n=1) | p-value (Log-rank test) |
|------------------------------------------|--------------|-------------------|-----------------------|------------|------------------------|
| **Form**                                 |              |                   |                       |            |                        |
| Unifocal                                 | 15 (60.0%)   | 6 (54.5%)         | 9 (64.3%)             | 1          | 0.33                   |
| Multiple sites                           | 10 (40.0%)   | 5 (45.5%)         | 5 (35.7%)             | 0          |                        |
| **Colour**                               |              |                   |                       |            |                        |
| White                                    | 18 (75.0%)   | 7 (70.0%)         | 11 (78.6%)            | 0          | 0.80                   |
| Red                                      | 1 (4.2%)     | 0 (0%)            | 1 (7.1%)              | 1          |                        |
| White and red                            | 5 (20.8%)    | 3 (30.0%)         | 2 (14.3%)             | 0          |                        |
| Unknown                                  | 1 (4.0%)     | - (0%)            | - (0%)                | 0          |                        |
| **Size**                                 |              |                   |                       |            |                        |
| < 2 cm                                   | 5 (22.7%)    | 2 (22.2%)         | 3 (23.1%)             | 1          | 0.97                   |
| 2 – 4 cm                                 | 9 (40.9%)    | 4 (44.4%)         | 5 (38.5%)             | 0          |                        |
| > 4 cm                                   | 8 (36.4%)    | 3 (33.3%)         | 5 (35.5%)             | 0          |                        |
| Unknown                                  | 3 (-)        | 2 (-)             | 1 (-)                 | 0          |                        |
| **Location**                             |              |                   |                       |            |                        |
| Tongue                                   | 5 (20.0%)    | 3 (27.3%)         | 2 (14.3%)             | 0          | 0.61                   |
| Lower lip                                | 3 (12.0%)    | 0 (0%)            | 0 (0%)                | 3 (24.4%)  | 1                      |
| Upper or lower alveolus and gingiva      | 2 (8.0%)     | 0 (0%)            | 0 (0%)                | 2 (14.3%)  | 0                      |
| Buccal mucosa                            | 2 (8.0%)     | 1 (9.1%)          | 1 (7.1%)              | 0          |                        |
| Hard palate                              | 1 (4.0%)     | 1 (9.1%)          | 1 (7.1%)              | 0          |                        |
| Intermaxillary commissures               | 2 (8.0%)     | 1 (9.1%)          | 1 (7.1%)              | 0          |                        |
| Multiple sites                           | 10 (40.0%)   | 5 (45.5%)         | 5 (35.7%)             | 0          |                        |
| **Clinical diagnosis**                   |              |                   |                       |            | 0.76                   |
| Homogenous leukoplakia                    | 11 (44.0%)   | 6 (54.5%)         | 5 (35.7%)             | 0          |                        |
| Non-homogenous leukoplakia               | 3 (12.0%)    | 0 (0%)            | 0 (0%)                | 3 (21.4%)  | 0                      |
| PVL                                      | 5 (20.0%)    | 2 (18.2%)         | 3 (21.4%)             | 0          |                        |
| Actinic cheilitis                        | 1 (4.0%)     | 0 (0%)            | 1 (7.1%)              | 1          |                        |
| Lichen planus                            | 3 (12.0%)    | 1 (9.1%)          | 2 (14.3%)             | 0          |                        |
| Lichenoid Dysplasia                      | 2 (8.0%)     | 2 (18.2%)         | 0 (0%)                | 0          |                        |
| **Anatomopathologic diagnosis**          |              |                   |                       |            | 0.02                   |
| Hyperplasia without dysplasia            | 11 (44.0%)   | 7 (63.6%)         | 4 (28.6%)             | 0          |                        |
| Mild or moderate dysplasia               | 14 (56.0%)   | 4 (36.4%)         | 10 (71.5%)            | 1          |                        |

PVL: Proliferative verrucous leukoplakia
Fig. 1. (a) Homogeneous leukoplakia on the tongue mucosa of a 77-year-old female patient. (b) Treatment by CO2 laser vaporization. (c) Persistent lesion 4 months after laser vaporization.

Fig. 2. (a) Non-homogeneous leukoplakia on the tongue mucosa of a 57-year-old female patient. (b-c) Treatment by CO2 laser vaporization. (d) Complete remission 1 year after laser vaporization.
Discussion
We considered all OPMDs diagnosed except those with severe epithelial dysplasia which were surgically excised (16). In the other lesions, recurrence after laser treatment occurred in 44% of the patients during a mean follow-up of mean 28.9 months. Our data showed a high rate of recurrence which was similar to that reported in some studies with CO₂ laser vaporization (Table 4): Brouns et al. reported a recurrence rate of 40% for oral leukoplakias in a mean period of 61.9 months (16), Pedrosa et al. observed recurrence rates of 40.7% for oral leukoplakias in a mean period of 43.8 months (17) and Mücke et al. reported a recurrence frequency of 38.2% for erosive lichen planus in a mean period of 42.7 months (9). In fact, the recurrence rate varies widely for CO₂ laser vaporization from 9.9% to 44% (9-11,13,14,16-20); Table 4). This variation can be attributed to the differences in terms of lesions treated.

| Reference          | Place        | Year | Number of OPMDs | OPMDs studied               | Mean Follow-up (months) | Recurrence rate (%) | Malignant transformation (%) |
|--------------------|--------------|------|-----------------|-----------------------------|-------------------------|---------------------|-------------------------------|
| Horch et al. (19)  | Germany      | 1986 | 40              | Leukoplakia, Erosive lichen planus | 37                     | 21.05%              | -                             |
| Roodenburg et al. (20) | Netherlands  | 1991 | 103             | Leukoplakia                 | 63.6                    | 9.7%                | 0%                            |
| Huerta et al. (10) | Spain        | 1999 | 34              | Homogenous leukoplakia, Plaque-like oral lichen planus | 12                     | 31.74               | -                             |
| Chandu et al. (11) | Australia    | 2005 | 73              | Leukoplakia                 | 47.2                    | 28.9%               | 7.3%                          |
| Van der Hem et al. (13) | Netherlands | 2005 | 282             | Leukoplakia                 | 52                      | 9.9%                | 1.1%                          |
| Deppe et al. (14)  | Germany      | 2012 | 148             | Non homogenous leukoplakia, Erosive lichen planus | 75                     | 30.4%               |                               |
| Brouns et al. (16) | Netherlands  | 2013 | 35              | Leukoplakia                 | 61.9                    | 40.0%               | 14.2%                         |
| Pedrosa et al. (17) | Portugal     | 2015 | 59              | Leukoplakia                 | 43.8                    | 40.7%               |                               |
| Mücke et al. (9)   | Germany      | 2015 | 68              | Erosive lichen planus       | 42.7                    | 38.2%               | 2.9%                          |
| Mogedas et al. (18) | Spain        | 2015 | 65              | Leukoplakia                 | 15                      | 33.8%               | 15.4%                         |
| Present study      | France       | 2017 | 25              | Leukoplakia, PVL, Actinic cheilitis, Lichen planus, Lichenoid Dysplasia | 28.9                   | 44.0%               | 4.0%                          |
treatment modalities, follow-up time and above all definition of recurrence. There is no consensus definition for recurrence in the literature. Some authors define it as a lesion occurring at the primary lesion site after a confirmed remission period (17). Others note that only one-third of recurrences occur at the same site and consequently define recurrence as being a new lesion recurring after excision that possibly differs from the initial one (12). This definition favours the use of the term "disorder" instead of lesion, especially for leukoplakia, recognizing the fact that recurrence (or malignant transformation) can occur elsewhere in the mouth or in the upper aerodigestive tract (7). Different definitions of recurrence are a barrier to a clear comparison between studies. Recurrence could also result from a concept of field changes or cancerization: genetic changes widespread in the oral mucosa, triggered by environmental factors (e.g. smoking and alcohol), leading to higher degrees of dysplasia and to development of cancer (21). This could explain the high recurrence rate observed in this study. The role of field cancerization is especially important in widespread lesions like PVL, as demonstrated by Bagán et al. (22). The surgical margins are more likely to be within an area of field change: as area is wider, with clinically normal epithelium, recurrence is more likely to occur.

We found no statistically significant association between exposure to patients’ characteristics and recurrence, except for the pathological diagnoses. Kaplan-Meier estimates indicated that, after 30 months of follow-up, the probability of being free from recurrence was approximately 75% for mild or moderate dysplasia lesions and about 50% for hyperplasia without dysplasia. In the literature, variables significantly associated with recurrence of OPMD treated with CO₂ laser vaporization are alcohol consumption and previous malignancy (11), gingiva location (18) and moderate to high-grade dysplasia (17). Our contradictory findings can be explained by the fact that severe dysplasia was not included in the study (so the remaining dysplasia had a low risk of recurrence) and our small sample size. A greater sample size is needed to increase the chance of finding a significant association, but is difficult to reach in a single-centre study, as potentially malignant lesions are rare (<5%).

The ultimate aim of the management of OMPD is the prevention of oral cancer. To date, there is no evidence that severe dysplasia was not included in the study (so the remaining dysplasia had a low risk of recurrence) and our small sample size. A greater sample size is needed to increase the chance of finding a significant association, but is difficult to reach in a single-centre study, as potentially malignant lesions are rare (<5%).

The most relevant characteristics that increase the risk of malignant transformation are nonhomogeneous subtype, size (>4 cm), presence of dysplasia and location on the tongue or floor of the mouth (7). Advanced age and female sex are also important determinants in assessing malignant potential (24). In the present study, the association between these characteristics and malignant transformation was not tested because of the small number of cases. However, the literature shows that cessation of smoking after surgical treatment considerably reduces the risk of malignant transformation (7,25) and that patients should be encouraged to quit and referred to smoking cessation programs if necessary.

After CO₂ laser vaporization, we noted minor complications in 9 cases (36%). Other researchers did not indicate the onset of complications (9,10,13,19), reported no complication (14,17,20) or significantly lower complication rates ranging from 2.9% to 7.7% (11,16,18). However, there is no standardized definition of a complication after treatment, so these findings may include different events. Exceptional cases of mental nerve paresthesia and anesthesia were reported (11,16).

Our study was not designed to evaluate the effect of the nature of the treatment. A comparative study with bilateral leukoplakia (one side of the lesion excised using CO₂ laser and the other side using scalpel) has shown that advantages of laser include less bleeding intraoperatively, less swelling and scarring post-operatively than scalpel (26). There was no significant difference in terms of post-operative pain. No RCT is available to compare CO₂ laser with conventional surgery in
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terms of recurrence and malignant transformation rate. Brouns et al. 2014 have managed 144 patients with oral leukoplakia with surgical excision, CO₂ laser vaporisation or observation only but was no unable to compare the treatment results due to their different indications (15). CO₂ laser treatment modalities are vaporization i.e. a selective removal of affected epithelium, excision or a combination of both. The only comparative study available on laser vaporisation and excision had used two different lasers for the treatment of leukoplakia (Nd:YAG and CO₂ respectively) which did not allow to compare the laser treatment modalities (27). Laser vaporization appears suitable for wide lesions or multiple lesions at sites that were less amenable for surgical excision like floor of the mouth and mucobuccal folds (15,27). It permits to limit the post-operative discomfort and the functional problems induced by excision in this case (13,27). The main disadvantage is that vaporization does not allow histological examination of the whole lesion (13,27). Incisional biopsies performed prior to treatment may not represent the entire lesion and so some dysplasia may have been missed, resulting in a measurement bias (23). Besides risk factors, definition criteria and follow-up period, the type of laser and the surgical technique used may also be related to treatment outcome. RCT are needed to better establish the effectiveness of the different treatments for OPMD (3). This study has several limitations. First, this is a retrospective study. It is based on complete records from the archives of the University Hospital of Bordeaux. Second, the sample size is small (25 patients) but similar to that reported in some studies with CO₂ laser vaporization (10,16) (Table 4). This is due to the characteristics of the studied lesions themselves which are rare (<5%) and require further follow-up to observe a potential recurrence or malignant transformation. We had a small sample size despite a four-year screening period, providing a small power to identify associated factors, but on the other hand, we had data of good quality from a homogeneous sample (severe dysplasia excluded, all treated by CO₂ Laser by the same surgeon) followed-up at least 12 months as indicated by Brouns et al. (14,16). These lesions should become even rarer as the prevalence of tobacco smoking is declining worldwide (WHO), pointing out the need for future systematic reviews and meta-analyses, in which our study can contribute, and collaborative multicentre studies.

In conclusion, we noted a high recurrence rate of OMPDs treated with CO₂ laser, particularly in those with hyperplasia. Randomized clinical trials should be used to evaluate the outcome of different treatment methods and multicentre studies could increase the power of statistical analyses. Standardized recurrence criteria are necessary for more accurate comparisons between studies. Long-term follow-up programmes are important to detect malignant transformation in its early stages and to minimize cancer treatment morbidity and mortality rates.

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Conflict of interest
All authors (AC, RWR, EA, JCF) state that there are no conflicts of interest. There were no financial or personal relationships that could inappropriately influence their work.