

An overview of the classification and predictive value of oral epithelial dysplasia

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Introduction

Oral precursor lesions can be defined as altered epithelial lesions which have an increased likelihood of progressing to squamous cell carcinoma. The nomenclature, natural history and predictive value of this group of lesions was reviewed at an expert workshop held in London in 2005, and has been reported in a series of recent papers [1-3]. The group recommended that the distinction between potentially malignant lesions and conditions should be abandoned in favour of a common terminology of *Oral potentially malignant disorders* [1,2]. This recognises the fact that even in patients with lesions such as leukoplakia, malignancy may arise elsewhere as a result of field change. The most common disorders recognised as potentially malignant are *leukoplakia* and *erythroplakia*. The WHO definition of these lesions is generally regarded as unsatisfactory, since it largely a definition by exclusion. The Working group recommended a new definition for Leukoplakia which recognises the lack of evidence about risk and the nature of the lesions: *'The term leukoplakia should be used to recognise white plaques of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer'* However even this remains unsatisfactory and a clear definition of precursor lesions may have to wait for further diagnostic criteria based on molecular or genetic markers. For the present time, the prognostic significance of an individual lesion is difficult to determine, and none of the currently available molecular markers have proved to be prognostically significant and none have yet been evaluated in large prospective studies.

The gold standard for the assessment of oral potentially malignant disorders remains the microscopic evaluation of haematoxylin and eosin stained sections for the presence of *epithelial dysplasia*. Some texts use the terms squamous intraepithelial neoplasia (SIN) or squamous intraepithelial lesions (SIL) (Table 1) [4]. The categories under each scheme are similar, but the terminology is not exactly the same. In the oral cavity, use of the SIL terminology of 'atypical hyperplasia' may lead to confusion because of the large number of common benign hyperplastic lesions which may be encountered. In oral and maxillofacial pathology therefore, *oral epithelial dysplasia* is regarded as the standard terminology [2-5].

Criteria for the diagnosis of oral epithelial dysplasia

The diagnosis and grading of oral epithelial dysplasia is based on a combination of architectural and cytological changes [4] (Table 2), but evaluation of these is subjective and has been subject to considerable inter- and intra-observer variations in the grading of lesions, with Kappa values showing only fair to moderate agreement between observers [6-8]. (Table 3). More recently there has been an attempt to more carefully define the criteria for grading of

epithelial dysplasia [5,6]. Largely this has involved an adaptation of the scheme used in cervical pathology where it has been traditional to grade cervical intraepithelial neoplasia (CIN) according to the thickness or levels of involved epithelium. It should be noted however that full thickness change analogous to CIN3 (carcinoma-in-situ) is rarely seen in the mouth. Nevertheless, the latest WHO classification [4] now recommends a more objective grading which does, to some extent, take account of levels of involvement. The criteria for grading of oral epithelial dysplasia are summarised as follows:

Mild dysplasia (grade I) demonstrates proliferation or hyperplasia of cells of the basal and parabasal layers which does not extend beyond the lower third of the epithelium. Cytological atypia is generally slight with only mild pleomorphism of cells or nuclei. Mitoses are not prominent, and when present are usually basally located and normal. Architectural changes are minimal.

Moderate dysplasia (grade II) demonstrates a proliferation of atypical cells extending into the middle one-third of the epithelium. The cytological changes are more severe than in mild dysplasia and changes such as hyperchromatism, and prominent cell and nuclear pleomorphism may be seen. Increased and abnormal mitoses may be present, but these are usually located in the basal layers. Architectural changes may be seen in the lower half of the epithelium where there may be loss of basal polarity and hyperplasia leading to bulbous rete pegs. However stratification and maturation are relatively normal, often with hyperkeratosis

In *severe dysplasia* (grade III) there is abnormal proliferation from the basal layer into the upper third of the epithelium. Cytological and architectural changes can be very prominent. All the changes seen in mild and moderate dysplasia are seen but in addition there is marked pleomorphism often with abnormally large nuclei with prominent or even multiple nucleoli. Prominent and suprabasal mitoses are usually evident and abnormal tripolar or star-shaped forms may be seen. Apoptotic bodies may also be prominent. Architectural changes are severe, often with complete loss of stratification and with deep abnormal keratinisation and even formation of keratin pearls. Abnormal forms of rete pegs are usual and we regard bulbous rete pegs as particularly significant in the diagnosis of severe dysplasia. Abnormal shaped rete pegs may also be seen, with lateral extensions or small branches. These are quite abnormal and may be the earliest signs of invasion. Occasional lesions may show prominent acantholysis with severe disruption of the architecture. Although the epithelium may be thickened, severe dysplasia is sometimes accompanied by marked epithelial atrophy. This is especially prominent in lesion from the floor of mouth, ventral tongue or soft palate and may be a feature of lesions which have presented clinically as erythroplakia. In these cases there may be minimal evidence of stratification or keratinisation, and atypical cells may extend to the surface.

Carcinoma in situ, is the most severe form of epithelial dysplasia and is characterised by full thickness cytological and architectural changes. In the oral cavity such changes are rare, and often, even in the presence of the most severe atypia, there is still an intact keratinised surface layer. Carcinoma in situ is thought by some to be a premalignancy but others regard it as evidence of actual malignant change but without invasion.

When grading epithelial dysplasia the pathologist should take into account both the cytological and architectural changes. Changes regarded as particularly significant include marked cell and nuclear pleomorphism, drop shaped rete pegs and abnormal mitoses. When the cytological changes are very marked this may indicate that a lesion should be upgraded.

Grading of epithelial dysplasia

The grading scheme outlined above uses a 5-point scale (Table 1) which is thought to provide good discrimination but, as discussed above, is notoriously subjective with low inter-observer agreement. Kujan et al. [9] explored the inter-observer agreement of 4 observers using the five point scale, and calculated the kapps values of each of the features used for the diagnosis (table 2). They showed that overall there was only low to moderate agreement (Kappa 0.00 to 0.53) but that the presence of mitotic figures, drop-shaped rete pegs, increase nuclear size and cellular pleomorphism were the features on which the pathologists most closely agreed. They suggested that a binary scoring scheme may be easier to use, less subjective and may better discriminatory powers. Many pathologists already use a simple scheme where lesions are reported as 'low risk' or 'high risk' and the expert working group [2] recommended that this scheme should be properly evaluated. In a recent study, Kujan et al [10] compared the WHO 5-point grading to a simple binary scheme and found that the kappa values (0.63 and 0.50 respectively) were similar and showed only moderate to good agreement. In this study, 80% of high risk lesions progressed compared to only 15% of low risk lesions. However it should be noted that the binary scheme merely reduces the categories to two by combining moderate and severe dysplasias as 'high risk' and hyperplasia and mild dysplasia as 'low risk'. No new criteria have been suggested and the allocation of lesions to each group still remains subjective. A decision still needs to be made on how to distinguish between lesions with 'mild' changes and those with 'moderate' changes. There has been no attempt to also use clinical criteria in the allocation to low and high risk categories

Malignant transformation in potentially malignant lesions

Although it is established that oral potentially malignant lesions and epithelial dysplasia are statistically more likely to progress to cancer, the actual mechanisms are poorly understood and it is not inevitable that a dysplastic lesion will progress to cancer. At present, there are no molecular markers which enable us to distinguish lesions that may progress from those that will not [2-5]. The degree of dysplasia is the best guide to potential progression of oral lesions, but dysplasia itself may not always be a reliable marker. Silverman et al as long ago as 1984 [11] showed that although 36% of dysplastic lesions progressed to carcinoma, so did 16% of non-dysplastic leukoplakic lesions. However it is known that epithelial dysplasia does correlate to those clinically non-homogeneous lesions which have the highest risk [12], (Table 4). Severe epithelial dysplasia has an overall malignant transformation rate of about 16% but studies show a wide range of 7% – 50% [11–21] (Table 5). Moderate dysplasias have a malignant transformation potential of 3% – 15%, whereas mild epithelial dysplasia shows a very low risk (less than 5%). It is always assumed, however, that there is a temporal progression of disease, analogous to multistage carcinogenesis, and that mild dysplasia will progress to severe dysplasia and then to carcinoma. There is very little empirical evidence however to support this attractive model.

With regards to the clinical lesion it is apparent that even fewer lesions actually progress [reviewed in ref 3]. Only about 50% of biopsied leukoplakias show dysplasia and overall the malignant transformation rate for leukoplakia is only about 0.1 - 2% per year. Ironically rates are lower in the developing world where tobacco chewing habits are most prevalent. In the west malignant transformation is estimated at about 5% of leukoplakias. Higher rates of about 20% have been reported in non-homogeneous lesions which are also more likely to show dysplasia on biopsy.

Summary and conclusions

Oral potentially malignant disorders are characterised most often by the appearance of white patches (leukoplakia) on the oral mucosa. Overall malignant progression in these lesions is only of the order of 5% and there are no currently accepted markers to distinguish those that may progress from those that may not. The current gold standard is the finding of epithelial dysplasia on a tissue biopsy. Diagnosis of dysplasia is subjective and considerable experience needs to be accrued before the significance of the variable features become fully apparent. The WHO guidelines are helpful in providing more objective criteria for grading. Overall however only about 50% of biopsied clinical leukoplakias show epithelial dysplasia and not all lesions progress. A maximum of 50% of severe dysplasias, 30% of moderate dysplasias and very few (less than 5%) mild dysplasia are thought to progress to cancer.

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Table 1: Classification schemes for epithelial dysplasia

Oral epithelial dysplasia	Squamous Intraepithelial Neoplasia (SIN)	Squamous Intraepithelial lesions ('Ljubljana System')	Classic Laryngeal System
Epithelial hyperplasia	n/a	Simple hyperplasia	Laryngeal Keratosis
Mild dysplasia	SIN 1	Basal/Parabasal Hyperplasia	Hyperplasia
Moderate dysplasia	SIN 2	Atypical Hyperplasia	Keratosis with dysplasia
Severe dysplasia	SIN 3		
Carcinoma <i>in situ</i>			Carcinoma <i>in situ</i>

(Based on Barnes et al, 2005 [4], Bouquot et al, 2006 [5])

Table 2: Cytological and architectural features of oral epithelial dysplasia [4].

<p>Cellular changes: Abnormal variation in nuclear size and shape (anisonucleosis and pleomorphism) Abnormal variation in cell size and shape (anisocytosis and pleomorphism) Increased nuclear/cytoplasmic ratio Enlarged nuclei and cells Hyperchromatic nuclei Increased mitotic figures Abnormal mitotic figures (abnormal in shape or location) Increased number and size of nucleoli</p> <p>Architectural (Tissue) changes: Loss of polarity Disordered maturation from basal to squamous cells Includes top-to-bottom change of carcinoma <i>in situ</i> Increased cellular density Basal cell hyperplasia Dyskeratosis (premature keratinization and keratin pearls deep in epithelium) Bulbous drop shaped rete pegs Secondary extensions (nodules) on rete tips</p>

Table 3: Three representative studies which have looked at inter-observer agreement in the diagnosis of epithelial dysplasia

	Kappa scores	% agreement
Brothwell et al. [6]	0.51 (0.42 - 0.58)	77 (75 – 85)
Karabulut et al. [7]	0.35 (0.27 - 0.45)	55 (49 – 69)
Abbey et al. [8]	0.46 (0.29 - 0.57)	82 (66 – 86)

Kappa values are for a diagnosis of the presence or absence of epithelial dysplasia and represent only fair to moderate agreement

Table 4: Correlation of dysplasia and the clinical appearance of oral leukoplakic lesions.

	Degree of dysplasia			
	None	Mild	Moderate	Severe
Homogeneous (n = 58)	60	22	14	3
Non-homogeneous (n = 51)	23	14	31	31

Data taken from Schepman KP et al 1998 [12]

Table 5: Malignant transformation rates (%) for microscopically diagnosed oral carcinoma in situ and/or severe epithelial dysplasia.

Reference	Country	No. patients	Cumulative follow-up (years)	Mean follow-up (years)	Malignant transformation rate (%)
Gupta et al. [13]	India	90	945	10.5	7.0
Schepman et al. [12]	Netherlands	166	415	2.5	12.0
Bouquot et al. [14]	USA	32	346	10.8	15.6
Silverman et al. [11]	USA	22	162	7.4	36.0
Banoczy & Csiba [15]	Hungary	23	145	6.3	21.8
Amagasa et al. [16]	Japan	12	120	10.0	50.0
Vedtofte et al. [17]	Denmark	14	55	3.9	35.7
Mincer et al. [18]	USA	16	48	3.0	18.8
Pindborg et al. [19]	India	21	63	3.0	14.3
Lumerman et al. [20]	USA	7	11	1.5	14.3
Jaber et al. [21]	England	480	?	?	3.2
Total/weighted mean		883	2310	5.9	15.6

Table taken from Bouquot J et al. 2006 [5]