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Evaluation of a new binary system of grading oral epithelial dysplasia for prediction of malignant transformation

Omar Kujan [a], Richard J. Oliver [a], Ammar Khattab [b], Stephen A. Roberts [c], Nalin Thakker [a], Philip Sloan [a,*]

[a] School of Dentistry, The University of Manchester, Manchester M15 6FH, United Kingdom
[b] Trafford General Hospital Trust, Manchester, United Kingdom
[c] Biostatistics Group, The University of Manchester, Manchester M15 6FH, United Kingdom

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Summary The aim of this paper is to assess the reproducibility of a novel binary grading system (high/low risk) of oral epithelial dysplasia and to compare it with the WHO classification 2005. The accuracy of the new system for predicting malignant transformation was also assessed. Ninety-six consecutive oral epithelial dysplasia biopsies with known clinical outcomes were retrieved from the Oral Pathology archives. A pilot study was conducted on 28 cases to determine the process of classification. Four observers then reviewed the same set of H&E stained slides of 68 oral dysplastic lesions using the two grading systems blinded to the clinical outcomes. The overall inter-observer unweighted and weighted kappa agreements for the WHO grading system were $K_s = 0.22$ (95% CI: 0.11–0.35), $K_w = 0.63$ (95% CI: 0.42–0.78), respectively, versus $K = 0.50$ (95% CI: 0.35–0.67) for the new binary system. Interestingly, all pathologists showed satisfactory agreement on the distinction of mild dysplasia from severe dysplasia and from carcinoma in situ using the new WHO classification. However, assessment of moderate dysplasia remains problematic. The sensitivity and specificity of the new binary grading system for predicting malignant transformation in oral epithelial dysplasia were 85% and 80%, respectively and the accuracy was 82%. The new binary grading system complemented the WHO Classification 2005 and may have merit in helping clinicians to make critical clinical decisions particularly for the cases of moderate dysplasia. Histological grading of dysplasia using established criteria is a reproducible prognosticator in oral epithelial dysplasia. Furthermore, the present study showed that more consensus scoring on either the degree of dysplasia, assessment of risk or the presence of each morphological characteristic by a panel should be encouraged.

* Corresponding author. Tel.: +44 161 275 6788; fax: +44 161 275 6797.
E-mail address: p.sloan@manchester.ac.uk (P. Sloan).

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Introduction

Oral epithelial dysplasia (OED) lesions may be morphological phenotypes of the different steps in the progression from normal to malignant tissue. Epithelial dysplasia was classified by the proposed WHO classification in 2003 as hyperplasia, mild, moderate, severe, or carcinoma in situ according to the presence and severity of the cellular atypia and to architectural features based on the thickness of dysplastic layers compared with the total epithelial height.[1] This proposed classification was published recently in the new WHO classification of tumors of the head and neck.[2] Traditionally, OED was considered as the progenitor for malignant changes.[1] Therefore, there was always a challenge for pathologists to assess the degree of dysplasia in potentially premalignant oral lesions with accuracy, for better prediction and management. The current histopathological grading of oral dysplasia lesions is notoriously unreliable mainly due to the lack of a validated grading system.[3] Many studies show wide variability in the diagnosis and grading of OED with results demonstrating only poor to moderate agreement on grading OED.[4–7] This is not only a problem for oral dysplasia but also for grading epithelial dysplasias in other parts of the body such as cervical intraepithelial neoplasia,[8] vulvar intraepithelial neoplasia,[9] and Barrett's oesophagus.[10]

Although one study has shown the high predictive value of DNA aneuploidy in OED,[11] histopathological evaluation based on morphology remains the routine method for diagnosis and grading OED.[12]

We have proposed and evaluated a new scheme based on the same morphological criteria used by the WHO classification 2005 (architecture and cytology changes), that grades the lesions into either ''low-risk'' or ''high-risk'' based on scoring the features.

We aimed to assess the inter-observer variability on the agreement of diagnosing and grading OED using both the WHO classification 2005 and our proposed binary system. We also examined the predictive value of the new system in terms of progression to malignancy.

Materials and methods

Case selection

This was a retrospective study based on data from the archive of the Oral Pathology laboratory of the School of Dentistry, University of Manchester. Sequential cases diagnosed at the original sign-out report during the period 1993–2001 as mild, moderate, severe dysplasia, or carcinoma in situ with known clinical outcomes were ascertained. For a patient to be included in the follow-up data, the follow-up biopsy and/or resection specimen had to be available. Where multiple biopsies had been taken over a period of follow-up, the initial biopsy was selected for the study. A set of 96 slides were included in the study that were originally signed out as follows: 30 with mild dysplasia, 24 with moderate dysplasia, 32 with severe dysplasia and 10 with carcinoma in situ.

We tested the hypothesis that a binary grading system categorizing lesions as ''low-risk'' or ''high-risk'' would be more valuable in grading oral epithelial dysplasia than a multiple level system. A pilot study, based on 28 cases of oral dysplastic lesions with known clinical outcomes, was first undertaken to determine the process of classification. Fourteen oral dysplasias that had transformed into squamous cell carcinoma and 14 that showed no progression were selected randomly from the included slides. The pathologist was blinded to the clinical outcomes of each case when the histological examination was done and both pathologists (O.K., P.S.) first performed their assessments independently of one another. A histological assessment scoring based on the architectural and cytological changes (Table 1) that were described in the WHO classification 2005 was made.[2] The definitive diagnosis of the cases was reached by consensus assessment.

Table 1 The architecture and cytology criteria used for grading epithelial dysplasia in the WHO classification 2005

Architecture criteria	Cytology criteria
1. Irregular epithelial stratification	1. Abnormal variation in nuclear size
2. Loss of polarity of basal cells	2. Abnormal variation in nuclear shape
3. Drop-shaped rete ridges	3. Abnormal variation in cell size
4. Increased number of mitotic figures	4. Abnormal variation in cell shape
5. Abnormally superficial mitoses	5. Increased nuclear–cytoplasmic ratio
6. Premature keratinisation in single cells	6. Increased nuclear size
7. Keratin pearls within rete ridges	7. Atypical mitotic figures
	8. Increased number and size of nucleoli
	9. Hyperchromatism

The association between the clinical outcomes and the histological assessment scoring was examined. The results revealed that the cut-point for a ''high-risk'' lesion (with potential susceptibility for malignant transformation) was based on observing at least four architectural changes and five cytological changes. However, the cut-point for a ''low-risk'' lesion (does not have the potential susceptibility for malignant transformation) is associated with observation of less than four architectural changes or less than five cytological changes.

All cases that were included in the pilot study were excluded from the final study. Thus, the final sample included in the study for observer agreement and clinical prediction of malignant transformation of oral epithelial dysplasia consisted of 68 slides that were originally signed out as follows: 21 with mild dysplasia, 17 with moderate dysplasia, 22 with severe dysplasia and 8 with carcinoma in situ.

Examiners/examination

Four observers scored the slides. Of these, three were academic staff, from the School of Dentistry, University of Manchester, with long experience of grading oral dysplastic lesions and the fourth was a general pathologist working