ORAL DISEASES

Oral Diseases (2014) 20, 1–5 doi:10.1111/odi.12208

www.wiley.com

ANNIVERSARY REVIEW

Challenges in predicting which oral mucosal potentially malignant disease will progress to neoplasia

C Scully

University College London, London, UK

Probably the greatest challenge to those managing patients with oral diseases is the dilemma of attempting to predict which oral erythroplakias, leukoplakias, lichenoid and other potentially malignant mucosal disease (PMD) such as oral submucous fibrosis will progress to neoplasia – notably oral squamous cell carcinoma (OSCC). The paper reviews progress over the past decade and the application to the clinical situation.

Oral Diseases (2014) **20**, 1–5

Keywords: oral; erythroplakia; leukoplakia; lichenoid; lichen; potentially malignant lesions; cancer; carcinoma; neoplasia

Introduction

Probably the greatest challenge to those managing patients with oral diseases is the dilemma of attempting to predict which oral erythroplakias, leukoplakias, lichenoid and other potentially malignant mucosal disease (PMD) such as oral submucous fibrosis will progress to neoplasia – notably oral squamous cell carcinoma (OSCC) (Table 1). This difficulty in prognostication was certainly recognized up to a decade ago (Lee *et al*, 2000; Scully *et al*, 2003), and even 5 years ago, it was re-iterated that, despite enumerable studies, accurately predicting which patients or lesions of PMD would develop OSCC was still impossible (Lodi and Porter, 2008). The size of the problem is shown, for example, in one Taiwanese study on a cohort of 1458 patients with oral PMD, of whom 44 developed cancer at the same site as the initial mucosal lesion – a transformation rate of about 3% (3.02%) over a mean follow-up of >3 years (42.64 months) (Hsue *et al*, 2007).

Furthermore, it has been recognized for over three decades and is increasingly appreciated that some patients with head and neck or oral cancer or PMD are also liable to second primary malignant neoplasms (second primary tumours; SPTs) – mainly in the upper aerodigestive tract – especially in the respiratory tract (Röth *et al*, 1984; Jégu *et al*, 2013).

It is worth reviewing progress made since then and examining the application to the clinical situation.

Potentially malignant disorders

Of all the oral PMDs, erythroplakias are the most dangerous, and although uncommon, most erythroplakias are malignant or destined so to become (Villa *et al*, 2011; Hardy *et al*, 2010). Far more common oral PMDs are leukoplakias, lichenoid lesions/lichen planus and oral submucous fibrosis. The discussion here is focused on oral leukoplakias, building on a recent publication (Arduino *et al*, 2013). The malignant potential of the other oral PMDs has been discussed recently elsewhere (Sreenivasan, 2013; Georgakopoulou *et al*, 2011, 2012; Angadi and Rekha, 2011; Wang *et al*, 2010).

Leukoplakias

Most oral leukoplakias are benign, but some progress and become OSCC (Napier and Speight, 2008) with a rate of 0.13-36.4% (Arduino *et al*, 2013) at an annual rate of 1.36% (CI: 0.69-2.03%) (Petti and Scully, 2006). The biggest challenge is to endeavour to determine which lesions will transform (Lee *et al*, 2000). Known risk factors for malignant transformation are shown in Box 1 (van der Waal, 2009, 2010). Indeed, malignant transformation may be present in a lesion which presents clinically as a leukoplakia, and this may even not be detected on histopathological examination of a biopsy specimen. There can be issues as to the reliability of the biopsy in representing what might be the behaviour in the lesion or elsewhere. Already half a century ago, it had been recognized that, 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). Of concern also is a study on oral leukoplakias reported three decades ago, in which patients with PMD were biopsied pre-operatively and then treated by laser excision to obtain a histopathology specimen (Chiesa *et al*, 1986). Despite pre-operative biopsies

Correspondence: Crispian Scully, University College London, London, UK. Email: Crispian.scully@ucl.ac.uk
Received 8 November 2013; revised 11 November 2013; accepted 11 November 2013

Table 1 Main oral potentially malignant disorders (PMD)

Lesion	*Main recognized aetiological factors*	*Clinical features*
Erythroplakia	Tobacco/alcohol/betel	Flat red plaque
Leukoplakia	Tobacco/alcohol, betel, human papilloma virus, sanguinarine	White or speckled plaque
Actinic cheilitis	Sunlight irradiation	White plaque/ erosions
Lichen planus/ lichenoid lesions	? Occasionally graft-*vs*-host disease, medications, dental materials, viruses	White plaque/ erosions
Chronic candidosis	*Candida albicans*	White or speckled plaque
Submucous fibrosis	Areca nut	Immobile mucosa

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).

negative for malignancies, the postoperative histopathology revealed malignancy in 6 of 59 lesions (10.2%). Speckled and erosive leukoplakias had the highest cancerization rate. A different study of 26 consecutive hitherto untreated patients presenting with a unilateral OSCC (18) or a PMD (8) examined 'mirror image' biopsies from clinically normal mucosa at corresponding anatomical sites and found that 15 patients (58%) had histologically abnormal tissue there (Thomson, 2002). Of the 15 with abnormalities, six had reactive change/cellular atypia associated with chronic irritation and seven had frank dysplasia, while two had carcinoma *in situ* or microinvasive carcinoma. A study of 101 mucosal lesions in 96 patients which examined the histopathological findings in the pre-operative biopsies compared with the histopathological findings of the complete lesions showed that seven lesions (7%) harboured a carcinoma and 70 lesions (69%) showed a degree of epithelial dysplasia or carcinoma in situ (Holmstrup *et al*, 2007). It is evident therefore, from several studies, that a negative biopsy result may not completely reliably exclude carcinoma or its potential; indeed, up to ~10% may contain malignant or dysplastic tissue. The evidence thus indicates that these lesions cannot be guaranteed to be innocent, even once a pre-operative biopsy result has shown no concern.

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. In one Danish study however, neither the site, demarcation, tobacco smoking nor degree of epithelial dysplasia influenced the risk of malignant development (Holmstrup *et al*, 2006). Nevertheless, it is dysplasia that has been the focus of most recognized and accepted practice.

Dysplastic changes

The criteria for grading epithelial dysplasia are based on architectural features and cytology; the presence, degree and significance of individual criteria are typically taken into account in pathologists' interpretations (Manchanda and Shetty, 2012). Pathologists play a significant role in identifying and grading the severity of dysplasia in PMD lesions. Consideration of three oral epithelial dysplasia classification systems (oral epithelial dysplasia scoring system, squamous intraepithelial neoplasia and Ljubljana classification) recommended epithelial dysplasia scoring for routine use while recognizing that a major limitation of using histological criteria for dysplasia is the subjectivity of the grading system (Warnakulasuriya *et al*, 2008).

Assessment of epithelial dysplasia can be of some prognostic help (Mithani *et al*, 2007). The risk of cancerous change in oral PMD is generally lower with mild dysplasia than with severe dysplasia. A recent workshop noted that the presence of dysplasia as assessed by light microscopic examination is one of the various prognostic predictors of malignant transformation long-used in PMD, but it is recognized that not all dysplastic lesions become malignant, while apparently non-dysplastic lesions may occasionally develop into cancer (Brennan *et al*, 2007). There are also other potential outcomes for a PMD in that it may persist clinically unchanged, it may enlarge or it may shrink or even disappear (Napier and Speight, 2008).

Nevertheless, to expect any pathologist to guarantee from examination of an incisional biopsy specimen, which probably contains a heterogeneous cellular picture (Califano *et al*, 2000; Braakhuis *et al*, 2004), that there is no carcinoma in situ or frankly invasive carcinoma present in the specimen is perhaps unrealistic and unreasonable. And the discussion above notes the extent to which the biopsy specimen may or may not in any event represent the whole lesion. 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). Other dysplasia grading systems may conceivably have advantages (Nankivell *et al*, 2013).

It is evident then that neither clinical nor the histological features can reliably prognosticate in PMD, but cellular and molecular studies have been long recognized to have a better potential (Zhang and Rosin, 2001). DNA studies such as ploidy, after initial enthusiasm (Scully *et al*, 2003) and then a chequered history and even suggestions they were of little benefit (Bremmer *et al*, 2011) are now indeed proving to be of some value (Torres-Rendon

et al, 2009; Bradley *et al*, 2010; Sperandio *et al*, 2013; Giaretti *et al*, 2012a,b, 2013) as are some of the molecular changes thus far characterized – especially chromosomal loss of heterozygosity profiles (Mithani *et al*, 2007; Pitiyage *et al*, 2009; Smith *et al*, 2009; Lingen, 2010; Zhang *et al*, 2012).

Molecular changes

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). This and their further studies have helped stimulate a number of other groups, several of whom have produced evidence of the potential usefulness of molecular markers (reviewed by Mithani *et al*, 2007; Pitiyage *et al*, 2009; Zhang *et al*, 2012) (Box 2). There are hundreds of research reports in this field, but one meta-analysis has shown that LOH on chromosomes 3p and/or 9p, DNA content, survivin and matrix metalloproteinase-9 can help predict progression in PMD (Smith *et al*, 2009). Chromosomal 3p and/or 9p loss in leukoplakias after attempts at lesional treatment may also be helpful predictors of prognosis because they were associated with 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). In contrast, histological diagnosis (moderate or severe dysplasia *vs* hyperplasia or mild dysplasia) had only a 1.7-fold increase in risk ($P = 0.11$).

Other prognostic indicators in PMD (reviewed by Arduino *et al*, 2013) that may help include the degree of expression of tumour suppressor genes (p53 and p16), epidermal growth factor receptor (EGFR), phosphatidylinositol-3-kinase and cyclins D1 and B.

Management of leukoplakia

It is evident therefore that the foundation of using dysplasia grade to make management choices is not as firm as one would wish. This is one of the main challenges for oral histopathology (Kujan *et al*, 2006), but the outcomes of research on molecular changes should make significant headway in this area and should improve management.

Management attempts for the treatment of leukoplakias have included non-surgical and surgical approaches. There is no evidence that any non-surgical treatments are effective in preventing dysplastic mucosal lesions progressing to carcinoma (Lodi *et al*, 2006). Therefore, 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, but reliable randomized controlled clinical trials to assess the effect of these methods in preventing the development of carcinoma are lacking. Indeed, some reports on the effectiveness of various surgical modalities in preventing malignant transformation have produced contradictory outcomes. 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). Thus, the concept that removing PMD surgically (by scalpel, laser or cryosurgery) can prevent the onset of carcinoma remains unproven – by no means a new conclusion (Einhorn and Wersall, 1967). There is indeed no evidence that surgical intervention reduces the risk of malignant transformation (Holmstrup, 2009). Indeed, one workshop concluded, 'Because of the lack of randomized controlled trials that have shown effectiveness in the prevention of malignant transformation, no recommendations can be provided for specific surgical interventions of dysplastic oral lesions either' (Brennan *et al*, 2007). Furthermore, recent studies have also confirmed the concept of field cancerization by demonstrating molecular abnormalities in clinically normal oral mucosa from patients with PMD (Giaretti *et al*, 2012a,b, 2013), which raises questions about precisely which area warrants treatment.

Clinicians are thus still faced with a series of dilemmas, a summation of which should always underpin full discussions with the patient and their advocates, in order for patients to be in a position to give valid consent to the management offered. Meantime, 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 [http://clinicaltrials.gov/ct2/show/NCT00402779?term=oral+cancer+prevention&rank=1 (accessed 12 October 2013)].

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).

References

Abbey LM, Kaugars GE, Gunsolley JC, Burns JC, Page DG, Svirsky JA (1995). Intraexaminer and interexaminer reliability in the diagnosis of oral epithelial dysplasia. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **80**: 188–191.

Angadi PV, Rekha KP (2011). Oral submucous fibrosis: a clinicopathologic review of 205 cases in Indians. *Oral Maxillofac Surg* **15**: 15–19.

Arduino P, Bagan J, El-Naggar A, Carrozzo M (2013). Urban legends series: oral leukoplakia. *Oral Dis* **19**: 642–659.

Braakhuis BJ, Leemans CR, Brakenhoff RH (2004). A genetic progression model of oral cancer: current evidence and clinical implications. *J Oral Pathol Med* **33**: 317–322.

Bradley G, Odell EW, Raphael S *et al* (2010). Abnormal DNA content in oral epithelial dysplasia is associated with increased risk of progression to carcinoma. *Br J Cancer* **103**: 1432–1442.

Bremmer JF, Brakenhoff RH, Broeckaert MA *et al* (2011). Prognostic value of DNA ploidy status in patients with oral leukoplakia. *Oral Oncol* **47**: 956–960.

Brennan M, Migliorati CA, Lockhart PB *et al* (2007). Management of oral epithelial dysplasia: a review. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **103**(Suppl 1): S19.e1–S19.e12.

Califano J, Westra WH, Meininger G, Corio R, Koch WM, Sidransky D (2000). Genetic progression and clonal relationship of recurrent premalignant head and neck lesions. *Clin Cancer Res* **6**: 347–352.

Chiesa F, Sala L, Costa L *et al* (1986). Excision of oral leukoplakias by CO_2 laser on an out-patient basis: a useful procedure for prevention and early detection of oral carcinomas. *Tumori* **30**: 307–312.

Einhorn J, Wersall J (1967). Incidence of oral carcinoma in patients with leukoplakia of the oral mucosa. *Cancer* **20**: 2189–2193.

Fischer DJ, Epstein JB, Morton TH, Schwartz SM (2004). Interobserver reliability in the histopathologic diagnosis of oral pre-malignant and malignant lesions. *J Oral Pathol Med* **33**: 65–70.

Georgakopoulou EA, Troupis TG, Troupis G, Gorgoulis VG (2011). Update of the cancer-associated molecular mechanisms in oral lichen planus, a disease with possible premalignant nature. *J BUON* **16**: 613–616.

Georgakopoulou EA, Achtari MD, Achtaris M, Foukas PG, Kotsinas A (2012). Oral lichen planus as a preneoplastic inflammatory model. *J Biomed Biotechnol* **2012**: 759626. doi:10.1155/2012/759626. Epub May 17.

Giaretti W, Maffei M, Pentenero M *et al* (2012a). Genomic aberrations in normal appearing mucosa fields distal from oral potentially malignant lesions. *Cell Oncol (Dordr)* **35**: 43–52.

Giaretti W, Pentenero M, Gandolfo S, Castagnola P (2012b). Chromosomal instability, aneuploidy and routine high-resolution DNA content analysis in oral cancer risk evaluation. *Future Oncol* **8**: 1257–1271.

Giaretti W, Monteghirfo S, Pentenero M, Gandolfo S, Malacarne D, Castagnola P (2013). Chromosomal instability, DNA index, dysplasia, and subsite in oral premalignancy as intermediate endpoints of risk of cancer. *Cancer Epidemiol Biomarkers Prev* **22**: 1133–1141.

Hardy H, Persac S, Péron JM (2010). Upper aerodigestive tract erythroplakia. *Rev Stomatol Chir Maxillofac* **111**: 213–215.

Holmstrup P (2009). Can we prevent malignancy by treating premalignant lesions? *Oral Oncol* **45**: 549–550.

Holmstrup P, Vedtofte P, Reibel J, Stoltze K (2006). Long-term treatment outcome of oral premalignant lesions. *Oral Oncol* **42**: 461–474.

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

Hsue SS, Wang WC, Chen CH, Lin CC, Chen YK, Lin LM (2007). Malignant transformation in 1458 patients with potentially malignant oral mucosal disorders: a follow-up study based in a Taiwanese hospital. *J Oral Pathol Med* **36**: 25–29.

Jégu J, Binder-Foucard F, Borel C, Velten M (2013). Trends over three decades of the risk of second primary cancer among patients with head and neck cancer. *Oral Oncol* **49**: 9–14.

Karabulut A, Reibel J, Therkildsen MH, Praetorius F, Nielsen HW, Dabelsteen E (1995). Observer variability in the histologic assessment of oral premalignant lesions. *J Oral Pathol Med* **24**: 198–200.

Kujan O, Khattab A, Oliver RJ, Roberts SA, Thakker N, Sloan P (2006). Why oral histopathology suffers inter-observer variability on grading oral epithelial dysplasia: an attempt to understand the sources of variation. *Oral Oncol* **43**: 224–231.

Lee JJ, Hong WK, Hotelman WN *et al* (2000). Predicting cancer development in oral leukoplakia: ten years of translation research. *Clin Cancer Res* **7**: 1702–1710.

Lingen MW (2010). Screening for oral premalignancy and cancer: what platform and which biomarkers. *Cancer Prev Res (Phila)* **3**: 1056–1059.

Lodi G, Porter S (2008). Management of potentially malignant disorders: evidence and critique. *J Oral Pathol Med* **37**: 63–69.

Lodi G, Sardella A, Bez C, Demarosi F, Carrassi A (2006). Interventions for treating oral leukoplakia. *Cochrane Database Syst Rev* **18**: CD001829.

Manchanda A, Shetty DC (2012). Reproducibility of grading systems in oral epithelial dysplasia. *Med Oral Patol Oral Cir Bucal* **17**: e935–e942.

Mithani SK, Mylar WK, Grumbine FL, Smith IM, Califano JA (2007). Molecular genetics of premalignant oral lesions. *Oral Dis* **13**: 126–133.

Nankivell P, Williams H, Matthews P *et al* (2013). The binary oral dysplasia grading system: validity testing and suggested improvement. *Oral Surg Oral Med Oral Pathol Oral Radiol* **115**: 87–94.

Napier S, Speight P (2008). Natural history of potentially malignant oral lesions and conditions: an overview of the literature. *J Oral Pathol Med* **37**: 1–10.

Petti S, Scully C (2006). Association between different alcoholic beverages and leukoplakia among non- to moderate-drinking adults: a matched case-control study. *Eur J Cancer* **42**: 521–527.

Pitiyage G, Tilakaratne WM, Tavassoli M, Warnakulasuriya S (2009). Molecular markers in oral epithelial dysplasia: review. *J Oral Pathol Med* **38**: 737–752.

Reibel J, Holmstrup P (2010). Premalignant disorders and cancer of the oral mucosa. *Ugeskr Laeger* **172**: 3040–3042.

Rosin MP, Lam WL, Poh C *et al* (2002). 3p14 and 9p21 loss is a simple tool for predicting second oral malignancy at previously treated oral cancer sites. *Cancer Res* **62**: 6447–6450.

Röth GJ, Schirner E, Hornstein OP, Simon M Jr (1984). Precancerous conditions and carcinomas of the lower lip. Coincidence with leukoplakia and carcinomas of the oral cavity and larynx. *Dtsch Med Wochenschr* **109**: 1229–1231.

Saini R, Poh C (2013). Photodynamic therapy: a review and its prospective role in the management of oral potentially malignant disorders. *Oral Dis* **19**: 440–451.

Scully C, Sudbo J, Speight PM (2003). Progress in determining the malignant potential of oral lesions. *J Oral Pathol Med* **32**: 251–256.

Slaughter DP, Southwick HW, Smejkal W (1953). Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. *Cancer* **6**: 963–968.

Smith J, Rattay T, McConkey C, Helliwell T, Mehanna H (2009). Biomarkers in dysplasia of the oral cavity: a systematic review. *Oral Oncol* **45**: 647–653.

Sperandio M, Brown AL, Lock C *et al* (2013). Predictive value of dysplasia grading and DNA ploidy in malignant transformation of oral potentially malignant disorders. *Cancer Prev Res (Phila)* **6**: 822–831.

Sreenivasan V (2013). The malignant potential of oral lichen planus—confusion galore. Oral Surg Oral Med Oral Pathol. *Oral Radiol* **115**: 415.

Thomson PJ (2002). Field change and oral cancer: new evidence for widespread carcinogenesis? *Int J Oral Maxillofac Surg* **31**: 262–266.

Torres-Rendon A, Stewart R, Craig GT, Wells M, Speight PM (2009). DNA ploidy analysis by image cytometry helps to

identify oral epithelial dysplasias with a high risk of malignant progression. *Oral Oncol* **45**: 468–473.

Villa A, Villa C, Abati S (2011). Oral cancer and oral erythroplakia: an update and implication for clinicians. *Aust Dent J* **56**: 253–256.

van der Waal I (2009). Potentially malignant disorders of the oral and oropharyngeal mucosa; terminology, classification and present concepts of management. *Oral Oncol* **45**: 317–323.

van der Waal I (2010). Potentially malignant disorders of the oral and oropharyngeal mucosa; present concepts of management. *Oral Oncol* **46**: 423–425.

Wang LH, Ting SC, Chen CH *et al* (2010). Polymorphisms in the apoptosis-associated genes FAS and FASL and risk of oral cancer and malignant potential of oral premalignant lesions in a Taiwanese population. *J Oral Pathol Med* **39**: 155–161.

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

Zhang L, Rosin MP (2001). Loss of heterozygosity: a potential tool in management of oral premalignant lesions? *J Oral Pathol Med* **30**: 513–520.

Zhang L, Poh CF, Rosin MP *et al* (2012). Loss of heterozygosity (LOH) profiles–validated risk predictors for progression to oral cancer. *Cancer Prev Res (Phila)* **5**: 1081–1089.