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Oral potentially malignant disorders: risk of progression to malignancy.

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OPMDs may progress to oral cancer, but assessment of the risk for an individual patient is difficult. This review describes the most important risk factors and presents an approach to risk assessment at each stage of the clinical evaluation of a patient.

Abstract

Oral potentially malignant disorders (OPMD) have a stastically increased risk of progessing to cancer, but the risk varies according to a range of patient or lesion related factors. It is difficult to predict the risk of progression for any individual patient and the clinician must make a judgement based an assessment of each case. The most commonly encountered OPMD is leukoplakia, but others including lichen planus, oral submucous fibrosis and erythroplakia may also be seen. Factors associated with an increased risk of malignant transformation include gender, the site and type of lesion, habits such as smoking and alcohol and the presence of epithelial dysplasia on histologic examination. In this review we attempt to identify the important risk factors, and present a simple algorithm that can be used as a guide for risk assessment at each stage of the clinical evaluation of a patient.

Introduction

The terminology of oral lesions, which may have the potential to progress to malignancy has varied over the years. At a World Health Organisation (WHO) workshop in 2007, it was recommended that the distinction between potentially malignant lesions and conditions should be abandoned in favour of a common terminology of o*ral potentially malignant disorders* (OPMD) (1,2) and this has now been accepted in the latest WHO classification (3). The term OPMD recognises the fact that even in patients with a defined lesion, such as leukoplakia, malignancy may arise elsewhere in the oral cavity as a result of field change, even in clinically normal mucosa (4,5). There are a number of disorders which have been associated with an increased risk of squamous cell carcinoma, including leukoplakia, erythroplakia, oral lichen planus, oral submucous fibrosis, actinic cheilitis, palatal lesions of reverse cigar smoking, discoid lupus erythematosus, and some inherited disorders such as dyskeratosis congenita and Fanconi's anaemia. From a clinical perspective, the vast majority of lesions of concern present as white patches, with or without a speckled or red component, and many of these will not have a specific diagnosis and must be managed as leukoplakia. Although these disorders have an increased statistical risk of malignant change, it is very difficult to predict the outcome for an individual patient. This review will focus on leukoplakia but other disorders will be mentioned where there is evidence of any defined risk factors.

The prognosis of oral potentially malignant disorders

The definition of leukoplakia remains unsatisfactory, but essentially it refers to a white lesion of the oral mucosa, that cannot be defined as a known disease or disorder and carries an increased risk of progressing to cancer (1-6). However, leukoplakia is a dynamic lesion which may vary in texture or colour over time, and is not always "white". Indeed, leukoplakias deemed to be at most risk are often speckled red and white lesions. Pure red lesions, or *erythroplakia* are much rarer, but have the greatest risk for malignant change (7). Although

progression to cancer is the most important outcome, only relatively few lesions progress and the remainder may persist unchanged, may enlarge or reduce in size, or may even resolve completely. Features that may be associated with increased risk of progression to malignancy are listed in Table 1, with our estimate of the strength of the association. Explanatory notes and relevant references are found in the following sections.

Clinical prognostic factors for progression to cancer

Site

The location of a lesion within the mouth may influence the risk of malignant transformation, but this is almost certainly related to aetiological factors and therefore may vary by geographical location and local habits. For example, in betel quid chewers the buccal mucosa is likely to be the most affected site, while in the developed world where smoked tobacco and alcohol are the most important aetiological factors, the floor of the mouth and lateral border of the tongue, are the most common sites for OPMD and oral cancer. In a UK study of 630 patients with dysplastic lesions, over 95% were leukoplakias and the most common sites (42% of lesions) were the lateral and ventral tongue and floor of the mouth (8). In addition, lesions at these sites were more likely to show severe epithelial dysplasia. Conversely, only 21% of lesions arose on the buccal mucosa, and these were mostly mild dysplasia. In a similar study in Australia, Dost et al (9) found that the buccal mucosa was the single most common site for OPMDs (31% of lesions in which 50% of these were OLP), but 40% were on the tongue and in the floor of the mouth. However, lesions on the tongue and floor of mouth were more likely to be dysplastic or malignant (OR. 2.6: p=0.005). It is noteworthy to recognise that ventral of tongue and floor of mouth are contiguous anatomic sites and some authors don't specify the exact location of a lesion on tongue surfaces. This may warrant a careful interpretation of the findings. In a cross-sectional study of 3,256 leukoplakias in the USA, the highest prevalence of severe dysplasia or carcinoma-in-situ was in the floor of mouth (13.5%) and tongue (5%) (10). These data suggest that these sites

are at the highest risk, but studies of actual malignant transformation have shown variable findings.

In Hungary, although only 8.2% of leukoplakias arose on the tongue, these accounted for 37.5% of lesions that underwent malignant transformation, equivalent to a transformation rate of 27% for tongue leukoplakias (11). Floor of mouth also had a high transformation rate with 13% of lesions developing into cancer. In contrast, although most of the leukoplakias (63%) were found on the buccal mucosa, only 4.0% of these lesions progressed (11). Similar data have been reported in England, where two studies showed high transformation rates of 24% (12) and 16% (13) for leukoplakias in the floor of the mouth (sublingual keratosis).

In contrast, some studies have been unable to establish a strong correlation between site and malignant transformation. Schepman *et al.* (14) studied 101 patients with lesions on the tongue or floor of mouth and 15 (14.9%) developed oral cancer, compared to 5 of 65 (7.7%) whose lesions were located elsewhere, but this was not statistically significant. In a second study by Dost *et al.* (15) the malignant potential of 383 dysplastic lesions in 368 patients was determined. Although the tongue (48.8% of lesions) and floor of mouth (11.5%), together were the most common sites, and the tongue had the highest transformation rate of 1.4% per year, the relationship between site and transformation was not significant. Holmstrup *et al.* (16) followed 236 patients with 269 lesions, and found a malignant transformation rate of 12% for lesions treated surgically and 4% for lesions observed. The only significant prognostic factors were size and type of lesion (homogenous versus non-homogenous). The site of the lesions was not significant.

In summary, most studies and clinical papers do emphasise the lateral and ventral tongue and floor of the mouth as areas of particular clinical concern, and this may be due to their over exposure to carcinogens due to pooling of saliva in alcohol and tobacco users (17). In their systematic review, Warnakulasuriya and Ariyawardana (6) found that, on a global basis, the buccal mucosa was the most common site overall (18.4% of lesions), but had the lowest

rate of malignant transformation (3.35%), whereas the tongue accounted for 16.14% of lesions, but was the most common site for transformation with a rate of 24.22%. The next most common site was the combined "tongue and floor of mouth" at a rate of 14.85%. However, these data may hide some geographic variations since they may apply to populations with the most common habits of smoked tobacco and alcohol. In other populations other sites may be more important and be associated with specific tobacco habits. For example, in Andhra Pradesh 71% of leukoplakias were located on the palate associated with reverse smoking, and in Kerala, 65% were on the buccal mucosa, associated with chewed tobacco (18).

Clinical appearance

Oral leukoplakia shows a variety of clinical appearances, and this had led to several definitions that were complicated and confusing Leukoplakias are uniformly white or plaque-like, with a flat or wrinkled surface that may contain fine cracks or fissures *(homogenous leukoplakia*) (Figure 1), while others are *non-homogenous* (Figure 2) and may have a warty, nodular or verrucous surface pattern ("verrucous leukoplakia") or may contain red areas or be speckled ("speckled leukoplakia" or "erythroleukoplakia"). There is consensus in the literature that non-homogenous lesions have a greater risk of malignant transformation than homogenous lesions (2-6), but it can be very difficult to compare studies because of the different locations and different ways of reporting malignant transformation. For example most large Indian studies are population or community based, often involving house-to-house surveys (18), whereas most studies in the developed world are based on hospital populations or retrospective analyses of pathology records. However, a systematic review (19) found a global prevalence of leukoplakia of 2.6% and a malignant transformation rate of 1.36% per year. Warnakulasuriya and Ariyawardana (6) carried out a systematic review of 24 studies and found an overall malignant transformation rate of between 1.5% and 34.0%, but there was a wide variation in the location or type of study. They found 8 studies which

compared homogenous and non-homogenous lesions, and all showed that non-homogenous lesions had the highest rate of progression. In their summary analysis they calculated an overall transformation rate of 3.0% for homogenous lesions and 14.5% for non-homogenous lesions (p=0.001). One of the largest series was published by Bánóczy (11) who summarised a series of papers (20-23) on a cohort of 670 Hungarian patients. Over a 30 year follow up period, 6% (40 cases) of leukoplakias progressed to cancer. They divided the lesions into three clinical variants: simplex (homogenous), and verrucous or erosive (speckled) (both non-homogenous). None of the homogenous lesions (simplex) progressed to cancer, whereas the transformation rate for verrucous lesions was 4.6% and for erosive was 28.0%. The overall rate for the non-homogenous group was 13.4%. Expressing this data in a different way, there were 82 erosive lesions which accounted for 74% of the oral cancers. The remaining 26% arose from 173 verrucous lesions. Although the actual data may vary, Bánóczy's finding that verrucous and, especially, speckled lesions have the highest rates of progression have been confirmed a number of times. In the largest Indian study to date (18) the overall malignant transformation rates were very low (0.3% – 2.19%) but homogenous lesions were much less likely to become malignant. In California, Silverman (24) showed that non-homogenous lesions (erythroleukoplakia) transformed in 23.4% of cases compared to 6.5% of homogenous lesions. In a series of Norwegian patients (25), 14 of 157 patients with leukoplakia developed cancer, but only one of these arose in a homogenous lesion (1.6%) while the remainder arose from non-homogenous lesions (13 from 97; 13.4%). Of these, 28 were described as nodular and 8 became malignant (28.6%). In Holmstrup *et al's* study (16), non-homogenous lesions showed a seven times increased risk of progression to cancer when compared to homogenous lesions (OR= 7.0; 95% CI, 1.7,28.5). Of all the factors which they analysed, the type of lesion was the most significant in predicting prognosis. A characteristic type of non-homogenous leukoplakia – proliferative verrucous leukoplakia - has been described and is discussed below.

The use of the terms homogenous and non-homogenous leukoplakia has been severely criticised since it may over-emphasise the importance of white lesions and divert clinicians' attention away from the more significant and dangerous red lesions (26). As noted above, the highest rates of malignant change were noted in lesions which were described as speckled or erosive (11) or as erythroleukoplakia (24) – in other words, emphasising that these lesions are not in fact true "leukoplakias" (white plaques) but have a red component. The seminal work of Mashberg is well known and although he did not primarily study OPMDs, his work shows that most early oral cancers are red or have a significant red component (erythroplasia) (27,28). In his first major study on this subject (27) Mashberg identified 158 asymptomatic, early lesions in 125 patients. One hundred and twelve lesions were invasive squamous cell carcinomas and 46 were carcinoma-in-situ. His major finding, which formed the basis of his later work and opinions (26,28) was that over 90% of the lesions had a red component and only 14 (9%) were described as white (of which 9 presented on the lips). Sixty lesions (38%) were entirely red and a further 98 (62%) were red and white (speckled, stippled or patchy). In later studies (reviewed in 28) he confirmed these findings in a cohort of 236 asymptomatic cancers, of which only 6% were white. The remainder were entirely red (32%), had a predominant red component (32%) or were mixed (29%). In his reviews (26,28) he emphasises the importance of redness as an early sign of cancer and expresses dismay at the over-emphasis of "leukoplakia" as a premalignant condition, which, he claims, is a major cause of the lack of progress in early diagnosis of cancer.

Erythroplakia is a well defined clinical lesion (3,7) but Mashberg is correct in that it is often not included in studies of OPMD (eg. 4,6,10,11,17) – probably because it is relatively uncommon and therefore more difficult to study. In their survey of 50,915 Indians, Mehta *et al*. (29) found 881 leukoplakias (1.73%) but there were only 9 cases of erythroplakia (0.02%) (7). In the USA, only 58 cases were identified among 64,345 biopsy samples (0.09%) (30). Reichart and Phillipsen (7) reviewed a number of population studies which showed a

prevalence of between 0.02% and 0.83%. As suggested by Mashberg (26,28), the majority of erthroplakias, show invasive carcinoma or carcinoma-in-situ, so the issue of progression to malignancy is a moot point, since the lesion should probably be managed as malignant at first presentation. In Shafer and Waldron's series of 58 cases (30) 51% showed invasive cancer and 40% showed severe epithelial dysplasia or carcinoma-in-situ at first biopsy. The remaining 9% showed mild or moderate dysplasia. For erythroplakias that do not show invasive cancer at first biopsy, the majority will show high risk histological features. The best estimates for malignant progression of these lesions can be derived from data for the malignant transformation of lesions showing severe epithelial dysplasia (including carcinoma-in-situ). A number of relevant studies are summarised in Table 2.

Size

In Holmstrup *et al's*. study (16) size was the only other factor which showed a statistical correlation with malignant transformation. Specifically, lesions greater then 200mm^2 were more likely to progress than lesions less than this size (OR=5.4; 95% CI, 1.1,26.1). In a study of 50 patients from Northern Ireland, Napier *et al.* (37), found that the risk of transformation was 6 times greater in patients with large confluent lesions that extended over more than one anatomical site compared to smaller localised lesions. Of 12 patients with such lesions, 7 developed oral cancer. They also found 11 patients with lesions at one anatomical site, five of whom developed cancer, a risk 4 times greater than in those with multiple lesions. It was notable that of the 27 patients with multiple non-confluent lesions, only 5 progressed to malignancy. Warnakulasuriya and Ariyawardana (6) recommended on the evidence from their systematic review that any leukoplakia that exceeds 200mm^2 has a higher risk for malignant transformation.

Age/duration

Most studies agree that although OPMDs are chronic and persistent, the risk of malignant change is higher within the first five years after diagnosis. In their systematic review, Warnakulasuriya and Ariyawardana (6) found 5 studies that had analysed transformation by age groups. Overall, although lesions tended to progress early in their natural history, transformation rates were higher in older individuals. In a large Swedish study, involving 782 patients with leukoplakia, the highest transformation rate (6.4% in five years) was found in those aged 70-89 years, compared to less than 1% in all age groups below 50 years (38). In Bánóczy's Hungarian series (11) the peak incidence of leukoplakia was in the sixth decade, but the highest rates of transformation were in the seventh decade (7.1%) or in patients over 71 (8.2%). They also noted however a transformation rate of 7.4% in the fourth decade. In his series of 157 Norwegian patients with leukoplakia, Lind (25) found that lesions tended to progress soon after first diagnosis. Of the 14 cases which progressed, 5 patients developed oral cancer in the first year and six within the next eight years. In the Netherlands, it was noted that the number of transformed lesions increased with longer follow-up times (14). They estimated that 50% of patients with leukoplakia would develop a tumour within 200 months of diagnosis, but the median time to malignant transformation was only 32 months. They found that overall, 12.4% of lesions transformed and that the mean age of first presentation of the patients who developed cancer was 67.1 years, compared to 55.8 years for patients who did not develop cancer.

The large studies from India and the developing world support the view that lesions are likely to develop and progress in older individuals since the highest incidences of leukoplakia are consistently in younger age groups than oral cancer (18,29,39,40). For example, the highest incidence of leukoplakia in Kerala was found in 35-54 year olds while the highest incidence of oral cancer was in the 55-74 year age group (40).

Gender

Warnakulasuriya and Ariyawardana's review (6) identified 12 studies that had looked at gender and malignant transformation. In nine of the twelve studies, the rate of transformation was greater in females than males, with an overall rate of 13.1% for females and 1.7% for males ($p<0.001$). The highest rate in females was 40.6%, reported from Northern Ireland (37) and the lowest was found in Denmark (3.7%) (41). In males the highest rate was 28.6% in the United Kingdom (13) and the lowest was 0% in the Netherlands (42). Another study in the Netherlands however, found 76 males with leukoplakia of whom 4 developed oral cancer (5.3%), but of 90 females with lesions 16 females progressed (17.7%) (14). In a Norwegian study, Lind (25) found lesions in 102 males and 55 females, but oral cancer developed in 8 males (7.8%) and six females (10.9%). Nonetheless, it is still unclear why women are more predisposed to malignant transformation than men. Global genomic arrays may illustrate a differential gene expression that explains this gender predilection.

The propensity for females to have a higher risk of malignant transformation is despite the fact that lesions are less common in females. In Sweden, Axell (43) found a male:female ratio of 6:1, but this reduced to 5:2 among non-smokers. In the USA the male:female ratio was reported as 2:1 (44). In the large Indian studies (18,29,39,40,45) females were much less likely to have lesions, but this was related to the fact that they were less likely to use tobacco.

Habits

Tobacco use and consumption of alcohol are well established aetiological factors for the development of OPMD, but there is also good evidence that risk of progression is related to the use of, or continued use of, these habits. Lesions in non-smokers (sometimes referred to as "idiopathic leukoplakia") seem to be at a higher risk of progression to cancer (17). In Schepman's study in the Netherlands (14) the three factors associated with the greatest risk of transformation, were non-homogenous lesions ($p=0.01$), being female ($p<0.025$) and female non-smokers ($p<0.05$). There were no statistically significant associations with

smoking in males, nor for alcohol in either gender. In another study in the Netherlands (42) 3 of 46 patients developed oral cancer and all were non-smokers. In California, Silverman *et al.* (24) found that lesions in smokers and non-smokers showed quite different patterns of behaviour. Forty five patients in their cohort of 257 developed an oral cancer during an average follow-up time of 7.2 years. There were 133 lesions in patients who were smokers and continued to smoke and of these, 21 (16%) transformed to oral cancer and 49 lesions (37%) either regressed or disappeared. Of 74 non-smokers, 24% (18 patients) developed oral cancer, but in only 2 patients (3%) did lesions regress or resolve. The remaining 50 patients stopped smoking after diagnosis and among these, 6 (12%) developed oral cancer, and in a further 22 (44%) lesions became smaller or resolved. In a Swedish study (38), the cumulative frequency of oral cancer development was 3.1% over 5 years in non-tobacco users compared to only 0.4% in smokers. In her large Hungarian studies, Bánóczy (11) found that the proportion of patients who smoked was higher in those with leukoplakia that did not progress (87%) than in those who developed carcinoma (78%) and concluded that there was a greater tendency for malignant transformation in leukoplakias not associated with tobacco. In a study in England, Ho *et al.* (46) found that the most significant predictor of malignant change was non-smoking status. They studied 91 patients with histologically diagnosed dysplasia, of whom 20 were never-smokers, 29 moderate smokers and 42 were heavy smokers. After 5 years of follow up, 13 never smokers (43%) developed cancer compared to 11% and 4% respectively in the other two groups ($p=0.001$).

These data suggest that although tobacco is an important aetiological factor for the formation of keratotic lesions, other factors must be important for these lesions to progress to malignancy. The increased risk in non-smokers suggests that an underlying genetic predisposition may also be involved in at least a proportion of cases. It should be noted however, that not all studies have been able to demonstrate a relationship between tobacco use and progression. Warnakulasuriya and Ariyawardana (6) did not identify any papers which analysed smoking as a factor, and neither Dost *et al.* (9) nor Holmstrup *et al.* (16)

found any significant associations between smoking and progression to malignancy. With regards to alcohol, there is much evidence to implicate it as an aetiological factor, but no evidence for a role as a risk factor for progression in established lesions (4,6,9,17,47). The use of betel quid and areca nut are also risk factors, and are considered below under oral submucous fibrosis.

Histological prognostic factors for progression to cancer

Epithelial dysplasia

Although it is established that OPMD are statistically more likely to become malignant, it is not inevitable that each lesion will progress to cancer. Although the clinical parameters described above may help in clinical risk assessment, the gold standard diagnostic procedure is to undertake a biopsy for histological examination. This will enable the pathologist to exclude any specific diagnosis, and to evaluate any tissue changes, the most significant of which are features of cytological atypia and distorted epithelial architecture, which together are referred to as *oral epithelial dysplasia* (OED) (2,3). It is not inevitable however, that a dysplastic lesion will transform into cancer, and non-dysplastic lesions may also progress. Silverman et al. (24) showed that 36% of dysplastic lesions progressed to carcinoma, but also that 16% of leukoplakic lesions without evidence of dysplasia progressed. Clinical or histological biomarkers are desperately needed to improve our ability to distinguish lesions that may progress from those that will not (2,48), but, given the complexity of the oral carcinogenesis process and the lack of any proven predictive biomarkers in large prospective cohorts, surgical biopsy and histopathological grading of OED is regarded as the gold standard in managing these patients (2-5,49,50).

Historically, several terms including dyskeratosis, epithelial atypia, squamous intraepithelial neoplasia (SIN) or squamous intraepithelial lesions (SILs) have been used to describe epithelial changes that precede development of oral cancer. However, for lesions of the oral

cavity, OED is still currently regarded as the preferred terminology (1-3,49). The latest 2017 WHO classification system (3) uses a combination of architectural and cytological features (Table 3) in an attempt to provide a more objective approach to the diagnosis and grading of OED. Pathologists should use these criteria to grade lesions, but several grading systems have been developed and there is, as yet, no international consensus as to which should be used (2,3). A major problem, is that the process of grading is subjective and has low levels of intra- and inter-observer agreement (2,15,51-53). Many pathologists grade lesions into mild, moderate, and severe dysplasia based on the extent and degree of the changes listed in Table 3 (2-4,49). Mild dysplasia defines a lesion where the architectural and cytological changes are minimal and are limited to the lower third of the epithelium, whilst moderate dysplasia demonstrates changes involving up to two-thirds of the full thickness of the epithelium. Severe dysplasia displays more marked changes, which may extend beyond the lower two thirds of the epithelium. Carcinoma-in-situ is regarded as the most severe form of severe dysplasia, and involves changes through the entire epithelial thickness, but in the oral cavity, even these lesions may show a degree of surface keratinisation. In an attempt to improve the reliability of grading, a number of authors have developed a binary grading scheme (54-56), which is now recommended by the WHO (3), although it is recognised that further validations and clinical studies are needed. More precisely, the 2017 WHO binary grading system uses metrics for evaluating cytological and architectural features (Table 3) to stratify oral epithelial dysplastic lesions into either low-grade or high-grade OED (3). However, in their studies, Kujan *et al.* (54,55) demonstrated that the binary system showed superior reliability and intra- and inter-observer agreement compared to the 5-scale WHO grading system from 2005 (57).

The ultimate goal of OED diagnosis and grading is to provide patients with the best management and care. Clinicians are more likely to intervene when they came across a patient with moderate or severe OED, whereas a “wait and see” policy may be adopted for lesions showing only mild dysplasia (58). Dost *et al.* (15) demonstrated that 4.1% of mild

dysplasias underwent malignant transformation and advocated the surgical removal of all OED cases, irrespective of their histopathological grade. Nevertheless, whether complete resection of all OED cases is warranted will not be discussed here, given that this topic is beyond the scope of our review and has been well reviewed by others (5,16,50,59).

As it stands, grading of OED is still the most important prognostic factor for malignant transformation (2-4). However, even for severe epithelial dysplasia studies have shown that the malignant transformation rate varies considerably, from 3% to 50% (Table 2), and appears to be heavily dependent on the study design and population characteristics (17). Most studies agree that the risk of progression increases with the grade of OED. A meta-analysis by Mehanna *et al.* (60) pooled data from 14 non-randomised cohort studies and estimated that the mean rate of malignant transformation was 12.1% (CI: 8.1%, 17.9%), with a wide variation between the different studies (0%-36.4%), and a follow-up time ranging from 0.5-16.0 years. They also found a significant correlation between the OED grade and malignant transformation. The estimated mean progression rate of mild/moderate dysplasia was 10.3% (CI: 6.1%, 16.8%) compared to 24.1% (13.3%, 39.5%) for severe dysplasia/CIS. Sperandio *et al*. (61) examined retrospectively the prognostic value of OED grading in a large cohort of 1,401 patients. Overall, 3.5% (49 of 1409) of patients developed oral cancer during a follow-up period of 5 to 15 years. The transformation rate of non-dysplastic lesions, was 0.012% (14 of 1,182) compared to 6% (6 of 105), 18% (14 of 76), and 39% (15 of 38) for mild, moderate, and severe dysplasia respectively. In Warnakulasuriya *et al's.* study (36), the severity of OED was the most significant prognostic indicator ($p<0.0001$). The transformation rates for mild, moderate and severe dysplasia were 4.8%, 15.7% and 26.7% respectively. These studies strongly support OED grading as an important marker for risk of malignant progression.

Using their binary system, Kujan *et al.* (55) graded 68 lesions as “high-risk” or low-risk” based on a combination of the architectural and cytological features shown in Table 3 (54). Twenty eight of 35 cases (80%) graded as high-risk progressed to cancer, compared to 5 of

33 low–risk lesions (15%). The binary grading had good prognostic value with a sensitivity and specificity of 0.85 and 0.80 respectively. In a similar study, Liu *et al.* (62) tested the diagnostic utility of the binary OED grading system in a cohort of 138 patients, with a mean follow-up period of 5.1 years. Of the low-grade lesions, 17 of 92 (18.5%) progressed to malignancy, compared to 20 of 46 (43.5%) high-grade lesions (p=0.004). They found that the degree of dysplasia was an independent risk factor for predicting malignant transformation, with high-grade dysplasia showing a 2.78-fold (CI 95%: 1.44-5.38) increased risk of cancer progression (62). Nankivell *et al.* (56) further validated the reliability and prognostic usefulness of binary OED grading. These studies show that the binary system may have a better prognostic value and superior reproducibility than the currently more widely used three scale grading system (3). With further evaluations, it is believed that a binary system will become the standard grading scheme (2,3). There is also good evidence that the accuracy and prognostic reliability of dysplasia grading can be improved by careful training and by consensus reporting by at least two pathologists (2,3,55,65,66).

Several studies however, have not been able to find a relationship between epithelial dysplasia and malignant progression. Warnakulasuriya and Ariyawardana (6) found 5 papers which had correlated OED grade to malignant transformation, only 3 of which found a significant relationship (14, 46, 62). Others have not been able to find a statistical correlation and have shown that non-dysplastic or low-grade lesions may also progress (15,16,24,63). This contradicts the view that leukoplakic lesions without dysplasia, or mildly dysplastic lesions are entirely harmless, and has led to calls to drop the “wait and see” approach and for more active surgical intervention in the management of OPMDs (15,16,59).

Despite these uncertainties, the majority of the literature supports the view that OED carries a significant risk for malignant transformation and that it must be considered in the process of managing the clinical risk of progression of OPMDs. However, clinicians should acknowledge that pathologists report on the tissue they receive and that the histopathological findings are highly dependent on correct and representative sampling of

the lesion. Holmstrup *et al.* (64) compared the biopsy diagnosis and the final diagnosis after surgical removal in 101 OPMDs. In 35% of cases they found that the biopsy had underdiagnosed the extent of disease, including 7 cases of squamous carcinoma which had shown only moderate, mild or no dysplasia on incisional biopsy, and may have been regarded as "low-risk" lesions. The authors concluded that histological grading of OED on biopsies is unreliable and that other factors must be considered for the prediction of malignant transformation of OPMDs.

Biomarkers as predictors of progression.

The Holy Grail in terms of risk assessment is to discover a biomarker that can be used in a histological or chairside test to predict malignant transformation of oral lesions. There have been many studies investigating various potential markers, but to date no single biomarker has proved to be of clinical value. In a systematic review, Smith *et al.* (67) found more than 2,500 publications addressing the issue of biomarkers in dysplasia, but only 13 met the criteria of longitudinal design, with adequate follow-up and well-defined diagnostic criteria. Overall they found that 113 biomarkers had been analysed. The most common of these was p53 (found in almost 90 papers and in six of the 13 included studies), followed by proliferation markers (Ki67 and PCNA; 20–40 papers). Other markers including cell cycle proteins, loss of heterozygosity (LOH), and a range of cell surface and stromal proteins were studied in relatively few papers. The authors recognised the limitations of a review of this sort, and the variability in the quality of identified papers. Nevertheless, they were able to suggest that LOH, survivin, MMP9 and DNA content may be associated with risk of progression. Overall, however they concluded that there is currently no strong evidence for the use of any biomarker in the prognosis of OPMDs.

Others have come to similar conclusions, and have been unable to identify any markers which have yet been fully evaluated or are suitable for use in a routine diagnostic setting (48,59,67-69). Many studies have examined various aberrations in the genome as potential

markers of progression (reviewed in 48,59,67-68). These include LOH and gene expression signatures but no single aberration has been found to be predictive. Analysis of DNA content (ploidy) provides a simple measure of gross genetic aberrations and is known to be highly associated with malignancy (70). Analysis of DNA aneuploidy may be one potentially useful biomarker that is yet to be fully exploited. Recently, Alaizari *et al.* (71) undertook a meta-analysis to determine if aneuploidy was a useful marker to predict malignant progression in OPMDs. They identified five studies that had assessed the predictive value of ploidy analysis (61,72-75), and found that aneuploid lesions had a 3.12 (CI: 1.86, 5.24) fold increased risk of malignant transformation. All studies also showed that aneuploidy was associated with increasing severity of dysplasia. In their own study for example (61), they found a significant correlation between dysplasia grade and DNA ploidy ($p<0.001$). Forty-nine of 110 (44.5%) cases of severe dysplasia were aneuploid compared to only 14.0% of mild dysplasias and 9.5% of non-dysplastic lesions. Of 32 lesions that progressed to malignancy 20, (62.5%) were aneuploid, compared to only 39 of 241 (16.2%) lesions which did not progress. Torres Rendon *et al.* (72) found that 14 of 42 (33.3%) OED that progressed were aneuploid, compared to only 5 of 44 (11.3%) that did not progress ($p=0.01$). Of 19 OED that were aneuploid 74% showed malignant progression compared to only 42% of the diploid lesions. Although further work and prospective trials are needed, these studies suggest that aneuploid dysplastic lesions have a higher risk of malignant progression. Aneuploidy can now be measured using image cytometry and its application to cytology samples may soon result in rapid and reliable non-invasive tests for risk assessment of oral lesions (76).

HPV associated epithelial dysplasia

In a meta-analysis of studies up to 1997, Miller and Johnstone (76) found that Human Papilloma Virus (HPV) was more likely to be detected in precancerous lesions than in normal oral mucosa. HPV was detected in 10% of normal tissues compared to 22.2% of

non-dysplastic leukoplakias, and 26.2% of dysplastic lesions. Subsequently, the relationship between high-risk HPV and oropharyngeal squamous cell carcinoma has become well established, but the role of HPV in OPMD remains uncertain. HPV-associated epithelial dysplasia is now well recognised (78) and increasing numbers of cases are being reported (79,80), but there are few studies with long-term follow up and the risk of progression of HPV positive lesions is not yet known. Recently however, a study by Lerman *et al.* (81) suggests that HPV positive OED may have a high risk of malignant progression. They undertook a detailed analysis of 53 cases of HPV-associated OED. All cases showed the characteristic histological features associated with HPV infection (78) and most (88.7%) arose in males and involved the tongue or floor of the mouth (77%). Eight of the 53 cases (15%) were associated with invasive squamous cell carcinoma. Further, p16 has been postulated as a good surrogate marker for high-risk HPV types as a high association of over 90% between the positive p16 and high-risk HPV types using DNA *in situ* hybridization was reported (81).

Risk of progression of other, defined, oral lesions

Proliferative verrucous leukoplakia

Proliferative verrucous leukoplakia (PVL) is a multifocal, recurrent and exophytic variant of leukoplakia with a high rate of malignant progression. In a systematic review and meta-analysis, Abadie *et al.* (82) examined 23 papers with follow-up data. They found a malignant transformation rate of 63.9%. Most papers were single case reports, but of 8 papers that reported on a series of more than ten cases, the rate of progression varied from 33% (83) to 100% (84). PVL is diagnostically challenging and can often only be diagnosed retrospectively after careful clinical and pathological correlation shows a history of persistent or recurrent and multifocal lesions. Early lesions are often flat plaque-like leukoplakias, but as the disease progresses, lesions become multifocal (proliferative) and increasingly exophytic or non-homogenous (verrucous). The existing evidence indicates a higher frequency in older females (>60 years of age) with gingiva the most commonly involved site

followed by buccal mucosa and tongue (82, 85-87). Gingival and palatal lesions are also the most likely to undergo malignant transformation (85, 88,89). The aetiopathogenesis is poorly understood and there appears to be no correlation with alcohol, tobacco chewing, smoking or HPV infection (82, 85, 86). The overall mortality rate is also somewhat unclear with some studies reporting 60% 5-year survival whereas others suggest it to be less aggressive. In their review, Pentenero *et al.* (85) estimated an overall mortality of 30%.

Histologically, PVL can show a range of features which may change over time. These include simple hyperkeratosis, and verrucous hyperplasia with a verruciform surface pattern and wide bulbous rete pegs. However, although there are prominent architectural changes, cytological atypia is minimal and conventional OED grading cannot be used as a predictive marker. A "pushing" invasive front, below the level of the basement membrane of the adjacent normal mucosa is suggestive of progression to verrucous carcinoma, but often lesions progress to conventional invasive OSCC. Immunocytochemical staining for proliferation markers (MCM-2) and DNA ploidy analysis have been suggested to aid prediction of malignant transformation (90). Because of their extent, lesions are usually excised conservatively, but recurrence rates remain high (>70%) even if a more radical approach is undertaken (82,85, 91). The average time for malignant transformation is estimated at 5-6 years after initial presentation. Close follow-up and repeat biopsies are essential to ensure early diagnosis and appropriate treatment.

Oral Lichen planus

Predicting the malignant potential of oral lichen planus (OLP) is challenging due to overlapping features with oral lichenoid lesions (OLL) and the presence of a 'lichenoid' inflammatory infiltrate which is commonly seen in dysplastic lesions. Many studies have not used strict diagnostic criteria, making the data very difficult to interpret. Although a small proportion of OLP lesions may progress to oral cancer, it is important to distinguish OLP from OLL since the latter seem to have a higher transformation rate. Two recent systematic

reviews showed that OLP had a malignant transformation rate of 1.09% (92) and 0.9% (93), while the rates for OLL were 3.2% and 2.5% respectively. Casparis *et al.* (94) undertook a retrospective analysis of 483 biopsies of OLP (n=381) or OLL (n=102) and found malignant transformation rates of 1.3% and 5% respectively.

Van der Meij *et al.* (95) have not been convinced that there is sufficient evidence to support the malignant potential of OLP. They reported that the literature showed rates of progression of 1.74% or less, but they were concerned regarding the veracity of the diagnostic criteria applied. In their study, they applied strict clinical and histopathological criteria for diagnosis and identified 67 patients with OLP and 125 with OLL. No patients with OLP progressed, but 4 (3.2%) patients with OLL developed squamous carcinoma. Of particular note, their criteria for a diagnosis of OLP included the requirement that lesions were bilateral and that they did not show evidence of epithelial dysplasia on histological examination. This is a controversial and much debated issue (92,96), and although some may accept epithelial dysplasia as a feature of OLP, we do not. We would agree with Van der Meij *et al.* (95) and regard the presence of epithelial dysplasia as excluding a diagnosis of OLP. When dysplasia is present, lichenoid features may be prominent, but we interpret them as a lichenoid tissue reaction (interface mucositis) in response to the dysplastic changes, and advocate that they should managed in the same way as other dysplastic lesions. This concept was first developed by Krutchkoff and Eisenberg in 1985 (97), who coined the term lichenoid dysplasia to describe oral epithelial dysplastic lesions with lichenoid features. They proposed that these lesions may be mistaken for OLP and that this misdiagnosis may, at least in part, explain the purported malignant potential of OLP. To some extent, this concept and the term lichenoid dysplasia has fallen out of favour. However, the need to more carefully define OLP (95) has resulted in more careful considerations of the histological features, and there are good reason why lichenoid dysplasia should be reconsidered as a diagnostic entity (98).

Despite these caveats, there remains some evidence that patients with OLP may be at a greater risk of developing oral squamous cell carcinoma (92,93,99,100). In their large

systematic review, Aghbari *et al.* (93) found an overall malignant transformation rate of 1.1% in papers published since 1972. However, when they restricted their analysis to papers published since 2003 that used the more precise criteria for diagnosis (95), the rate reduced to 0.9%. Risk factors associated with a significantly greater rate of malignant transformation were smoking (OR=2; 95% CI, 1.25, 3.22), alcoholics (OR=3.52; 95% CI, 1.54, 8.03) and HCV infection (OR=5; 95% CI, 1.56, 16.07). In a similar review, Landini *et al.* (100) identified 65 reports of malignant transformation in lichen planus, but only 35 of these studies included both clinical and histological criteria for diagnosis. The overall rate of malignant transformation was 2.28%. However, for studies with precise criteria the rate was only 1.53% compared to 2.74% in the group without histological verification. Other studies agree with these findings and have also found that females may be at higher risk and that lesions involving tongue appear to have a higher predilection for transformation (92,94). It is also noted that erosive lesions may have a greater potential for progression. This, and the higher risk in smokers and those who use alcohol, raises the distinct possibility that the association between OLP and oral cancer is coincidence, or that OLP has a predisposition to cancer development, only because the atrophic mucosa is more susceptible to the action of these carcinogens (99)

Interestingly, an association of OLP with viral infections has also been reported. A recent meta-analysis (101) shows that patients with erosive OLP have a higher risk of HPV infection (HPV 16 and HPV18) suggesting a potential causal role in OLP progression. Similarly, a possible association with Hepatitis C virus has also been reported (92,93,102). However, it remains unclear whether the presence of infection is related to colonisation due to change in mucosal surface or if the virus plays an active role in OLP pathogenesis and progression to cancer.

Sperandio *et al*. (103) identified 14 patients with well documented lichen planus, who developed oral cancer. They analysed DNA content in these and found that 4 had aneuploid lesions. By comparison, 68 cases of OLP that had not progressed to cancer were all diploid.

They suggested that DNA ploidy analysis may be useful to aid prediction of malignant transformation in a proportion of case.

Taken together, these data provide some evidence that patients with lichen planus may be at greater risk of developing oral cancer, but more precise and internationally agreed criteria for diagnosis need to be established. Risk factors for malignant transformation that have been shown to be statistically significant include smoking and alcohol use, and infection with HCV. Erosive lesions, lesions on the tongue and the presence of aneuploidy may also be associated with progression.

Oral submucous fibrosis

Oral submucous fibrosis (OSF) is a chronic disorder of the oral and pharyngeal mucosa characterised by fibrosis of the submucosa resulting in stiffness, limited opening and atrophy and whitening of the oral epithelium. Although often thought to have a complex multifactorial aetiology it is now recognised that OSF is directly associated with use of areca nut (104-106) and is predominantly seen among the populations of South and South East Asia or in Asian populations within the UK, USA and other developed countries (104). However, only 1% -2% of areca nut users develop the disease suggesting that genetic predisposing factors are also involved (104-106). The importance of OSF as a potentially malignant disorder was first recognised in 1956 (107) and since there have been numerous studies to determine the risk of progression. An early long-term follow-up study in India followed 99 patients with OSF for 17 years, and found a transformation rate of 7.6% (108). However, this was a small study and more recent larger studies have suggested a lower rate. In a recent review, Ray *et al*. (109) found that the transformation rate varied from 1.9% to 7.6%.

Some of the largest studies have been undertaken in Taiwan, where areca nut use is particularly prevalent. Hsue *et al.* (110) identified 1458 patients with OPMDs in a retrospective review of histopathology records. There were 402 patients with OSF of whom

8 (1.9%) developed oral cancer. They also identified 37 patients with OSF and epithelial dysplasia and 2 (5.4%) of these progressed to cancer. Of note, they found that the rate of progression of OSF (1.9%) was less than for epithelial dysplasia (4.65%; 6/129), hyperkeratosis (3.55%; 15/423;), verrucous hyperplasia (3.09%; 10/324) and lichen planus (2.10%; 3/143). In a similar study in Taiwan, Wang *et al.* (111) reviewed 5071 patients with OPMDs and found an overall malignant transformation rate of 4.32%. Of 994 patients with OSF, 37 (3.72%) developed oral cancer. They also identified 186 patients with OSF and dysplasia of whom 9 (4.84%) developed carcinomas. It is noteworthy that these two studies were carried out in the same hospital and on the same population, but 10 years apart. The malignant transformation rates are quite different, including that for lichen planus, which was only 0.52% in the second study (111) compared to 2.10% in the earlier study (110), but the number of cases is small. Both these studies showed that patients with epithelial dysplasia and OSF had a higher transformation rate than OSF alone, suggesting that presence of OED in a biopsy of OSF is a predictor of high risk. A more recent study in Taiwan has shown a malignant transformation rate of 9.13% for OSF – one of the highest rates recorded (112). This was a population-based study that used the records of the Taiwanese National Health Insurance program to identify cases of OSF and oral cancer during follow-up. They identified 778 patients diagnosed with OSF over a twelve-year period, and compared the rate of development of oral cancer to 43568 non-OSF age and gender matched controls. OSF patients were more likely to be male (87.1%) and to also have lesions of oral leukoplakia (24.6% compared to 0.1% of controls). In the OSF group, 71 patients (9.13%) developed oral cancer compared to 123 in the control cohort (0.28%). The mean duration of malignant transformation was 2.5 years and 5.1 years in the OSF and controls groups respectively. Among the OSF group, they identified 191 patients who had lesions of OSF and leukoplakia. The malignant transformation rate in this group was 15.1% (29/191) compared to 7.1% (42/587) in patients with OSF alone. In terms of risk, OSF patients were almost 30 times more likely to develop oral cancer than non-OSF patients (HR=29.84; 95% CI, 20.99,42.42) and in patients with OSF and leukoplakia the risk almost doubled

(HR=52.46; 95% CI, 34.88,78.91). There is some evidence that squamous carcinoma developing in OSF is a clinicopathologically distinct disease, but studies from different geographic regions vary (103). Nevertheless, studies from the Tata Memorial in Mumbai (113,114) have shown that oral squamous carcinomas associated with OSF were seen more often in males, at a younger age and at a lower stage. Lesions were also thinner and less invasive and had an overall better survival.

These studies show that OSF is an important OPMD with reported rates of malignant progression from 1.9% to 9.13%. There is good evidence that the risk of progression of OSF is greater if histopathological analysis shows the presence of epithelial dysplasia and if patients have concomitant lesions of leukoplakia.

Chronic hyperplastic candidiasis

There is no consensus as to whether or not chronic hyperplastic candidiasis (CHC; candidal leukoplakia) should be regarded as an OPMD. The latest WHO classification (3) lists "Chronic candidiasis" as an OPMD, but gives no explanation or criteria for diagnosis, while others do not include candidiasis as an OPMD (2,5). Anecdote and clinical experience gives mixed opinions. Chronic candidal lesions may have the clinical appearance of a high-risk lesion, being often raised and speckled (non-homogenous), but they are most often encountered at sites which are rare for development of oral cancer – the buccal commisures and dorsum of the tongue. On histological examination lesions of CHC often show evidence of cytological atypia, but this is usually confined to an increase in (normal) mitotic figures and basal cell hyperplasia without pleomorphism, and may be regarded as reactive in nature. Lesions may also resolve after antifungal therapy, suggesting that lesions that are primarily caused by *Candida* infection are not potentially malignant. Conversely, there is a significant association between fungal infection and the presence of epithelial dysplasia (115,116), but the debate regarding causation or association has not been resolved. Barrett *et al.* (116) reviewed 4724 mucosal biopsies and found evidence of PAS-positive fungal hyphae in 223

(4.7%). There was a significant association between fungal infection and squamous papilloma, median rhomboid glossitis and epithelia dysplasia ($p<0.01$). In particular, moderate and severe epithelial dysplasia were infected in 18.0% and 15.2% of cases respectively, with lesions on the tongue being most frequently infected. They also showed that dysplastic lesions, which were infected with candida, were almost three times more likely to show a higher grade of dysplasia in a subsequent biopsy, suggesting a positive correlation between *Candida* and progression of dysplasia. There is also some biological evidence that candida may be directly involved in carcinogenesis. This includes the finding that *Candida* isolated from leukoplakic lesions may produce carcinogenic nitrosamines (117) or acetaldehydes (118) and that *Candida albicans* can act as a promoter in a mouse model of 4NQO induced cancer (119). Despite this, it has not been possible to show a true causal relationship between *Candida* and epithelial dysplasia and cancer. Two in-depth reviews (120,121) have concluded that the there is insufficient evidence to regard chronic hyperplastic candidiasis as an OPMD, but nevertheless advise that the association with *Candida* infection should be regarded as suspicious and that lesions must be kept under careful review and removed if they do not resolve with appropriate anti-fungal therapy. More recently, Sanjaya *et al.* (122) have suggested that *Candida* has an indirect causal role in oral cancer and have hypothesised that in patients with tobacco smoking habits, production of nitrosamines by *Candida albicans* enhances the process of dysplasia development and progression to cancer. They do not propose a role for *Candida* in the absence of tobacco as a co-factor.

An approach to clinical risk assessment

Assessing the risk of malignant change in OPMDs can be difficult, since any decision at each stage of the management pathway is not binary, and the clinician may be faced with a number of options. The process of undertaking a clinical assessment can be considered in three stages – clinical history, clinical examination, and surgical biopsy and histopathological

evaluation. In Figure 3 we have attempted to graphically indicate the features encountered at each stage that may be associated with risk. The starting point is identification of a suspicious lesion, which for this purpose we define as a lesion which cannot be diagnosed as a specific disorder on clinical examination. Specific lesions such as lichen planus or OSF have defined risks, and are not illustrated (see text). In Figure 3, the features encountered at each stage are given a risk profile, green, amber or red, indicating low, medium or high risk respectively. For example, the history is the first stage of clinical assessment and here, female non-smokers would be regarded as at a higher risk than males. At clinical examination, erythroplakia has a higher risk that leukoplakia, but non-homogenous lesions have a higher risk than homogenous lesions, and speckled lesions are at a higher risk than verrucous lesions. Histopathological evaluation is a paramount and will be considered a critical in making informed decision about OPMD's management. Nonetheless, a holistic approach that combines the three stages of evaluation is essential to have the optimal outcomes of risk assessment of OPMDs.

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Figure 1

Homogenous leukoplakia on right lateral border of tongue; a biopsy showedmild epithelial dysplasia.

Figure 2

Non-homogenous leukoplakia on the lateral border of the tongue. The lesion shows irregular red and white areas and may be termed “speckled leucoplakia”. Histologic examination showed severe epithelial dysplasia.

Figure 3.

A simple algorithm for clinical risk assessment of OPMDs. The clinician is faced with a suspicious oral lesion, and at each stage of the assessment process the risk of individual features are illustrated as green (low risk), amber (medium risk) or red (high risk). The levels of risk and explanations are given in the text.