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Oral precursor lesions and malignant transformation – who, where, what, and when?

M.L. Goodson [a], P. Sloan [b], C.M. Robinson [b], K. Cocks [c], P.J. Thomson [a,*]

[a] *Oral & Maxillofacial Surgery, School of Dental Sciences, Framlington Place, Newcastle upon Tyne, NE2 4BW, UK*
[b] *Department of Cellular Pathology, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP, UK*
[c] *KC Stats Consultancy, www.kcstats.co.uk*

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Abstract

Oral potentially malignant disorders (PMD) are recognisable mucosal conditions that have an unpredictable risk of transformation to squamous cell carcinoma (SCC), a lethal and deforming disease of rising incidence. Contemporary management is based on clinical recognition of suspicious lesions and incisional biopsy to enable histopathological assessment and grading of dysplasia, together with excision of high-risk lesions and long-term surveillance. However, it is impossible to predict clinical outcome or risk of malignant transformation. Our aim was to evaluate the relevance of previously identified oral precursor lesions for the development of SCC and staging of disease. We therefore retrospectively reviewed 1248 cases of SCC diagnosed in oral and maxillofacial surgery units at Newcastle upon Tyne and Sunderland hospitals between 1996 and 2009. Of them, 58 identifiable precursor lesions became malignant but only 25 had been dysplastic on initial biopsy; 19 of 33 non-dysplastic lesions exhibited lichenoid inflammation only. SCC arose most often on the ventrolateral tongue and floor of the mouth, with a mean transformation time of 29.2 months. Transformation time was significantly shorter in men ($p = 0.018$) and those over 70 years of age ($p = 0.010$). Patients who consumed more than 21 units of alcohol/week and those who had had interventional laser surgery to treat precursor lesions, had higher-staged tumours ($p = 0.048$). Although retrospective, this study shows that the results of incisional biopsy and grading of dysplasia have limited use as predictive tools, and supports the view that cancer may arise in the absence of recognisable epithelial dysplasia. Our findings confirm the importance of clinical vigilance and active surveillance in the management of all patients with clinically suspicious oral lesions, irrespective of the histological findings.

Keywords: Oral potentially malignant disorders; precursor lesions; epithelial dysplasia; interventional laser surgery; malignant transformation

Introduction

Oral potentially malignant disorders (PMD)

Oral squamous cell carcinoma (SCC) is a lethal and deforming disease because of local invasion of tumour, orofacial destruction, metastasis to the cervical lymph nodes, and blood-borne dissemination. Oral cancers may be preceded by potentially malignant disorders, recognisable mucosal diseases such as localised leukoplakia or erythroplakia, or more widespread conditions, all of which harbour a considerably increased risk of developing SCC.[1] Estimates of the incidence and prevalence of PMD vary between different geographical areas and populations, but suggest an overall figure of between 2% and 3%, with most presenting as leukoplakia on the floor of the mouth, ventrolateral tongue, and buccal

* Corresponding author. Professor of Oral & Maxillofacial Surgery. Tel.: +441912088290.
E-mail address: peter.thomson@ncl.ac.uk (P.J. Thomson).

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mucosa. Whilst previously a disorder predominantly of older men, increasing evidence suggests that a much younger population is now at risk.[2] Historically, there has been little consensus on management, although most authorities now recommend incisional biopsy for histological assessment followed by excision of the whole lesion for definitive histological diagnosis and effective treatment.[1,3]

Clinical behaviour and malignant transformation

Despite the ability to identify PMD, clinicians have been unable to predict the behaviour of lesions or quantify the risk of malignant transformation. Overall estimates of outcome, which have suggested that 40% change very little or progress only slightly with time, 20% regress, and 20% progress to malignancy, are anecdotal and retrospective, and the natural history of these disorders remains poorly documented.[2,4]

It is generally accepted that identification of epithelial dysplasia (a variable presence of disorganisation and dysmaturation of tissue) with light microscopy is the strongest predictor of future malignant transformation in oral premalignant disorders.[1,5,6] Despite recent interest in molecular markers to predict malignant transformation, no single marker has been found to be predictive with sufficient sensitivity and specificity to be used routinely.[7]

As rates of malignant transformation vary between 0.1% and 40% worldwide it is difficult to counsel individual patients, although it is generally assumed that more severely dysplastic lesions have the greatest risk.[7] A recent systematic review quoted a 12% cancer rate over a mean transformation time of 4.3 years.[8]

It is recognised that non-dysplastic conditions, such as lichenoid lesions, may undergo malignant transformation although evidence is limited, and reported rates are usually below 1%.[9–11] Lichenoid lesions are not always followed up continuously although some authors have recommended that it should be done to detect early cancerous change.[12,13]

It is now known that multifocal mucosal disorders such as proliferative verrucous leukoplakia have a high risk of malignant transformation, often in the absence of dysplasia.[14] As this association has been recognised relatively recently, lesions previously considered innocuous may have an increased risk.

We still do not know what proportion of oral SCCs develop from PMDs. Currently we are unable to predict the behaviour of individual lesions as neither clinical state nor histological stage influences outcome.[7,15]

Aim

Our aim therefore was to identify the nature of pre-existing oral lesions, to assess the influence of clinicopathological features on the risk of, and time to, malignant transformation, and the clinical staging of resultant SCC in a group of patients in whom SCC arose at the site of a previously identified precursor lesion.

Methods

Data

We used the oral cancer database held by the Department of Pathology at the Royal Victoria Infirmary in the Newcastle upon Tyne Hospitals NHS Foundation Trust to identify all patients who presented between January 1997 and December 2008 with SCC that had arisen from a previously biopsied precursor lesion at the same site. Histopathological reports and diagnoses for both the precursor and cancerous lesions were retrieved electronically, and hospital case notes were retrospectively reviewed to retrieve additional clinicopathological data on age, sex, smoking and alcohol habits, and on the appearance and site of the precursor lesion, interventions, time to development of SCC, and differentiation and staging of the tumour.

Inclusion and exclusion criteria

Patients who had developed SCC at the same site as a previously identified oral precursor lesion were included. Those with a previous history of cancer of the upper aerodigestive tract were excluded as were those in whom carcinoma had arisen within 6 months of diagnosis of the precursor lesion to avoid potential errors in biopsy sampling.

Histopathological review

Paraffin-embedded histological sections were obtained from the 58 precursor lesions. Slides were anonymised to enable blinded review and re-diagnosis by 2 experienced oral pathologists (PS and CMR) who examined them independently, and then by consensus, provided a final definitive histopathological report for each specimen.

Statistical analyses

Univariate analyses of all the clinicopathological factors that could potentially influence time to development of SCC and tumour stage were done using linear regression and chi square or Fisher's exact tests, respectively. Multivariate analysis was done using linear and logistic multiple regression models with the most significant variables ($p < 0.2$), and backwards selection was done to retain only covariates significant at the 5% level for the final model. Kappa coefficients were used to assess agreement between the 2 pathologists, first, in comparison with the original diagnosis of the precursor lesion, and secondly, for variability between them. All statistical analyses were done using SAS/STAT® 9.3 software (SAS Institute Inc, Cary, USA).