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內文：

一、Introduction

1. Accurately predicting which patients or lesions of PMD would develop OSCC was still impossible.
2. Second primary malignant neoplasms (second primary tumours; SPTs) – mainly in the upper aerodigestive tract –especially in the **respiratory tract** (Röth et al, 1984; J┐egu et al, 2013).

二、Potentially malignant disorders

1. **Erythroplakias** are the most dangerous, and although uncommon, most erythroplakias are malignant or destined so to become.
2. Far more common oral PMDs are leukoplakias, lichenoid lesions/lichen planus and oral submucous fibrosis.

三、Leukoplakias

1. Most oral leukoplakias are benign.
   - a Some progress and become OSCC (Napier and Speight, 2008) with a rate of 0.13-36.4% (Arduino et al, 2013).
   - b The biggest challenge is to endeavour to determine which lesions will transform (Lee et al, 2000).
   - c **Speckled** and **erosive** leukoplakias had the highest cancerization rate.
   - d Known risk factors for malignant transformation (van der Waal, 2009, 2010)

Box 1
Main risk factors for oral leukoplakia transformation

- Male gender
- Long duration
- Non-homogeneous appearance
- Tongue/floor/soft palate location
- >200 mm size
- Dysplasia present

(adapted from van der Waal, 2009, 2010).

   - e Neither the **site**, **demarcation**, **tobacco smoking** nor **degree of epithelial dysplasia** influenced the risk of malignant development (Holmstrup et al, 2006).
2. **Malignant transformation**
   - a May be present in a lesion which presents clinically as a leukoplakia, and this **may even not be detected** on histopathological.
   - b In OSCC, the epithelium elsewhere in the area was abnormal with '**field cancerization**' and 11% contained another cancer and the concept of**'second primary tumours'(SPTs)** arose (Slaughter et al, 1953).
   - c A negative biopsy result may **not** completely reliably exclude carcinoma or its potential; indeed, **up to ~10% may contain malignant or dysplastic tissue**.

d The evidence thus indicates that these lesions cannot be guaranteed to be innocent, even once a pre-operative biopsy result has shown no concern.

3. To date, possibly the most important marker of malignant development is a **non-homogeneous clinical appearance** (Reibel and Holmstrup, 2010), but this is typically supported by biopsy and histopathological assessment of epithelial dysplasia.

四、Dysplastic changes

1. Oral epithelial dysplasia classification and recognition:
   a Major limitation of using histological criteria for dysplasia is the **subjectivity of the grading system**.
   b Assessment of epithelial dysplasia can be of some prognostic help (Mithani et al, 2007).
2. The risk of cancerous change in oral PMD
   a Generally **lower with mild dysplasia than with severe dysplasia**.
   b **Not all dysplastic lesions become malignant**, while apparently **non-dysplastic lesions may occasionally develop into cancer** (Brennan et al, 2007).
   c Potential outcomes for a PMD: persist clinically unchanged, enlarge or shrink or even disappear (Napier and Speight, 2008).
3. To expect any pathologist to guarantee is perhaps unrealistic and unreasonable.
   a Biopsy specimen may or may not in any event represent the whole lesion from examination of an incisional biopsy specimen may or may not in any event represent the whole lesion
   b The reliability of dysplasia grading has also been questioned after a number of studies over the past two decades demonstrated low-to-moderate interpathologist, and even intrapathologist, consensus for the presence or absence of and the grading of dysplasia, even among specialist oral pathologists (Abbey et al, 1995; Karabulut et al, 1995; Fischer et al, 2004; Kujan et al, 2006).
4. **Cellular and molecular studies** have been long recognized to have a better potential (Zhang and Rosin, 2001).

五、Molecular changes

1. The hypothesis that **chromosomal loss of heterozygosity** (LOH) might be a potential tool in the management of oral PMD was raised by the group in British Columbia, Canada, over a decade ago (Zhang and Rosin, 2001).
2. LOH on chromosomes 3p and/or 9p, DNA content, survivin and matrix metalloproteinase-9 can help predict progression in PMD (Smith et al, 2009).

Box 2
Loss of chromosomal heterozygosity (LOH) in oral PMD and risk factor for malignant transformation
- high risk – LOH for 9p, 17p and 4q
- intermediate risk – LOH for 9p alone or LOH 9p plus either 17p or 4q
- low risk – LOH for chromosome 9p only

(adapted from Zhang *et al*, 2012).

3. Chromosomal 3p and/or 9p loss in leukoplakias after attempts at lesional treatment may also be helpful predictors of prognosis
   a 26.3-fold increase in risk of developing oral SPT compared with those that retained both of these arms ($P < 0.001$), with 60% of cases with LOH developing SPT in 2 years (Rosin et al, 2002).

b In contrast, histological diagnosis (moderate or severe dysplasia vs hyperplasia or mild dysplasia) had only a 1.7-fold increase in risk (P = 0.11).

4. Other prognostic indicators in PMD: degree of expression of tumour suppressor genes (**p53** and **p16**), epidermal growth factor receptor (**EGFR**), **phosphatidylinositol-3-kinase** and **cyclins D1 and B**.

六、Management of leukoplakia

1. Non-surgical and surgical approaches.
2. There is no evidence that any non-surgical treatments are effective in preventing dysplastic mucosal lesions progressing to carcinoma (Lodi et al, 2006).
3. Moderate and/ or severely dysplastic lesions are usually managed by removing the clinical lesion surgically by **scalpel**, sometimes by **laser** (van der Waal, 2010) or **photodynamic therapy** (Saini and Poh, 2013) or other techniques.
4. Even a retrospective study to evaluate the long-term outcome of leukoplakias and erythroplakias treated either surgically or without surgical interventions showed that **surgical treatment was insufficient to prevent malignant transformation** of the dysplastic lesions treated (Holmstrup et al, 2006).
5. The concept of **field cancerization** by demonstrating molecular abnormalities in clinically normal oral mucosa from patients with PMD (Giaretti et al, 2012a,b, 2013), raises questions about precisely which area warrants treatment.
6. On the positive side, it would appear that we are on the verge of a major breakthrough in prognostication using DNA and molecular studies as evidenced also by a prospective real-time study using LOH profiling in a clinical trial

題號	題目
1	The histopathological features of leukoplakias are as below, EXCEPT: (A) Thickened keratin layer of the surface (hyperkeratosis) (B) Chronic inflammatory cells within subjacent connective tissue. (C) All leukoplakic lesion demonstrate dysplasia on biopsy. (D) Thickened spinous layer(acanthosis) may be exist.
答案(C)	出處：：Oral and Maxillofacial Pathology, Brad W. Neville et al., 3rd ed. p.394
題號	題目
2	Which of the statement of leukoplakia is correct? (A)‘Leukoplakia’represents a pathological diagnostic term. (B) Long-term follow-up after lesion removal is extremely important due to frequent recurrence. (C) With a high rate of malignant transformation, leukoplakia is the most dangerous potentially malignant disorders (PMD). (D) Leukoplakia occurs on the mouth floor and ventral tongue has least shown malignant transformation.
答案(B)	出處：Oral and Maxillofacial Pathology, Brad W. Neville et al., 3rd ed. p.396