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Management of oral leukoplakia by ablative fractional laser-assisted photodynamic therapy: A 3-year retrospective study of 48 patients

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Abstract

Objectives: This study aimed to review the results of oral leucoplakia (OL) using ablative fractional laser-assisted photodynamic therapy (AFL-PDT) and to further evaluate the risk factors for recurrence and malignant transformation.

Materials and Methods: Forty-eight patients diagnosed with OL using histopathology were enrolled in this study. All patients received one session of AFL-PDT. Therapeutic efficacy was evaluated 1 month posttreatment. Follow-up was scheduled every 3 months in the first year and every 6 months thereafter.

Results: An overall positive response rate of 87.5% (42/48) was achieved, including 62.5% (30/48) complete responses and 25.0% (12/48) partial responses. During the 3-year follow-up period, the recurrence and malignant transformation rates were 37.5% (18/48) and 8.3% (4/48), respectively. Lesions on gingiva/palate seemed to be associated with recurrence ($p < 0.001$; odds ratio [OR]: 1.64, 95% confidence interval [CI]: 1.13–2.37). The severity of epithelial dysplasia ($p = 0.02$; OR: 2.93, 95% CI: 1.96–4.42) and recurrence ($p = 0.016$; OR: 3.14, 95% CI: 2.04–4.84) were associated with a predisposition to malignant transformation.

Conclusions: AFL-PDT is an effective management of OL, but requires close follow-up. OL lesions on the gingiva/palate are predisposed to recurrence. OLs that recur with moderate/severe epithelial dysplasia have a higher risk of transforming into oral squamous cell carcinoma.

KEYWORDS

ablative fractional laser, malignant transformation, oral leukoplakia, photodynamic therapy, recurrence

INTRODUCTION

The World Health Organization (WHO) defined oral leucoplakia (OL) as "a white patch or plaque that cannot be characterised clinically or pathologically as any other disease." The prevalence of OL is approximately 3%,[1,2] of which 10%–36% of cases occur in oral squamous cell carcinoma (OSCC).[1,2] Consequently, OL is considered one of the most common oral mucosal diseases and premalignant disorders.

Treatment modalities for OL include scalpel excision, laser therapy, cryotherapy, topical application of bleomycin and vitamin A, and systemic administration of β-carotene, lycopene, and retinoids.[3,4] Photodynamic therapy (PDT) is an attractive treatment for OL, since large or multiple lesions can be treated with low toxicity, minimal invasiveness, and high selectivity.[5,6] However, the penetration depth of photosensitizers into the lesion is a significant limitation for PDT efficacy.[7,8] Ablative fractional laser (AFL) has been proven to be effective

through in vitro and in vivo studies.[9,10] AFL is also recommended by the guidelines for topical PDT[11] for enhancing the uptake of topically applied photosensitizers and intensifying PDT response during the treatment of premalignant diseases. One case study[12] has reported that an OL with a large area was successfully treated by AFL-assisted PDT (AFL-PDT) but not by PDT alone, which demonstrated the therapeutic effect of AFL in AFL-PDT. However, the efficacy of AFL-PDT for OL has not been summarised. In this study, we reviewed the results of OL patients who were treated with AFL-PDT and evaluated the therapeutic effects, recurrence, malignant transformation, and associated risk factors.

MATERIALS AND METHODS

Patients

Consecutive OL patients treated at the Department of Oral Mucosal Disease, Shanghai Ninth People's Hospital, between March 2018 and August 2018 were recruited for this study. Approval was obtained from the ethics committee before initiation (2016-115-T64).

Patients with untreated OLs were screened for inclusion. The inclusion criteria were OL as verified by the diagnostic standard[13] and an age range of 18–75 years. The exclusion criteria were pregnancy/lactation, histopathological diagnosis of other mucosal diseases, severe malignancies, and poor general condition.

Treatment procedures

The OL lesion was prepared to facilitate the penetration of 5-aminolevulinic acid (ALA Zhangjiang Pharmaceuticals) before the application of ALA. After local anaesthesia, the stratum corneum was carefully removed with AFL (Juehua Medical Devices Co., Ltd.). The following AFL parameters were used: a square pattern with a coverage rate of 9%, wavelength of 10.6 μm, fluence of 15 W/cm^2, pulse duration of 52.5 ms, interval of 1.0 ms, and spot pitch of 0.6 mm. Vaporised crusts were cleared with saline cotton swabs and subsequently lifted. The prepared 20% ALA gel was applied to the lesion and successively covered with a piece of glutinous rice paper, plastic wrap, and gauze for saliva isolation. A high-potency vacuum device was used for salivary suction. The illumination procedure was performed 3 h after occlusion of the ALA and involved the administration of red light (Yage LED-IB photodynamic therapy instrument Co., Ltd.) at a wavelength of 630 nm, light dose of 180 J/cm^2, and fluence rate of 100 source. Light was imaged on the lesion surface at a spot of 1-cm diameter for 5 min. Each spot was overlapped with adjacent spots by 3 mm to cover the entire lesion. In each treatment session, the treatment area was limited to 4 cm^2 or a diameter of 3 cm. Each treatment area underwent one session of AFL-PDT treatment.

Follow-up

Follow-up was performed 1 month postoperatively, every 3 months in the first year, and every 6 months thereafter. The treated area was measured using a periodontal probe and was recorded using a digital camera. An experienced expert in oral mucosal disease performed the clinical examination, including treatment response, clinical recurrence, and malignant transformation.

Therapeutic efficacy was evaluated in terms of the clinical treatment response at 1 month postoperatively and classified as complete response (CR, 100% reduction in lesion size), partial response (PR, more than 30% reduction in lesion size), or no response (NR, less than 30% reduction in lesion size or even worsening).

Clinical recurrence was evaluated at every follow-up, except for the first time, and described as being present or absent. A biopsy was performed once the lesion appeared nonhomogenous, which indicates a higher potential for malignant transformation.[14] Patients completed the follow-up and received treatment once the lesion transformed into OSCC at any time during the study.

Statistical analysis

Logistic regression was used to evaluate the odds ratios (ORs) and associations among the variables. An asymptotic 95% confidence interval (CI) for the OR was calculated. All tests were two-sided, and $p < 0.05$ were considered statistically significant. All analyses were performed using SPSS version 13.0 (SPSS Inc.).

RESULTS

Patients

A total of 48 patients with OL who met the inclusion criteria and underwent AFL-PDT were enrolled in the study. Of the 48 patients, the population consisted of 62.5% (30/48) female and 37.5% (18/48) male. The patient characteristics at baseline were as follows: average age (SD) of 60.7 (11.9) years; tobacco history (yes/no), 29.2% (14/48)/70.8% (34/48); alcohol history (yes/no), 12.5% (6/48)/87.5% (42/48). Of the lesions, 41.7% (20/48) were located on the margin surface of the tongue, followed by the cheek mucosa (37.5%, 18/48), gingiva (8.3%, 4/48), palate (6.2%, 3/48), dorsal surface of the tongue (4.2%, 2/48), and floor of the mouth (2.1%, 1/48). Mild, moderate, severe, and no dysplasia were observed in 56.3% (27/48), 31.3% (15/48), 8.3% (4/48), and 4.2% (2/48) of the overall OL patient population, respectively.

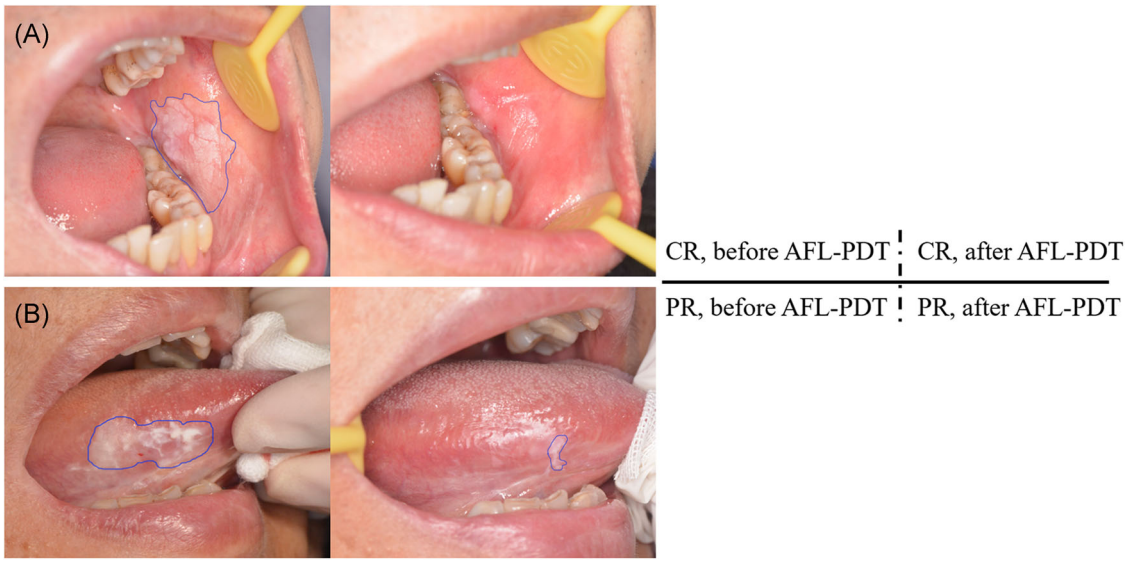

FIGURE 1 Clinical pictures of different efficacies. The OL lesion (blue line) showed a complete response (CR, A) or a partial response (PR, B) to ablative fractional laser-assisted photodynamic therapy (AFL-PDT)

Treatment response

After one session of AFL-PDT, 87.5% (42/48) of the OL patients achieved an overall positive response, whereas 12.5% (6/48) did not exhibit any change. Among the 42 responders, 30 and 12 showed CR (Figure 1A) and PR (Figure 1B) to AFL-PDT, respectively.

Clinical recurrence

During the 3-year follow-up, 37.5% (18/48) of the OLs recurred, with an average recurrence time of 6.4 months. Recurrence was observed in 30.0% (9/30) CR lesions, 50.0% (6/12) PR lesions, and 50.0% (3/6) NR lesions. The main characteristics of the recurrence group are presented in Table 1. Univariate analyses revealed that sex, smoking, alcohol history, and epithelial dysplasia did not reach statistical significance ($p > 0.05$). Notably, univariable analyses and Kaplan–Meier curves for time to recurrence (Figure 2) showed that gingiva/palate was significantly associated with recurrence ($p < 0.001$; OR: 1.64, 95% CI: 1.13–2.37).

Malignant transformation

During the 3-year follow-up period, the cumulative incidence of malignant transformation was 8.3% (4/48). Among them, CR and NR to AFL-PDT was observed in two cases in each condition. The clinicopathological parameters of each patient with malignant transformation are presented in Table 2. Univariate analyses revealed that the severity of epithelial dysplasia ($p = 0.02$; OR: 2.93, 95% CI: 1.96–4.42) and recurrence ($p = 0.016$; OR: 3.14, 95% CI: 2.04–4.84) predisposed the patients to malignant

TABLE 1 Univariable analysis of risk factor for recurrence OL after AFL-PDT treatment

Characteristics	Non-recurrence OL	Recurrence OL	Univariable analysis
Total, *n* (%)	30 (62.5)	18 (37.5)	OR (95% CI)
Sex			$p = 0.363$
Female	17 (56.7)	13 (43.3)	1.0 (ref)
Male	13 (72.2)	5 (27.8)	1.99 (0.56–7.00)
Tobacco			$p = 0.521$
Yes	10 (71.4)	4 (28.6)	1.0 (ref)
No	20 (58.8)	14 (41.2)	0.57 (0.15–2.20)
Alcohol			$p = 0.179$
Yes	2 (33.3)	4 (66.7)	1.0 (ref)
No	28 (66.7)	14 (33.3)	4.00 (0.65–24.55)
Lesion location			$p < 0.001$
Others	30 (73.2)	11 (26.8)	1.0 (ref)
Gingiva/palate	0 (0.0)	7 (100.0)	1.64 (1.13–2.37)
Epithelial dysplasia			$p = 0.127$
No/mild	21 (72.4)	8 (27.6)	1.0 (ref)
Moderate/severe	9 (47.4)	10 (52.6)	2.92 (0.87–9.82)

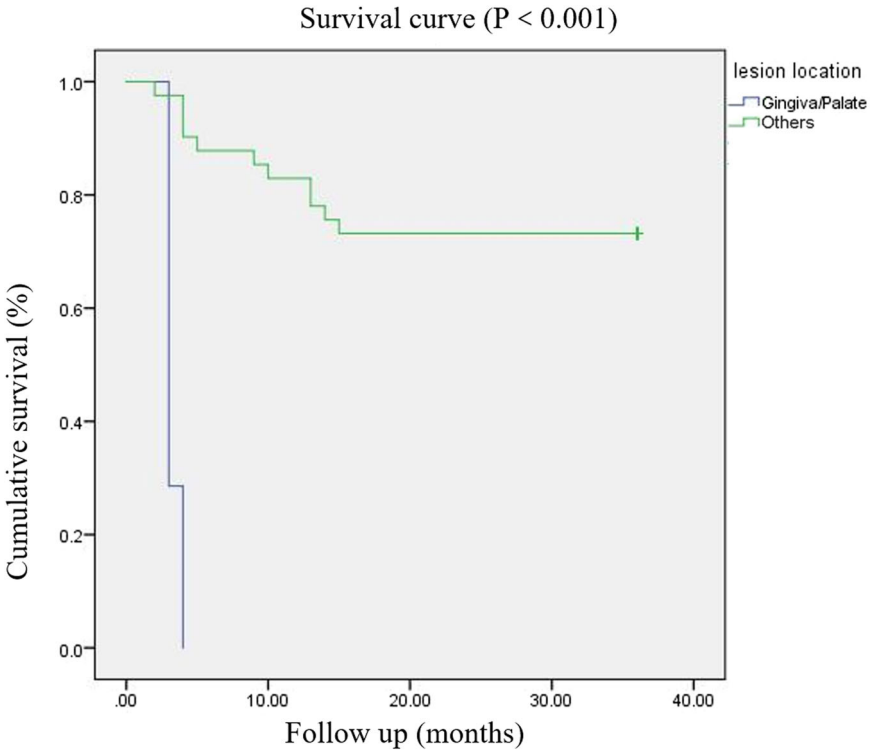

FIGURE 2 Kaplan–Meier curves for time to recurrence showed significance for lesion location ($p < 0.001$)

TABLE 2 Clinicopathological parameters of patients with malignant transformation

	Sex	Age (year)	Tobacco	Alcohol	Location	Epithelial dysplasia	Recurrence time (month)	Malignant transformation time (month)
1	F	67	No	No	Tongue, margin	Moderate	10	13
2	F	70	No	No	Gingiva	Moderate	3	7
3	M	43	Yes	Yes	Tongue, margin	Moderate	9	13
4	F	62	No	No	Tongue, margin	Severe	14	15

Abbreviations: F, female; M, male.

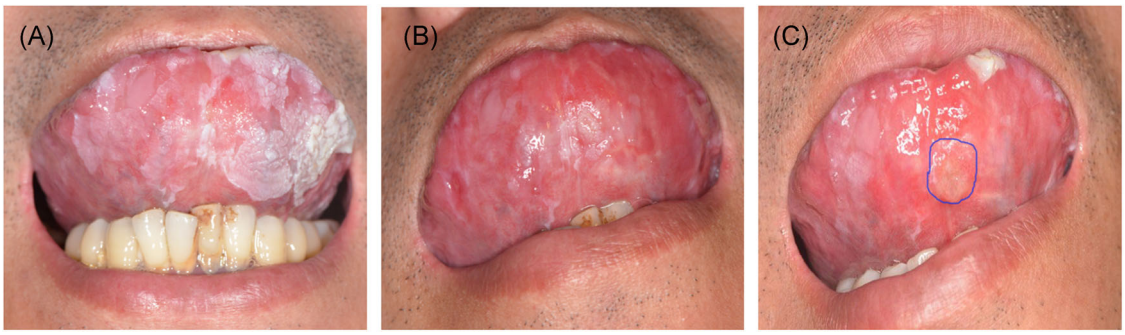

FIGURE 3 Representative images for OL patients with malignant transformation. (A) A lesion on the tongue. (B) Most of the lesion disappeared with congestion at 1 month follow-up. (C) The histopathology of the non-homogenous lesion showed squamous cell carcinoma

transformation. No difference was observed in sex, location, and tobacco and alcohol history ($p > 0.05$). Clinical images of a representative patient with malignant transformation are shown in Figure 3.

DISCUSSION

In a retrospective study evaluating PDT for OL,[15] an overall response rate of 86.2% was achieved, including 55.2% CR and 31.0% PR, following 4.08 ± 1.73 PDT

sessions. Other studies also reported a positive response of 72.3%–83.3% in patients who underwent 6–10 sessions of PDT.[16,17] The results of this study showed that 87.5% of the lesions responded to only one session of AFL-PDT, which indicates that AFL can greatly improve the effectiveness of PDT treatment for OL, and AFL-PDT shows excellent efficacy in OL treatment. The recurrence rates reported by two retrospective studies[18,19] that evaluated AFL for OL were 33.8% during an average 15-month follow-up and 32% in a >6-month follow-up. Studies[20,21] evaluating the effectiveness of PDT for OL have reported recurrence rates that ranged from 18.1% to 30.8% during 3–19 months follow-up. Both recurrence rates in AFL and PDT for OL were higher than that in this study (37.5% recurrence during a 3-year follow-up). Compared with AFL and PDT, AFL-PDT may be a more effective management strategy for OL treatment and reducing the risk of OL recurrence.[22] In this study, each treatment area was limited to 4 cm^2 or a diameter of 3 cm. When the lesion area exceeded the size limit, it was divided into multiple smaller areas for treatment. Each treatment area underwent one session of AFL-PDT. This method may confirm the efficacy of AFL-PDT.

Intriguingly, lesions in the gingiva/palate ($p < 0.001$; OR: 1.64, 95% CI: 1.13–2.37) exhibited a higher risk of recurrence than that of other lesions. Alfonso et al.[18] and Yuri et al.[23] reported a consistent result, that the gingiva was the most common recurrence site. The gingiva/palate is subjected to friction and pressure when chewing. Furthermore, the mucosa of both sites was too thin to undergo operation with a sufficient safety margin,[23] and consequently, gingiva and palate lesions were risk factors for recurrence. Interestingly, among the 18 enrolled lesions on the cheek mucosa in this study, 17 lesions responded to AFL-PDT, and only three lesions recurred. None of the patients developed OSCC. These results suggest that compared to other sites, AFL-PDT is particularly suitable for lesions on the cheek mucosa.

A systematic review and meta-analysis[24] suggested that malignant transformation of OL is independent of laser treatment, including AFL, Nd: YAG laser, KTP laser, or diode laser. Based on the possibility of selective destruction of pathological tissues with accumulated photosensitizers, PDT has been successfully used in oncology.[25] The malignant transformation rate of this study was 8.3%, which was comparable with the rates reported by other studies.[1,2] This study cannot yet evaluate the influence of AFL-PDT on malignant transformation of OL because of the relatively small sample size and short follow-up period.

The severity of dysplasia was a common risk factor for malignant transformation,[26,27] which was also verified in this study ($p = 0.02$; OR: 2.93, 95% CI: 1.96–4.42). In the present study, 22.2% (4/18) of recurrent OLs transformed into OSCC, which was higher than that of non-recurrent OLs ($p = 0.016$; OR: 3.14, 95% CI: 2.04–4.84). Three of four cases of malignant transformation were found in the margins of the tongue, which is recognized as a high-risk site for OL malignant transformation.[28,29] Our findings should remind clinicians to arrange close follow-up for OL recurrence, especially when lesions occur on the margin of the tongue. In the present study, OLs which showed CR to AFL-PDT recurred and even transformed into OSCC. This suggests that clinicians should not take CR patients lightly, and close follow-up is still required.

CONCLUSION

In conclusion, AFL-PDT is an effective management of OL, but requires close follow-up. OL lesions on the gingiva/palate are predisposed to recurrence. OLs that recur and those with moderate/severe epithelial dysplasia have a higher risk of malignant transformation. Randomised controlled studies with larger sample sizes and longer follow-up times are needed to evaluate the influence of AFL-PDT on OL malignant transformation.

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CONFLICT OF INTERESTS

The authors declare are no conflict of interest.

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