Abstract

Introduction
Molecular changes in oral leukoplakia (OL) or in adjacent clinically normal mucosa might influence the persistence/recurrence of OL, allowing an opportunity for transformation into squamous cell carcinoma. This paper discusses the surgical management of patients with OL.

Short communication
Clinicians must understand that available treatment options are limited in their capacity to prevent oral cancer. Surgical resection is still currently the best technique for management of OL. Patients with OL also need to adjust their lifestyle.

Conclusion
We call for further studies to improve our understanding.

Introduction
According to a workshop coordinated by the WHO Collaborating Centre for Oral Cancer and Precancer, the term oral leukoplakia (OL) applies to "white plaques of questionable risk, having excluded (other) known diseases or disorders that carry no increased risk for cancer". OL typically presents as a white lesion of oral mucosa and is diagnosed when all other possible causes of white oral lesions are excluded. A provisional diagnosis is made only when clinical examination is performed and any other clinical diagnosis is excluded.

Histological examination should support the diagnosis being mandatory for histological grading of epithelial dysplasia. The extent or grade of dysplasia is currently the accepted reference method by which the malignant potential of OL is gauged to predict OL malignant transformation. Key dysplastic features of stratified squamous epithelium include cellular atypia and loss of stratification. Generally, dysplasia is classified by degree as mild, moderate or severe.

Despite being the gold standard method to predict malignant potential, there is little agreement between pathologists regarding epithelial dysplasia grading, and even nondysplastic lesions may transform. Subjectivity in the grading of OL, arbitrarily set grading thresholds, lack of calibration and limited knowledge of which criteria best predict malignant transformation may explain these disparities. However, a meta-analysis has shown that the grade of dysplasia in OL and eventual malignant transformation correlate significantly. Although excision may not eliminate this transformation, the likelihood is at least reduced.

Homogeneous OL lesions are flat, thin, uniformly white in colour and carry a low risk of malignant transformation. On the other hand, mixed white and red lesions, with irregularly flat, nodular or verrucous areas, qualify as nonhomogeneous, and these are at high risk of progression to cancer. The term oral verrucous leukoplakia signifies lesions with multifocal presentation that are resistant to treatment and are at a high risk of emergent cancer. The primary risk factors for malignant transformation of OL are: (i) female gender, (ii) lesion chronicity, (iii) nonsmoker status, (iv) heterogeneous features, (v) tongue and floor of mouth sites, (vi) size >200 mm², (vii) severity of dysplasia, (viii) aneuploidy and (xi) loss of heterozygosity. Some molecular markers have shown promise in predicting the progression of premalignant oral lesions to squamous cell carcinoma, but none as yet are in routine clinical use.

Surgical techniques for managing patients with OL vary. However, randomized clinical trials have not addressed their efficacies in terms of preventing recurrent OL or its malignant transformation. This paper assesses the surgical treatment and what is achieved of patients with OL.

Short Communication
Treatment of OL
At present, there is no scientific evidence that any manner of intervention prevents the development of squamous cell carcinoma in OL. Recurrences may arise after surgical resection, based on mucosal field changes, which explains why widespread lesions pose a substantial threat of persistence/recurrence or malignant transformation. By definition, the concept of field cancerization denotes the presence of microscopic epithelial changes surrounding an oral cancer. Now we realize that even clinically normal mucosa, devoid of dysplasia at a microscopic level, might harbour molecular alterations predisposed to malignant transformation. Surgical excision is therefore ineffective in eradicating OL or preventing eventual malignancy. Instead, it is widely used for its potential as a diagnostic tool. Of course, this benefit may be curtailed, if incisional biopsy is done rather than complete excision.
Development of a squamous cell carcinoma is not at all unusual in a white plaque displaying no earlier clinical signs of malignancy. In short, excisional biopsy of OL does not prevent malignant transformation (primary prevention), but it does promote early diagnosis of cancer (secondary prevention) and is indicated for every lesion. In one retrospective study of OL, the incidence of oral squamous cell carcinoma was determined in patients treated surgically and/or medically and in those managed only by regular clinical follow-ups. Given that the two groups did not differ significantly, one may argue that OL lesions destined for malignant transformation will suffer such fate regardless of active intervention. However, a bias related to group heterogeneity cannot be excluded, because the patients were not randomly assigned.

CO2 laser resection is the most commonly used laser method for treatment of OL. The rate of recurrence after CO2 laser resection varies from 7.7% to 66%, with malignant transformation occurring in 7.7–14.2%. Continuous smoking after surgical removal and widespread lesions are prognostic indicators for recurrence after laser surgery. The haemostasis achieved by laser ablation is clearly advantageous as well as the ability to preserve surrounding tissue and the positive wound healing attached. Unfortunately, no tissue is available for histopathological examination.

Photodynamic therapy has also been used to manage patients with OL and oral erythroplakia. In patients with OL, results have proved unsatisfactory, but a high success rate (66–95%) has been reported with erythroplakia. The less keratinized surface and more decisive dysplasia of the latter perhaps facilitate greater penetration by photosensitizer.

Despite extensive investigations and a number of advances in systemic therapy for patients with potentially malignant oral lesions, there is no standard approach for prevention of head and neck malignancies. A serious drawback of chemoprevention is the relapse of lesions after discontinuing treatment.

**Discussion**

**Recurrence Versus Second Primary OL**

Resection is the most common treatment modality in OL. However, clinicians must bear in mind that molecular alterations may or may not be manifested in ‘clinically normal mucosa’ (Figure 1). When surgical margins are involved, removal of the lesion will not eliminate ‘altered clones’. Thus, any relapse should be considered a persistent/recurrent disease. In the event that the margins do not present molecular alterations, any new lesion appearing at the same site is better viewed as a second primary OL. Currently, there is no proof that recurrent and second primary OL differ in respective risks of malignant transformation or indicated treatments. Future studies may help illuminate the clinical relevance of any distinction in this regard.

**Conclusion**

Any expression of molecular alterations in ‘clinically normal mucosa’ at the margins of OL carries an increased risk of progression to squamous cell carcinoma. Because the means of assessing surgical margins may not be routinely available, clinicians must factor this into treatment decisions. In general, all patients with OL should be monitored regularly. Despite a lack of evidence, surgical resection still remains the best practice for management of OL, regardless of histologic grade. Lifestyle modifications (i.e. cessation of smoking and alcohol consumption) in patients with OL are also warranted.

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