Oral tongue leukoplakia: analysis of clinicopathological characteristics, treatment outcomes, and factors related to recurrence and malignant transformation

Shih-Wei Yang1,2 · Yun-Shien Lee3,4 · Liang-Che Chang2,5 · Cheng-Han Yang2,5 · Cheng-Ming Luo1,2 · Pei-Wen Wu1,2

Received: 31 October 2020 / Accepted: 7 December 2020 / Published online: 7 January 2021
© The Author(s) 2021

Abstract
Objectives The tongue is identified as a high-risk site for oral leukoplakia and malignant transformation. The purpose of this study is to investigate the clinicopathological characteristics and treatment outcomes of tongue leukoplakia and assess the factors related to recurrence and malignant transformation.

Materials and methods One hundred and forty-four patients who received carbon dioxide laser surgery for tongue leukoplakia from 2002 to 2019 were analyzed statistically.

Results The follow-up period was 54.90 ± 54.41 months. Thirty patients showed postoperative recurrence (20.83%), and 12 patients developed malignant transformation (8.33%). The annual transformation rate was 2.28%. Univariate analysis showed that a history of head and neck cancer, size of lesion area, clinical appearance, and pathology were significant factors for both recurrence and malignant transformation. In the multivariate logistic regression, a history of head and neck cancer and size of lesion area were independent prognostic factors for recurrence, and a history of head and neck cancer was the only independent factor for postoperative malignant change.

Conclusions Clinicians should adopt more aggressive strategies for tongue leukoplakia patients with a history of head and neck cancer.

Clinical relevance These results may help clinicians gain a better understanding of oral tongue leukoplakia.

Keywords Leukoplakia · Tongue · Malignant transformation · Recurrence · Carbon dioxide laser

Introduction
Oral squamous cell carcinoma (OSCC) accounts for about 3–5% of all the malignant tumors in the human body and affects more than 300,000 people worldwide annually; the incidence is higher in South Asian and Southeast Asian populations [1, 2], including regions endemic for the use of betel quid products [3, 4]. Radical surgeries with adequate peripheral and deep margins for oral cavity tumors and neck dissection are usually indicated for patients with OSCC. The oral cavity, which serves as a point of entry, a site for breakdown and tasting of food, and a sound resonance chamber, is unavoidably destroyed by surgery, possibly compromising the functions of swallowing, pronunciation, and chewing. Early diagnosis of OSCC is of paramount importance since patients who receive early treatment may show less functional morbidity, less cosmetic disfigurement, and lower cost of care and have a better outcome and higher quality of life postoperatively [5–7]. Although OSCC can develop de novo, various studies have established that most oral cancers are preceded by some visible clinical changes on the oral mucosa, or potentially malignant lesions [1, 3]. At a World Health Organization workshop in 2005, the term oral potentially malignant disorders (OPMDs) was suggested as a replacement for
premalignant oral lesions and conditions [8]. In comparison with the normal oral mucosa, OPMDs, which encompass a number of lesion types, including leukoplakia, erythroplakia, oral lichen planus, oral submucous fibrosis, and other miscellaneous lesions, are characteristics of an increased risk of malignant transformation [1, 9, 10]. Oral leukoplakia (OLK) is the most common type of OPMD and has been widely studied [2, 5, 9–13]. The risks of malignant transformation of OLK have always been the focus of clinical attention. The risk factors for malignant transformation include female gender, old age, large size, location on the tongue or floor of mouth, non-homogeneous leukoplakia, a history of smoking/betel nut chewing, and high-grade dysplasia on initial biopsy [5, 10, 13–18]. Most studies on OLK were conducted in all parts of oral cavity mucosa, including the buccal area, tongue, gums, labial region, floor of mouth, palate, and retromolar mucosa. To the best of our knowledge, few studies on tongue leukoplakia have been conducted to date [13, 19, 20]. The aim of this study was to investigate the clinicopathological characteristics and treatment outcomes of oral tongue leukoplakia and analyze the factors related to the recurrence and malignant transformation of tongue leukoplakia treated by surgical excision with carbon dioxide (CO₂) laser, including postoperative recurrence and malignant transformation.

Materials and methods

This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (License No.: 201901384B0). Medical records of patients with OLK that received transoral laser excision at the Department of Otolaryngology of Keelung Chang Gung Memorial Hospital, from Sept 2002 to Oct 2019, were retrospectively reviewed. Information regarding patient enrollment, treatment, and the inclusion and exclusion criteria are listed in Table 1. Clinicopathological characteristics and factors related to the treatment outcomes, including gender, age, body mass index, history of radiotherapy, alcohol drinking, cigarette smoking, betel quid chewing, diabetes mellitus, metformin treatment, past history of head and neck cancer, clinical presentation, area of the lesion(s), pathological results, occurrence of leukoplakia at sites other than the tongue, Candida infection, and subsites of tongue, were analyzed. The history of betel quid chewing, alcohol consumption, and tobacco use were obtained by detailed questioning at the patients’ first visit to the outpatient department. The criteria for a positive assignment were at least 1 quid daily for at least 1 year for chewers of betel quid, at least 1 cigarette per day for at least 1 year for cigarette smokers, and drinking more than 4 days a week for at least 1 year for alcohol drinkers [21]. The CO₂ laser used was an UltraPulse Encore (Lumenis®, Inc., Yokneam, Israel). A power setting of 8–10 W in a continuous-wave mode was chosen. Excision was conducted using a hand-held delivery device, and the spot size was adjusted to 1 mm in diameter. The hand piece was provided with a helium–neon aiming beam to facilitate targeting of the leukoplakia lesion. The outlines of the resection margins were situated at least 2–3 mm outside the targeted lesion to achieve adequate excision and obtain adequate tissue not affected by laser cauterization for histopathological diagnosis. The area of the leukoplakia was measured directly on the excised specimen.

Table 1 The protocol of patient enrollment, treatment, and the inclusion and exclusion criteria of patients

| 1. Enrollment of patients | Thorough oral cavity examination by an otolaryngologist |
|--------------------------|--------------------------------------------------------|
|                         | Written consent signed by every patient before surgery  |
|                         | Preoperatively the types of leukoplakia [8, 10] photographed and later reviewed by two specialist of otolaryngology |
| 2. Carbon dioxide laser surgical intervention [21–23] | Power setting 8–10 W, continuous-wave mode |
|                         | Laser spot size: 1 mm |
|                         | Excision with a surgical margin of 3 mm |
|                         | The excised wound left for secondary intention |
| 3. Pathological diagnosis | All surgical specimens examined by 2 different pathologists |
|                         | Binary grading system of pathology by the WHO [24] |
| 4. Inclusion criteria | Clinical diagnosis of leukoplakia on the mobile tongue and treated with CO₂ laser |
|                         | All the lesions of leukoplakia were synchronous |
|                         | Patients’ age 20 or older |
| 5. Exclusion criteria | Patients’ age younger than 20 years |
|                         | Other kinds of OPMDs, such as submucous fibrosis, lichen planus, and erythroplakia |
|                         | Previous treatment of tongue leukoplakia at other medical facilities |
|                         | Surgical margins involved by hyperkeratosis or dysplasia |
|                         | Pathology not available or no agreeable pathological diagnosis made |
|                         | Overt carcinoma on inspection |
|                         | Exophytic, papillary, warty, and verrucous appearance of proliferative verrucous leukoplakia |
|                         | Initial pathological diagnoses being carcinoma or malignancies |
|                         | Obvious ulceration |
|                         | Papilloma with a gross papillary appearance |
|                         | Treated by laser vaporization |

OPMDs oral potentially malignant disorders

Clin Oral Invest (2021) 25:4045–4058

 Springer
condition” described leukoplakia involving other parts of the oral mucosa in addition to the mobile tongue. In cases with more than one site of leukoplakia lesion, all the lesions were synchronous. The area of tongue leukoplakia in a patient was a summation of all tongue leukoplakia lesions if more than one lesion occurred. When the patient had more than one lesion, the highest degree of pathology and most severe form of morphology of oral tongue leukoplakia were documented for analysis and statistical calculation on a per capita basis.

All surgical procedures were conducted by one doctor (S.-W.Y.) under local anesthesia [21–23]. The postoperative follow-up was uneventful.

All the clinicopathological factors related to postoperative recurrence and malignant transformation were statistically analyzed in univariate analysis. The factors significantly related to postoperative recurrence and malignant transformation in the univariate analysis were further analyzed by the multivariate logistic regression model.

Statistical analysis

Results were presented descriptively, with factors related to postoperative recurrence and malignant transformation of tongue leukoplakia. For univariate analysis, Fisher’s exact test and logistic regression were performed for discrete and continuous variables, respectively. For multivariate analysis, multiple logistic regression was performed. Odds ratio (OR) and 95% confidence intervals (CIs) were calculated using a two-tailed test of significance (P < 0.05) for each factor. Survival analyses were performed using Kaplan–Meier curves with log rank tests (for factor with two groups of subjects).

We made the following considerations: (1) if the 95% CI excludes the null value (1.0), and the p value of OR (or HR) of the risk factor must be < 0.05; (2) if the value of the OR (or HR) was greater than 1.0, the risk was increased; and (3) if the value was less than 1.0, the risk was reduced or indicated a protective effect. Fisher’s exact tests were calculated using the MATLAB version R2015a (Mathworks Inc., Natick, MA, USA). Kaplan–Meier curves with log rank tests and a multivariate logistic regression model using the Statistical Package SPSS version 22 (SPSS Inc., Chicago, IL, USA) were used to determine the distinct factors affecting postoperative recurrence and malignant transformation of oral tongue leukoplakia treated with CO2 laser.

Results

Clinicopathological characteristics

Overall, 753 patients with 1591 OPMD lesions underwent CO2 laser surgery at the department from 2002 to 2019. Excluding patients with OPMDs not occurring on the oral tongue, initial diagnosis of carcinoma, and clinical tongue OPMDs other than leukoplakia, 144 patients with 241 lesions of tongue leukoplakia were enrolled (Fig. 1). Among the 144, 108 were male (75.0%) and 36 were female (25.0%), and their ages ranged from 25 to 83 years with a median age of 52.0 years and an average age of 52.17 ± 11.68 years. The average follow-up period was 54.9 ± 54.41 months. Multiple lesions occurred on the tongue or other sites of the oral cavity in some patients. Homogeneous and non-homogeneous leukoplakia could occur on different sites of the oral cavity or on the same site in the cases with postoperative recurrence. Pathological results of different severity also possibly occurred in the different or recurrent sites of lesions in a single patient. It is not possible to correlate every patient with a single morphological description or pathological findings unless the patient had only one leukoplakia lesion. Therefore, the more severe form of morphology and the highest degree of pathological severity of tongue leukoplakia were recorded on a per capita basis. In this study, 78 (54.17%) out of 144 patients had OLK at other sites in addition to tongue leukoplakia, or multifocal lesions such as buccal leukoplakia in 71 patients, retromolar leukoplakia in 16, gum leukoplakia in 9, labial leukoplakia in 5, floor of mouth leukoplakia in 3, and palate leukoplakia in 2. Among the 66 patients (45.83%) with only tongue leukoplakia, 53 patients had only 1 lesion of tongue leukoplakia during the cohort follow-up. Ninety-seven patients (67.36%) had homogeneous tongue leukoplakia and 47 (32.64%) had non-homogeneous tongue leukoplakia. The numbers of cases of pathologically squamous hyperplasia, mild dysplasia, moderate dysplasia, and severe dysplasia/carcinoma in situ (CIS) were 37, 62, 22, and 23, respectively. If a binary classification was adopted [24], high-risk lesions (45 cases, including moderate dysplasia and severe dysplasia/CIS) was outnumbered by low-risk lesions (99 cases, including squamous hyperplasia and mild dysplasia). The average area of tongue leukoplakia was 1.66 ± 1.84 cm², median 1.11 cm². There were 30 patients (20.83%) who showed postoperative recurrence and 12 patients (8.33%) showed postoperative malignant transformation of tongue leukoplakia. Among the 12 cases who developed malignant changes, 1 case had ventrolateral tongue cancer and buccal cancer, the other 11 cases had only tongue cancer, including 3 occurring on the dorsal tongue and 8 on the ventrolateral tongue. The time to develop recurrence and carcinoma was 3.62 ± 3.65 and 3.65 ± 2.54 years, respectively. The annual recurrence rate was 5.76%. The cumulative malignant transformation rate was 8.33% and annual transformation rate (ATR) was 2.28%. The demographic and clinicopathological data are shown in Table 2.

Univariate and multivariate analyses

Past history of head and neck cancer, clinical presentation, area of the lesion(s), and pathology were significant risk factors associated with both postoperative recurrence and
malignant transformation (Table 3, Figs. 2, 3, and 4). Gender, age, body mass index, history of radiotherapy, alcohol drinking, cigarette smoking, betel quid chewing, diabetes mellitus, metformin treatment, occurrence of leukoplakia at sites other than tongue, Candida infection, and subsites of tongue did not show statistical significance. In addition, postoperative recurrence was a significant associated factor related to postoperative malignant transformation \((P = 0.017, \text{Table 3, Fig. 5})\). The results of the multivariate analysis demonstrated that a history of head and neck cancer and area of the lesions were the 2 independent prognostic factors associated with recurrence and a history of head and neck cancer was the only independent prognostic factor associated with postoperative malignant transformation (Table 4).

**Discussion**

In the present study of oral tongue leukoplakia treated by CO\(_2\) laser excision, a history of head and neck cancer, size of the lesion area, clinical appearance, and pathology were found to be significant factors related to recurrence and malignant transformation. Postoperative recurrence itself was also a significant factor associated with malignant transformation. OLK is the most common OPMD [2, 5, 9–13], but it is still an enigmatic condition with regard to a successful treatment outcome and prediction of malignant transformation. Among the risk factors associated with malignant transformation of OLK, tongue has been a site of particular concern [5, 14, 15, 26, 27], including the ventral or lateral tongue [10, 13, 16, 28, 29], but few studies focusing solely on tongue leukoplakia have been conducted. In a study of 35 patients with tongue leukoplakia treated with surgery in Japan, CO\(_2\) laser was found to be an effective tool for tongue leukoplakia. However, no follow-up duration was recorded and no factors related to the treatment outcomes were analyzed [20]. The present series is the first to analyze the factors associated with postoperative recurrence and postoperative malignant transformation of tongue leukoplakia at both the dorsal and ventrolateral sites. A history of head and neck cancer, morphology, area, and pathology were significantly associated with the postoperative recurrence and malignant change. Besides, postoperative recurrence was also a significant factor related to postoperative malignant change. In the multivariate logistic regression analyses, a history of head and neck cancer and area were independent prognostic factors for postoperative recurrence and a history of head and neck cancer was the only independent prognostic factor for postoperative malignant transformation (Table 4).

The relationship between a history of head and neck cancer in the context of postoperative recurrence and malignant transformation has been studied in several studies [23, 29–32]. In a cross-sectional study of prevalence and risk factors of carcinoma and dysplasia in 1046 patients with OLK in Taiwan, a

### Table 2

| Clinicopathological characteristics of patients who received laser surgery for tongue leukoplakia \((n = 144)\) |
|-----------------------------------------------|
| **Case No.** | **Percent** |
|-----------------------|-------------|
| **Gender** | | |
| Female | 36 | 25.00% |
| Male | 108 | 75.00% |
| **Age** (mean ± standard deviation: 52.17 ± 11.72 years old) | | |
| < 65 | 121 | 84.03% |
| ≥ 65 | 23 | 15.97% |
| **History of head and neck cancer** | | |
| No | 111 | 77.08% |
| Yes | 33 | 22.92% |
| **History of radiotherapy** | | |
| No | 131 | 90.97% |
| Yes | 13 | 9.03% |
| **Alcohol drinking** | | |
| No | 93 | 64.58% |
| Ex-drinker | 37 | 25.69% |
| Current drinker | 14 | 9.72% |
| **Smoking** | | |
| No | 40 | 27.78% |
| Ex-smoker | 44 | 30.56% |
| Current smoker | 60 | 41.67% |
| **Betel quid chewing** | | |
| No | 74 | 51.39% |
| Ex-chewer | 62 | 43.06% |
| Current chewer | 8 | 5.56% |
| **Diabetes mellitus** | | |
| No | 112 | 77.78% |
| Yes | 30 | 20.83% |
| **Metformin taken** | | |
| No | 0 | 0.00% |
| Yes | 114 | 79.17% |
| **Occurrence of leukoplakia in addition to tongue** | | |
| No (single) | 66 | 45.83% |
| Yes (multifocal) | 78 | 54.17% |
| **Candida infection** | | |
| No | 128 | 88.89% |
| Yes | 16 | 11.11% |
| **Subsites of tongue leukoplakia** | | |
| Dorsal tongue mucosa | 40 | 25.48% |
| Ventrolateral tongue mucosa | 117 | 74.52% |
| **Morphological outlooks** | | |
| Homogeneous | 97 | 67.36% |
| Non-homogeneous | 47 | 32.64% |
| **Histopathological diagnosis** | | |
| Squamous hyperplasia | 37 | 25.69% |
| Mild dysplasia | 62 | 43.06% |
| Moderate dysplasia | 22 | 15.28% |
| Severe dysplasia/carcinoma in situ | 23 | 15.97% |
history of head and neck cancer was not a factor related to the presence of dysplasia or carcinoma in the pathological diagnosis of OLK [16]. In two other cohort studies of patients with OLK treated with CO2 laser, a history of head and neck cancer was not a factor associated with recurrence either [23, 32]. As for malignant transformation, in a study of 70 patients with OLK treated with a high-dose isotretinoin induction regimen (1.5 mg/kg/day) for 3 months and a 9-month maintenance therapy with either low-dose isotretinoin (0.5 mg/kg/day) or β-carotene (30 mg/day), a history of oral cancer was one of the significant predictive factors of cancer risks [33].

Exogenous factors, such as tobacco use, alcohol drinking, or betel quid chewing, or inherent factors, such as genetic aberrations, are all possible etiologies for OLK [34]. The risk factors associated with the occurrence of OLK are similar to those for oral cancers, including tobacco consumption, alcohol use, and betel quid chewing [15, 28]. In a study of 43 patients with OLK treated by CO₂ laser in Australia, alcohol consumption was found to be a significant factor associated with recurrence [35]. In our previous study on 114 patients with OLK treated by CO₂ laser, tobacco use and betel nut chewing were factors related to postoperative recurrence [23]. However, in other studies, alcohol drinking and cigarette smoking were not factors associated with recurrence of OLK [36–38]. As for the role of oral habits in the development of

**Table 2** (continued)

| Case No. | Percent |
|----------|---------|
| **Postoperative recurrence** | |
| No       | 114     | 79.17% |
| Yes      | 30      | 20.83% |
| **Postoperative malignant transformation** | |
| No       | 132     | 91.67% |
| Yes      | 12      | 8.33%  |
| **Body mass index** | 27.26 ± 15.06 |
| **Area (cm²) of the lesion(s)** | 1.66 ± 1.84 |
| **Cumulative malignant transformation rate** | 8.33% |
| **Duration of follow-up (months)** | 54.90 ± 54.41 |
| **Annual recurrence rate** | 5.76% |
| **Annual transformation rate** | 2.28% |

*Two pieces of missing data in the group of diabetes mellitus (n = 142)\(^a\)

*Four pieces of missing data in the group of metformin taken (n = 140)\(^b\)

*If a patient has other sites of oral leukoplakia in addition to tongue, the patient will be categorized as “yes”\(^c\)

*Thirteen patients had both dorsal and ventrolateral tongue leukoplakia\(^d\)

*If the patient has more than 1 site of tongue leukoplakia, the area is the sum of all tongue leukoplakia lesions\(^e\)

*The annual recurrence rate and annual transformation rate is calculated by the recurrence rate and malignant transformation rate divided by the average time of development of recurrence or carcinoma (year)\(^f\)

**Fig. 1** The algorithm for identifying study cohorts
Table 3  Univariate analysis of postoperative recurrence and malignant transformation of patients with tongue leukoplakia (n=144)

|                        | Postoperative recurrence | Postoperative malignant transformation |
|------------------------|--------------------------|----------------------------------------|
|                        | No (n=114)               | Yes (n=30)                             | No (n=132)               | Yes (n=12)                             |
|                        | Odds ratio (95% confidence interval) | P value | Odds ratio (95% confidence interval) | P value |
| Gender                 |                          |          |                                      |          |
| Female                 | 28                       | 8        | 1.0                                  | 34       | 2        | 1.0 |
| Male                   | 86                       | 22       | 1.10 (0.49-2.46)                     | 98       | 10       | 2.36 (0.71-7.85) |
| Age                    |                          |          |                                      |          |
| <65                    | 96                       | 25       | 1.0                                  | 111      | 10       | 1.0 |
| ≥65                    | 18                       | 5        | 1.04 (0.38-2.89)                     | 21       | 2        | 1.29 (0.24-6.79) |
| Body mass index<sup>a</sup> | 25.83±4.54<sup>b</sup> | 26.62±4.62 | 1.04 (0.95-1.13)                     | 26.1±4.62<sup>c</sup> | 24.91±3.68 | 0.94 (0.81-1.09) |
| History of head and neck cancer |          |          |                                      |          |
| No                     | 96                       | 15       | 1.0                                  | 107      | 4        | 1.0 |
| Yes                    | 18                       | 15       | 2.56 (1.16-5.66)                     | 25       | 8        | 5.96 (1.71-20.77) |
| History of radiotherapy |                          |          |                                      |          |
| No                     | 104                      | 27       | 1.0                                  | 121      | 10       | 1.0 |
| Yes                    | 10                       | 3        | 0.70 (0.25-2.01)                     | 11       | 2        | 1.67 (0.28-9.97) |
| Alcohol drinking       |                          |          |                                      |          |
| No                     | 76                       | 17       | 1.0                                  | 85       | 8        | 1.0 |
| Ex-drinker             | 26                       | 11       | 1.89 (0.78-4.56)                     | 33       | 4        | 1.29 (0.36-4.57) |
| Current drinker        | 12                       | 2        | 0.75 (0.15-3.64)                     | 14       | 0        | 0.00 (0.00-65,535.00) |
| Smoking                |                          |          |                                      |          |
| No                     | 34                       | 6        | 1.0                                  | 38       | 2        | 1.0 |
| Ex-smoker              | 35                       | 9        | 1.46 (0.47-4.54)                     | 39       | 5        | 2.44 (0.45-13.33) |
| Current smoker         | 45                       | 15       | 1.89 (0.66-5.38)                     | 55       | 5        | 1.73 (0.32-9.37) |
| Betel quid chewing     |                          |          |                                      |          |
| No                     | 62                       | 12       | 1.0                                  | 68       | 6        | 1.0 |
| Ex-chewer              | 46                       | 16       | 1.80 (0.78-4.16)                     | 56       | 6        | 1.21 (0.37-3.97) |
| Current chewer         | 6                        | 2        | 1.72 (0.31-9.58)                     | 8        | 0        | 0.00 (0.00-65,535.00) |
| Diabetes mellitus      |                          |          |                                      |          |
| No                     | 91<sup>d</sup>           | 21<sup>e</sup> | 1.0                                  | 103<sup>f</sup> | 9        | 1.0 |
| Yes                    | 22<sup>d</sup>           | 8<sup>e</sup>  | 1.14 (0.49-2.64)                     | 27<sup>f</sup> | 3        | 0.87 (0.24-3.19) |
| Metformin taken        |                          |          |                                      |          |
| No                     | 93<sup>e</sup>           | 21<sup>Ⅰ</sup> | 1.0                                  | 104<sup>e</sup> | 10       | 1.0 |
| Yes                    | 18<sup>e</sup>           | 8<sup>Ⅰ</sup>  | 1.28 (0.54-3.06)                     | 24<sup>e</sup> | 2        | 0.60 (0.16-2.25) |
| Occurrence of leukoplakia in addition to tongue |                   |          |                                      |          |
| No (single)            | 54                       | 12       | 1.0                                  | 60       | 6        | 1.0 |
|                              | Postoperative recurrence | Postoperative malignant transformation |
|------------------------------|--------------------------|----------------------------------------|
|                              | No (n=114)               | Yes (n=30)                             | No (n=132)               | Yes (n=12)                             |
| **Odds ratio (95% confidence interval)** | **P value**              | **Odds ratio (95% confidence interval)** | **P value**              |
| Yes (multifocal)             | 60                       | 18                                     | 0.89 (0.42–1.88)         | 72                                    | 6                                  | 0.64 (0.20–2.09)                     | 0.70                                  |
| Candida infection \textsuperscript{c} |                           |                                        |                          |                                        |                                    |                                      |                                       |
| No                           | 105                      | 23                                     | 1.0                      | 118                                   | 10                                  | 1.0                                  |                                        |
| Yes                          | 9                        | 7                                      | 2.07 (0.74–5.79)         | 14                                    | 2                                   | 1.01 (0.21–4.71)                     |                                        |
| Subsites of tongue leukoplakia |                           |                                        |                          |                                        |                                    |                                      |                                       |
| Dorsal tongue: absent        | 87                       | 17                                     | 1.0                      | 98                                    | 6                                   | 1.0                                  |                                        |
| Dorsal tongue: present       | 27                       | 13                                     | 1.94 (0.88–4.26)         | 34                                    | 6                                   | 2.36 (0.69–8.03)                     |                                        |
| Subsites of tongue leukoplakia |                           |                                        |                          |                                        |                                    |                                      |                                       |
| Ventrolateral tongue: absent  | 22                       | 5                                      | 1.0                      | 25                                    | 2                                   | 1.0                                  |                                        |
| Ventrolateral tongue: present| 92                       | 25                                     | 1.51 (0.63–3.60)         | 107                                   | 10                                  | 1.30 (0.32–5.25)                     |                                        |
| Morphological outlooks       |                           |                                          |                          |                                        |                                    |                                      |                                       |
| Homogeneous                  | 84                       | 13                                     | 1.0                      | 93                                    | 4                                   | 1.0                                  |                                        |
| Non-homogeneous              | 30                       | 17                                     | 3.07 (1.42–6.64)         | 39                                    | 8                                   | 4.62 (1.37–15.55)                     |                                        |
| Area (cm\textsuperscript{2}) of the lesion(s) \textsuperscript{d} | 1.35 ± 1.55              | 2.83 ± 2.34                           | 1.46 (1.17–1.81)         | 1.53 ± 1.60                           | 3.04 ± 3.32                         | 1.35 (1.06–1.70)                     | 0.013                                  |
| Pathology                    |                           |                                          |                          |                                        |                                    |                                      |                                       |
| Low-risk lesion (hyperplasia and mild dysplasia) | 86                       | 13                                     | 1.0                      | 95                                    | 4                                   | 1.0                                  |                                        |
| High-risk lesion (moderate dysplasia and severe dysplasia) | 28                       | 17                                     | 2.66 (1.25–5.68)         | 37                                    | 8                                   | 4.25 (1.28–14.19)                     |                                        |
| Postoperative recurrence     |                           |                                          |                          |                                        |                                    |                                      |                                       |
| No                           | NA                       | NA                                     | NA                       | 110                                   | 4                                   | 1.0                                  |                                        |
| Yes                          | NA                       | NA                                     | NA                       | 22                                    | 8                                   | 5.39 (1.58–18.39)                     |                                        |

\textsuperscript{a} Univariate analysis was calculated by logistic regression for continuous predictor variables

\textsuperscript{b} Four pieces of missing data in this group (n=110)

\textsuperscript{c} Four pieces of missing data in this group (n=128)

\textsuperscript{d} One piece of missing data in this group (n=113)

\textsuperscript{e} One piece of missing data in this group (n=29)

\textsuperscript{f} Two pieces of missing data in this group (n=130)

\textsuperscript{g} Three pieces of missing data in this group (n=111)

\textsuperscript{NA} data not available

When the factor(s) is(are) statistically significant (p < 0.05), the number(s) is (are) presented in italic.
malignant changes of OLK, similar conflict between the published reports was also found; oral habits were significant factors in some academic works [5, 29, 39] and non-significant in others [21, 38, 40–42]. In the present study, oral habits were not factors related to the recurrence or malignant transformation of oral tongue leukoplakia. Regarding the etiopathogenesis of oral cancers related to cigarette smoking, alcohol drinking, and betel quid chewing [43], discontinuation of oral habits is still highly recommended for patients with tongue leukoplakia. Genetically altered epithelial cells might not be revealed by routine histopathological examinations, even in locations with normal histology [44, 45]. In addition, genetic alteration, which paves the path to neoplastic transformation, may precede marked phenotypic changes [4]. Studies investigating the molecular changes of multiple lesions with different pathological severities from benign hyperplasia to carcinoma in the same patient and multiple primary malignant tumors in the same patient have been performed previously. The results showed that the genetic alterations of OPMD and OSCC in the same patient were clonally related [46, 47]. From a study of 87 lesions in 83 patients, including benign squamous hyperplasia, dysplasia, carcinoma in situ, and carcinoma, the surrounding mucosa of the precancerous or carcinomatous lesions shared common genetic alterations and was found to arise from a single progenitor clone, indicating that the genetic molecular changes might be more extensive than what could be detected clinically or microscopically [48]. These molecular biological researches support the field cancerization concept and could account for the role of a history of head and neck cancer in the postoperative recurrence and malignant transformation in this study. In the present study, a history of head and neck cancer was a significant factor and a history of head and neck cancer in the postoperative recurrence was also found [36, 52]. Non-homogeneous OLK was more often related to postoperative recurrence (2.83 ± 2.34 cm² vs. 1.35 ± 1.55 cm²) and malignant transformation (3.04 ± 3.32 cm² vs. 1.53 ± 1.60 cm²) and also an independent prognostic factor for recurrence (Table 3). Patients with larger OLK were also reported to have poorer scores in the quality of life questionnaire evaluation [51]. Thus, physicians should pay more attention and adopt a more delicate and robust strategy in treating large area of tongue leukoplakia and postoperative follow-ups.

The outlooks of OLK can be divided into 2 major categories: homogeneous leukoplakia and non-homogeneous leukoplakia. The description and criteria are the same as mentioned in previous studies [9, 21]. Non-homogeneous OLK was a predictive factor that tended to be associated with recurrence in the Kaplan–Meier survival analysis model in our previous work (P = 0.029) [23]. Similar findings indicating that non-homogeneous OLK was more often related to postoperative recurrence were also found [36, 52]. Non-homogeneous leukoplakia has been proposed to be a strongly associated factor with an increased risk of malignant development of OPMDs, including OLK [7, 10, 18, 28, 47, 53–55]. In our earlier study

### Table 4

|                          | Postoperative recurrence | Postoperative malignant transformation |
|--------------------------|--------------------------|----------------------------------------|
|                          | Odds ratio (95% CI)      | P value                                | Odds ratio (95% CI)      | P value                                |
| History of head and neck cancer | 4.35 (1.64–11.56)        | 0.003                                  | 4.57 (1.10–19.09)        | 0.037                                  |
| Morphological outlooks   | 1.70 (0.41–7.02)         | 0.46                                   | 1.43 (0.17–12.44)        | 0.74                                   |
| Area (cm²) of lesion(s)  | 1.45 (1.14–1.84)         | 0.002                                  | 1.20 (0.89–1.61)         | 0.23                                   |
| Pathology                | 1.52 (0.37–6.34)         | 0.56                                   | 1.53 (0.18–13.43)        | 0.7                                    |
| Postoperative recurrence | NA                       | NA                                     | 3.99 (0.93–17.13)        | 0.063                                  |
| Constant                 | NA                       | 0.095                                  | NA                       | 0.001                                  |

NA not available

When the factor(s) is(are) statistically significant (p < 0.05), the number(s) is (are) presented in italic.
of 114 patients with OLK treated with CO₂ laser, non-homogeneous OLK was a significant predictor for malignant transformation in the Kaplan–Meier survival analysis model [21]. According to another study of 31 patients with homogeneous OLK, 34 with non-homogeneous OLK and 12 with erythroplakia treated with CO₂ laser in London, non-homogeneous OLK was more often associated with post-treatment malignant transformation [52]. However, a contradictory result was obtained in a meta-analysis of malignant change of OLK treated with CO₂ laser. The results demonstrated that the rate of malignant transformation was 5.78% in homogeneous OLK and 5.35% in non-homogeneous OLK. The authors advocated that evidence was still lacking in terms of a relationship between malignant transformation and risk factors of OLK patients managed with CO₂ laser [41]. In this series, non-homogeneous tongue leukoplakia was a significant predictive factor for more recurrence and higher malignant transformation rate after surgical excision than the homogeneous type (Table 3, Fig. 3a, b). Non-homogeneous OLK was at a higher risk of harboring dysplasia and carcinoma [16]. After reviewing host and biologic factors, the ratio of patients showing a history of head and neck cancer (19/47 vs. 14/97, \(P = 0.0007\), data not shown), the area of tongue leukoplakia (2.10 ± 2.23 vs. 1.45 ± 1.58 cm², \(P = 0.043\), data not shown), and the ratio of patients showing high-risk dysplasia (39/47 vs. 6/97, \(P < 0.0001\), data not shown) in the tongue non-homogeneous leukoplakia in this study were higher than those in the homogeneous lesions, which might

FIG. 2 a Kaplan–Meier analysis with a log rank test of recurrence rate of tongue leukoplakia after carbon dioxide laser surgery according to patients without a history of head and neck cancer (\(n = 111\)) (blue line) versus without a history of head and neck cancer (\(n = 33\)) (red line). b Kaplan–Meier analysis with a log rank test of postoperative malignant transformation rate of tongue leukoplakia after carbon dioxide laser surgery according to patients without a history of head and neck cancer (\(n = 111\)) (blue line) versus with a history of head and neck cancer (\(n = 33\)) (red line).
reflect the disease severity and explain why the treatment outcome of non-homogeneous leukoplakia was poorer than that of homogeneous leukoplakia. Non-homogeneous appearance is an ominous sign for tongue leukoplakia and should be managed aggressively.

Pathological examination is the standard diagnostic process and is essential for all cases of OLK because the lesions may contain foci of OSCC [13, 16, 44, 56], which indicates prompt definite treatment. Pathological demonstration of dysplasia is another important issue for OLK. The occurrence of dysplasia in an OLK lesion indicates a high probability of postoperative recurrence [23, 49] or malignant transformation [21, 54, 55, 57] in several studies. However, there were results contradictory to the concept, and those authors thought that the presence of any degree of epithelial dysplasia did not have any influence on the risk of postoperative recurrence [35, 36, 38] or malignant development [17, 44]. According to a study of 368 patients with oral epithelial dysplasia from Australia, 4.1% of cases with mild dysplasia showed malignant development and the severity of epithelial dysplasia was not associated with the risk of malignant transformation; therefore, complete excision of all the epithelial lesions with different degrees of dysplasia was suggested [58]. Since there is still no consensus in the literature concerning the relationship between malignant transformation and risk factors and considering the lack of any proven biomarkers in large cohort studies, histopathological grading of
Dysplasia is regarded as the gold standard in treating these patients [10]. In the present study, high-risk dysplasia, including moderate and severe dysplasia and carcinoma in situ, was a significant predictive factor for recurrence and malignant transformation ($P < 0.05$; Table 3, Fig. 4a, b). We think clinicians should remain alert to the presence of dysplasia, especially high-risk dysplasia, considering its relationship to postoperative recurrence and malignant transformation.

Thirty patients out of 144 showed recurrence after surgical excision in the present study. The recurrence rate was 20.83% and the annual recurrence rate was 5.76%. The status of postoperative recurrence of tongue leukoplakia was consistent with that of other studies of OLK whose annual recurrence rates were approximately 5–10% [23, 38, 59]. Postoperative recurrence was a significant associated factor and independent prognostic factor for malignant transformation in our previous study [21]. Besides, recurrence was also significantly associated with cancer transformation ($P < 0.001$) in a prospective longitudinal multicenter study of 180 patients who underwent surgical removal of OLK [36]. In the present study, recurrence itself was found to be a significant predictive factor for postoperative malignant transformation ($P = 0.017$; Table 2, Fig. 5), but not an independent prognostic predictor in the multivariate logistic regression model.
The cumulative malignant transformation rate and ATR of the mobile tongue leukoplakia were 8.33% and 2.28%, respectively (Table 2). In a meta-analysis of malignant transformation of OLK, 24 studies were audited and the overall rate of malignant transformation of OLK treated with CO2 laser was 4.5% [41]. In another systematic review of 24 articles on malignant transformation of oral leukoplakia, the estimated overall malignant transformation rate was 3.5% [60]. The timing of malignant development of OLK is unpredictable [26]. In this regard, the follow-up periods of the published studies might be different, and we think that the annual transformation rate is scientifically more reasonable than the overall cumulative transformation rate. ATR was not frequently investigated in the literature [42, 47, 61] and all the published studies were conducted on all sites of the oral cavity. The differences in treatment types among those studies, including surgical removal, medical treatment, or biopsies alone, might make the basis of comparison less robust. The follow-up time varied from 2.42 to 4.75 years. The ATR ranged from 1.2 to 2.6%. From the perspective of ATR, 2.28% for tongue leukoplakia in the present study did not seem to be higher than the other studies of OLK.

Proliferative verrucous leukoplakia (PVL), which has high rates of recurrence and malignant change, is a unique subtype of OLK. Clinically, the diagnosis of PVL is consistently a challenge. In addition to the criteria proposed by Hansen et al. in 1985 and Villa et al. in 2018 [62, 63], observation of the recurrent and aggressive clinical behaviors and the potential of malignant development of the lesion may be of help in diagnosing PVL. We tried to prevent PVL cases from entering the present study, so we recruited the cases of multifocal OLK patients whose lesions were synchronous and excluded the cases with new lesions of OLK after treatment and the cases with exophytic, papillary, warty, and verrucous appearance of OLK (Table 1).

There are some limitations in this study. First, some missing data were found in some of the variables due to their retrospective nature. Second, although we chose excision of the whole leukoplakia lesion instead of vaporization, the quality of histopathological diagnosis on the tissue might have been altered due to the thermal injury induced by the laser. If the pathologists could not make an agreeable pathological diagnosis, the case(s) would be excluded. Third, the sample size of oral tongue leukoplakia was relatively small. In our experience, it is difficult to enroll a large number of patients in a single-center facility. Large-scale, multicenter, and prospective cohort studies are warranted to further investigate the disease.

Conclusions

For oral tongue leukoplakia, clinicians should adopt more aggressive treatment strategies for patients with a history of head and neck cancer.

Acknowledgments The authors thank all the members of the Department of Otolaryngology and Pathology, Keelung Chang Gung Memorial Hospital, for their invaluable help.

Author contributions Conceptualization: S.-W.Y., Y.-S.L., and C.-M.L. Data curation: Y.-S.L., and C.-M.L. Formal analysis: S.-W.Y., Y.-S.L., L.-C.C., and P.-W. W.
Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent The Chang Gung Medical Foundation Institutional Review Board has approved this study (certificate number: 201901384B0). Due to the retrospective nature of this study, the ethical committee waived the need for informed consent from the every enrolled patients.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

1. Parakh MK, Ulaganambi S, Ashifa N, Premkumar R, Jain AL (2020) Oral potentially malignant disorders: clinical diagnosis and current screening aids: a narrative review. Eur J Cancer Prev 29:65–72.

2. de Vicente JC, Donate-Perez Del Molino P, Rodrigo JP, Allonca E, Hermida-Prado F, Granda-Diaz R, Rodriguez Santamarta T, Garcia-Pedrero JM (2019) SOX2 expression is an independent predictor of oral cancer progression. J Clin Med 8:1744

3. Mello FW, Miguel AFP, Dutra KL, Porporatti AL, Wamakulasuriya S, Guerra ENS, Rivero ERC (2018) Prevalence of oral potentially malignant disorders: a systematic review and meta-analysis. J Oral Pathol Med 47:633–640

4. Saito T, Sugira C, Hirai A, Notani K, Totsuka Y, Shindoh M, Kohgo T, Fukuda H (1999) High malignant transformation rate of widespread multiple oral leukoplakias. Oral Dis 5:15–19

5. Shearston K, Faisch B, Tai S, Hove D, Farah CS (2019) Malignant transformation rate of oral leukoplakia in an Australian population. J Oral Pathol Med 48:530–537

6. Wang TY, Chiu YW, Chen YT, Wang YH, Yu HC, Yu CH, Chang YC (2018) Malignant transformation of Taiwanese patients with oral leukoplakia: a nationwide population-based retrospective cohort study. J Formos Med Assoc 117:374–380

7. Chiang WF, Liu SY, Lin JF, Chiu SF, Guo SB, Chou CT, Chang CH (2020) Malignant development in patients with oral potentially malignant disorders detected through nationwide screening: outcomes of 5-year follow-up at a single hospital. Head Neck 42:67–76

8. Wamakulasuriya S, Johnson NW, van der Waal I (2007) Nomenclature and classification of potentially malignant disorders of the oral mucosa. J Oral Pathol Med 36:575–580

9. Wamakulasuriya S (2018) Clinical features and presentation of oral potentially malignant disorders. Oral Surg Oral Med Oral Pathol Oral Radiol 125:582–590

10. Speight PM, Khurram SA, Kujan O (2018) Oral potentially malignant disorders: risk of progression to malignancy. Oral Surg Oral Med Oral Pathol Oral Radiol 125:612–627

11. Farah CS, Fox SA (2019) Dysplastic oral leukoplakia is molecularly distinct from leukoplakia without dysplasia. Oral Dis 25:1715–1723

12. van der Waal I (2018) Knowledge about oral leukoplakia for use at different levels of expertise, including patients. Oral Dis 24:174–178

13. Jeong WJ, Paik JH, Cho SW, Sung MW, Kim KH, Ahn SH (2012) Excisional biopsy for management of lateral tongue leukoplakia. J Oral Pathol Med 41:384–388

14. Mangold AR, Torgerson RR, Rogers RS 3rd (2016) Diseases of the tongue. Clin Dermatol 34:458–469

15. Porter S, Guieros LA, Leao JC, Fedele S (2018) Risk factors and etiopathogenesis of potentially premalignant oral epithelial lesions. Oral Surg Oral Med Oral Pathol Oral Radiol 125:603–611

16. Lee JJ, Hung HC, Chiang CP, Liu BY, Jeng JH, Chang HH, Kuo YS, Lan WH, Kok SH (2006) Carcinoma and dysplasia in oral leukoplaikias in Taiwan: prevalence and risk factors. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 101:472–480

17. Holmstrup P, Vedtofte P, Reibel J, Stoltze L (2006) Oral potentially malignant disorders: clinical diagnosis and current screening aids: a narrative review. Eur J Cancer Prev 29:65–72.

18. Silverman S Jr, Gorsky M, Lozada F (1984) Oral leukoplakia and malignant transformation. A follow-up study of 257 patients. Cancer 53:563–568

19. Shigeoka M, Koma YI, Kodama T, Nishio M, Akashi M, Yokozaki H (2020) Intraepithelial CD163(+) macrophages in tongue leukoplakia biopsy: a promising tool for cancer screening. Oral Dis 26:527–536

20. Matsumoto K, Suzuki H, Asai T, Wakabayashi R, Enomoto Y, Kitayama M, Shigeoka M, Kimoto A, Takeuchi J, Yutori H (2015) Clinical investigation of carbon dioxide laser treatment for lingual leukoplakia. J Oral Maxillofac Surg Med Pathol 27:493–497

21. Yang SW, Wu CJ, Lee YS, Chen TA, Tsai CN (2010) Postoperative recurrence as an associated factor of malignant transformation of oral dysplastic leukoplakia. ORL J Otorhinolaryngol Relat Spec 72:280–290

22. Yang SW, Lee YS, Chang LC, Hsieh TY, Chen TA (2015) Outcome of excision of oral leukoplakia. Br J Oral Maxillofac Surg 53:142–147

23. Yang SW, Tsai CN, Lee YS, Chen TA (2011) Treatment outcome of dysplastic oral leukoplakia with carbon dioxide laser emphasis on the factors affecting recurrence. J Oral Maxillofac Surg 69:e78–e87

24. Wamakulasuriya S, Reibel J, Bouquet J, Dabelsteen E (2008) Oral epithelial dysplasia classification systems: predictive value, utility, weaknesses and scope for improvement. J Oral Pathol Med 37:127–133

25. Ishii J, Fujita K, Komori T (2003) Laser surgery as a treatment for oral leukoplakia. Oral Oncol 39:759–769

26. Awadallah M, Idle M, Patel K, Kademan D (2018) Management update of potentially premalignant oral epithelial lesions. Oral Surg Oral Med Oral Pathol Oral Radiol 125:628–636
27. Kuribayashi Y, Tsushima F, Morita KI, Matsumoto K, Sakurai J, Uesugi A, Sato K, Oda S, Sakamoto K, Harada H (2015) Long-term outcome of non-surgical treatment in patients with oral leukoplakia. Oral Oncol 51:1020–1025

28. Villa A, Sonis S (2018) Oral leukoplakia remains a challenging condition. Oral Dis 24:179–183

29. Wu W, Wang Z, Zhou Z (2019) Risk factors associated with malignant transformation in patients with oral leukoplakia in a Chinese population: a retrospective study. J Oral Maxillofac Surg 77:2483–2493

30. Beyele AF, Farwell DG (2017) Oral leukoplakia and oral cavity squamous cell carcinoma. Clin Dermatol 35:461–467

31. Mogedas-Vegara A, Hueto-Madrid JA, Chimenos-Kustner E, Bescos-Atin C (2015) The treatment of oral leukoplakia with the CO2 laser: a retrospective study of 65 patients. J Cranio-maxillofac Surg 43:677–681

32. Chiesa F, Boracchi P, Tradati N, Rossi N, Costa L, Giardini R, Mogedas-Vegara A, Hueto-Madrid JA, Chimenos-Kustner E, Pacheco JJ, Vescovi P, Meleti M (2017) Type of surgical treatment: important factors that predict the risk of recurrence and malignancy. J Oral Pathol Med 46:682–688

33. Dong Y, Chen Y, Tao Y, Hao Y, Jiang L, Dan H, Zeng X, Chen Q, Zhou Y (2019) Malignant transformation of oral leukoplakia treated with carbon dioxide laser: a meta-analysis. Lasers Med Sci 34:209–221

34. Brouns E, Baart J, Karagozoglu K, Aartman I, Bloemena E, van der Wal JE, Roodeburg JL (2005) The results of CO2 laser surgery in patients with oral leukoplakia: a follow-up study of a hospital-based population of 166 patients with oral leukoplakia from The Netherlands. Oral Oncol 34:270–275

35. Caligano J, van der Riet P, Westra W, Nawroz H, Clayman G, Piantadosi S, Corio R, Lee D, Greenberg B, Koch W, Sidransky D (1996) Genetic progression model for head and neck cancer: implications for field cancerization. Cancer Res 56:2488–2492

36. Yang SW, Lee YS, Chang LC, Hwang CC, Chen TA (2020) Clinopathological characteristics and treatment outcomes of oral leukoplakia by carbon dioxide laser excision in the elderly patients. Head Neck 42:1014–1023

37. Jayasooriya PR, Dayaratne K, Dissanayake UB, Warnakulasuriya S (2012) Oral cancer development in patients with leukoplakia – an update. J Oral Pathol Med 41:682–684

38. Brouns ER, Baart JA, Karagozoglu KH, Aartman IH, Bloemena E, van der Waal I (2013) Treatment results of CO2 laser vaporisation in a well-defined cohort of 144 patients. Oral Dis 19:212–216

39. Ko YC, Huang YL, Lee CH, Chen MJ, Lin LM, Tsai CC (1995) Betel quid chewing, cigarette smoking and alcohol consumption related to oral cancer in Taiwan. J Oral Pathol Med 24:450–453

40. Holmstrup P, Vedelcke P, Reibel J, Stoltze K (2007) Oral premalignant lesions: is a biopsy reliable? J Oral Pathol Med 36:262–266

41. Tabor MP, Brakenhoff RH, Ruijter-Schippers HJ, van Der Wal JE, Snow GB, Leemans CR, Braakhus BJ (2002) Multiple head and neck tumors frequently originate from a single preneoplastic lesion. Am J Pathol 161:1051–1060

42. Scheepman KP, van der Meij EH, Sneele LE, van der Waal I (1998) Malignant transformation of oral leukoplakia: a follow-up study of a hospital-based population of 166 patients with oral leukoplakia from The Netherlands. Oral Oncol 34:270–275

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.