原文題目(出處)：	How should we manage oral leukoplakia? Br J Oral & Maxillofac Surg 2013;51: 377-83
原文作者姓名：	Anand Kumar, Luke Cascarini, James A. McCaul, Cyrus J. Kerawala, Darryl Coombes, Daryl Godden, Peter A. Brennan
通訊作者學校：	Maxillofacial Department, Nothwick Park Hospital, Northwest London Hospitals NHS Trust, Harrow, Middlesex, United Kingdom
報告者姓名(組別)：	Int. C 黃筠婷
報告日期：	102.10.08

內文：

A. Introduction
   1. The purpose of identifying potentially malignant disorders of the oral cavity is to
      a. initiate timely and adequate intervention
      b. prevent malignant transformation
      c. enable early diagnosis of malignancy

B. Oral leukoplakia
   1. prevalence of potentially malignant disorders varies by the geographical location and population studied
   2. global prevalence of oral leukoplakia: 0.5 ~ 3.4%
   3. point prevalence: 2.6%
   4. malignant transformation rate: 0.13 ~ 17.5%
   5. Prevalence increases with advancing age:
      a. less than1%in men younger than 30 years
      b. 8%in men and2% in women over 70 years
   6. aetiological factor: Smoking(most commonly), alcohol, HPV infection, candidiasis, and reduced concentrations of serum vitamin A and beta-carotene

Definition
   1. "a predominantly white lesion of the oral mucosa that cannot be characterised as any other definable lesion"
   2. "OL should be used to recognise white plaques of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer"

Classification
   1. Be classified into homogeneous and non-homogeneous subtypes Considering the macroscopic appearance.
   2. Homogeneous plaques are predominantly white, of uniform flat, thin appearance with shallow cracks of surface keratin, and have a smooth, wrinkled, or corrugated surface with a consistent texture throughout
   3. Non-homogeneous plaques are predominantly white, or white and red (erosive leukoplakia, erythroleukoplakia) and may be either irregularly flat, nodular (speckled), or verrucous
   4. Proliferative verrucous oral leukoplakia is a subtype of verrucous leukoplakia, and is characterised by a multifocal presentation, resistance to treatment, and high rate of malignant transformation

Histopathology
   1. Can be distinguished as dysplastic and non-dysplastic lesions

2. The presence of dysplasia has been associated with a risk of progression to cancer.
3. The grading of dysplasia is subjective, and little agreement among and between observers, and not enough knowledge about which criteria best predict malignant potential
4. The binary system for histopathological grading was proposed to reduce variability between observers
    a. graded as low risk (mild and moderate dysplasia) and high risk (severe dysplasia and carcinoma in situ) depending on the architecture and cytological changes
    b. the sensitivity and specificity were 85% and 80% respectively
    c. the accuracy was 82%

Malignant Transformation

1. Independent risk factors: age, site and type of lesion, and dysplasia

Appearance

1. Low risk of malignant transformation: homogeneous lesions
2. Intermediate risk of malignant transformation: mixed white and red lesions (or speckled leukoplakia)
3. Highest risk of malignant transformation: pure erythroplakia (red lesions)
4. None of these macroscopic features is reliably diagnostic of any histological grade of precursor lesion, and histological analysis of the lesions is mandatory to discover their biological potential

Site and age

1. Predictive indicators of malignant transformation
    a. Lesions on the tongue or floor of the mouth
    b. larger lesions (more than 200mm^2)
    c. Non-smokers
    d. Elderly patients (over 60 years of age) with lesions on the lateral or ventral tongue
    e. Non-homogeneous lesions with high-grade dysplasia

Dysplasia

1. one of the most important indicators of malignant potential: Epithelial dysplasia
2. dysplastic oral leukoplakia carries a 5-fold greater risk of malignant transformation than non-dysplastic oral leukoplakia, and its predictive value depends on the prevalence of leukoplakia in a given population
3. oral cancer-free survival: 86.6% at 3 years, 82.0% at 5 years
4. High-grade dysplasia v. s. low-grade dysplasia of 5-year oral cancer-free survival: 59% compared with 90.5%

DNA content (DNA ploidy)

1. an important predictor of the malignant potential of leukoplakia or erythroplakia
2. abnormal DNA content was a significant predictor for progression to cancer with a hazard ratio (HR) of 3.3
3. A study by Bremmer et al.: DNA aneuploidy was associated with the development of cancer (HR 3.7, 54% sensitivity and 60% specificity). They also found no association between patient-related clinical factors and the risk of malignant transformation, and a relatively low correlation between ploidy and grade of dysplasia. They concluded that lesions that show DNA aneuploidy have a significantly higher risk of malignant

transformation

4. no reliable markers to predict the malignant transformation of oral leukoplakia. It has been reported that Ki-67(Mib-1) and bromodeoxyuridine, and the combined biomarker score of chromosomal polysomy, p53, and loss of heterozygosity might be strong predictors for malignant transformation, but this is not generally adopted in clinical practice

C. Diagnosis
1. provisional diagnosis of oral leukoplakia is made when other possible aetiological factors have been ruled out
2. An arbitrary period of 2–4 weeks seems to be an acceptable time to look for regression after possible causative factors have been eliminated. A biopsy examination is essential if a lesion persists beyond this period to rule out any other specific disorder
3. Gold standard: Incisional biopsy with scalpel and histopathological examination of the suspicious tissue
4. Punch biopsy is a useful alternative and can be used in multiple and diffuse mucocutaneous lesions; incisional biopsy is done for large (more than 1.0 cm), multiple, or diffuse lesions.
5. In those that contain areas of erythroplakia and leukoplakia, lesions with erythroplakia must be given priority because they have the most cellular activity.
6. Oral transepithelial brush biopsy with computer-assisted analysis helps to differentiate between precancerous and cancerous cells, and has 52% sensitivity and 29% specificity. The drawback is that if it is positive or inconclusive then a tissue biopsy is indicated. It can also be used as a follow-up tool.
7. Toluidine blue, Lugol's iodine, and whitening of the oral mucosa induced by acetic acid have been used to help to identify and demarcate potentially malignant mucosal lesions, but subjective interpretations make them unreliable and there is no convincing evidence available to support their use in clinical practice.
8. Optical diagnostic techniques detect a change in the optical property at a molecular level, and an alteration in the interaction between light and tissue is used to differentiate normal from malignant tissue
9. Autofluorescence spectroscopy and imaging systems can differentiate normal oral mucosa from abnormal tissue(82–100% sensitivity, 63–100% specificity)
10. Multispectral imaging systems and trimodal spectroscoy have been shown to diagnose precancerous or cancerous tissue accurately. Even though they can diagnose precancerous lesions reliably, they can be expensive and time consuming, which limits their efficacy in daily clinical practice

D. Management
1. Various non-surgical and surgical treatments have been reported, but currently there is no consensus on which is best.
2. Operation can include conventional surgery, electrocoagulation, cryosurgery, and laser surgery (excision or evaporation)
   a. conventional surgery:
      (1) involves excision of the lesion with or without a skin graft or other dressing material
      (2) not feasible for extensive lesions or those in certain anatomical

locations

b. electrocoagulation
   (1) thermal damage in the underlying tissue which causes postoperative pain and oedema
   (2) considerable scarring

c. cryosurgery
   (1) postoperative pain and oedema

d. laser surgery (excision or evaporation)
   (1) Carbon dioxide, Nd: YAG, argon, and potassium-titanyl-phosphate (KTP)
   (2) Advantages:
      ✓ haemostatic effects
      ✓ minimal electrocontractility with good wound healing
      ✓ minimal damage to the surrounding tissue which reduces acute inflammatory reaction and postoperative pain
      ✓ produces satisfactory mobility of the oral mucosa and minimum oral dysfunction
   (3) Cure rates: 33.9 ~ 82%
   (4) Recurrence: 7.7 ~ 66%
   (5) Another study: cure rates-82%, Local recurrence-9.9%, Malignant transformation-1.1%
   (6) Disadvantages of evaporation: no tissue is available for histopathological examination

3. Non-surgical treatments to prevent malignant transformation may also be considered.
   a. cause minimal adverse effects, particularly in patients with widespread oral leukoplakia that involves a large area of the oral mucosa, or in those with medical problems who have high surgical risks
   b. Use of carotenoids (beta-carotene, lycopene), vitamins A, C, and K, fenretinide, bleomycin, and photodynamic therapy
   c. randomised controlled trials for non-surgical treatment have not shown evidence that they effectively prevent malignant transformation and recurrence

E. Prognosis
   1. No reliable ways to predict the behaviour of individual lesions or to guide clinical management without biopsy examination, particularly patients with multiple oral precancerous lesions and extensive areas of mucosa that may show signs of dysplastic change
   2. Widespread lesions have been shown to have higher rates of malignant transformation than those that are more localised.
   3. A study by Holmstrup et al. identified 2 factors that are of prognostic value: size and type of lesion
      a. Non-homogeneous leukoplakia had an odds ratio of 7.0 for cancer to occur compared with homogeneous leukoplakia
      b. There is no substantial reported evidence for the size of the lesions to develop into cancer but this study showed that in those that exceeded200mm2 the odds ratio for cancer to occur was 5.4 as opposed to smaller lesions.
   4. The risk of malignant transformation has been reported to be between 6.6% and 36.4%, although a recent meta-analysis indicated a rate of 12.1%

5. High malignant transformation rate (22%) at 5years among patients diagnosed with oral epithelial dysplasia
6. 5-year malignant transformation rate with factors such as not smoking, lateral tongue site, and non-homogeneous appearance: 40% or more.
   a. lesions on the lateral border of the tongue: 53% at 5 years
   b. lesions on the floor of the mouth: 8% at5 years
7. Recurrence after surgical treatment: 10–35% of cases, development of cancer after operation: 3–9% of cases; 2.6–9% were after laser surgery
8. Several reports have suggested that operation does not seem to prevent premalignant lesions from developing malignancy
   a. clinical type and size of lesion
   b. site
   c. demarcation
   d. presence of any type of epithelial dysplasia
   e. smoking

Follow-up

1. Thirty-five percent of the total lesions had a more severe histopathological diagnosis, and compared with biopsy specimens taken on average 10.4months earlier, 7%showed the presence of carcinoma.
2. an incisional biopsy has been taken the lesions should be followed up by observations at close intervals (every 3–6months) independent of the presence or absence of epithelial dysplasia
3. Some authors recommend lifelong follow-up at intervals of 6–12 months in patients who have had treatment, and have not had treatment may need follow-up visits at 3-month intervals

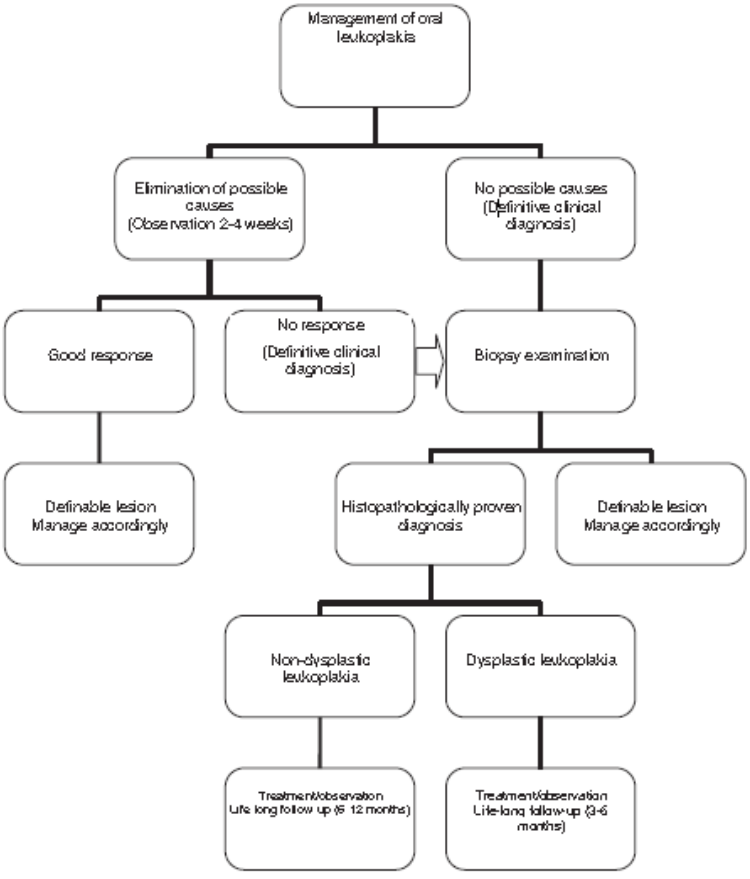

Fig. 1. Management of leukoplakia.

F. Summary

1. Oral leukoplakia is a common premalignant condition
2. early detection and screening for oral cancer have the potential to reduce them morbidity and mortality of disease, methods of screening have yet to be proved successful
3. Incisional biopsy is mandatory for diagnosis, planning treatment, and for ascertaining the prognosis of the lesion
4. The risk factors for malignant transformation include age, site, size, appearance, presence of dysplasia, and abnormal DNA content, but there is no single predictive factor or any reliable biomarker predictive
5. There is no universal consensus on the most appropriate treatment. Complete excision of high-risk lesions is recommended, and specialists should closely follow up these patients for life.
6. Factors associated with increased risk of malignant transformation are patients
   a. who do not smoke
   b. are over 60 years of age
   c. lesions that are non-homogeneous or are wide spread
   d. lesions on the lateral border of the tongue
   e. lesions larger than 200mm2
   f. histopathologically confirmed epithelial
   g. dysplasia.

題號	題目
1	下列哪一個 Leukoplakia 可能出現的區域最不可能有 dysplasia 的現象? (A) Tongue (B) Ginigiva (C) Lip vermilion (D) Oral floor
答案(B)	出處：Oral and Maxillofacial Pathology, Brad W. Neville et al., 3rd ed. p.391
題號	題目
2	下列哪一項對 leukoplakia 相關的敘述有誤? (A) 盛行率隨著病人年紀的增加而增加 (B) 為口內最常見的 precancerous lesion (C) 手術完全移除後的復發率很低，因此通常不需要長期的 follow up (D) 其惡性轉變率和病灶 dysplasia 的程度有關
答案(C)	出處：Oral and Maxillofacial Pathology, Brad W. Neville et al., 3rd ed. p.388~397