Perspectives on Oral Squamous Cell Carcinoma Prevention – Proliferation, Position, Progression and Prediction

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Abstract

Squamous cell carcinoma arising from oral mucosal epithelium remains a lethal and deforming disease due to tumour invasion, oro-facial destruction, cervical lymph node metastasis and ultimate blood-borne dissemination. Worldwide, 300,000 new cases are seen each year, with a recent and significant rise in incidence affecting particularly the young. In order to rationalize perspectives on preventive strategies in oral cancer management, this paper addresses a number of fundamental questions regarding carcinogenesis: Proliferation - what epithelial cell changes precede tumour development? Position – why are certain oral sites so predisposed to cancer? Progression - why do some precursor lesions progress to invasive carcinoma and others do not? Prediction - how can we predict individual patient and/or lesion behaviour to prevent disease progression? By improving our understanding of oral carcinogenesis, can we thereby facilitate more effective primary, secondary and tertiary preventive strategies and ultimately reduce the global burden of OSCC?

Introduction

In the 21st century, oral squamous cell carcinoma (OSCC) remains a lethal and deforming disease exhibiting rising incidence, particularly in younger patients, and a global significance of over 300,000 new cases presenting each year[1]. Despite substantive advances in diagnosis and management, 50% of OSCC patients still die within 5-years; even following successful treatment intervention, long term prognosis is compromised by late initial presentation of advanced tumours and ultimately widespread, multi-focal disease extending throughout the upper aerodigestive tract[1].

The transformation of normal stratified squamous oral mucosa into premalignant and subsequently malignant tissue remains poorly understood, although it is recognized that it is a complex, multistep and multifactorial process in which accumulated genetic alterations disrupt the normal functioning of oncogenes and tumour suppressor genes[1]. Disruption of the cell cycle is characterized in its earliest phase by dysregulation, enhanced proliferation and changes in differentiation, DNA repair, apoptosis and cellular immunity[1,2].

Phenotypical epithelial tissue disorganisation and dysmaturation changes preceding OSCC are recognisable microscopically, may be defined into varying grades of severity of epithelial dysplasia, and are clinically identifiable as oral potentially malignant disorders (PMD) which can then be treated by low-morbidity interventional laser surgery[1].

In order to rationalize perspectives on preventive strategies and address long-standing dilemmas relating to the early diagnosis of OSCC and the role of interventional management in influencing disease progression, this paper will review the following inter-related topics:

1. Proliferation - What epithelial cell changes precede tumour development? Can we characterize the extent and significance of disruption to cell proliferation during carcinogenesis?

2. Position - Why are certain oral sites so predisposed to cancer? Can we determine the significance of anatomical site effects and field change cancerization within the oral cavity?

3. Progression – Why do some oral precursor lesions progress to invasive carcinoma and others do not? Can we improve our understanding of the natural history of PMD?

4. Prediction - How can we predict individual patient and/or lesion behaviour? Can we rationalize the diagnosis and interventional management of PMD and thereby reduce the burden of OSCC disease?

By delineating and stratifying risk for oral carcinogenesis both within a population and for individual patients, can we then facilitate effective primary, secondary and tertiary preventive strategies to reduce the burden of OSCC?

Proliferation

Epithelial cell proliferation, differentiation and ultimately apoptosis are strictly regulated mechanisms that maintain normal oral mucosa structure and function. Within the progenitor compartment (located within basal and immediately supra-basal cells), postulated epithelial proliferative units containing stem cells undergo self-renewal and, by asymmetric division, produce daughter keratinocytes for terminal differentiation[3]. Lack of confirmed biological markers prevents reliable identification of oral epithelial stem cells which is unfortunate, as they are the likely focus of initial carcinogenesis[1,4].

The acquisition of genetic, phenotypic and functional alterations in stem cells leads to loss of normal cell cycle restraint initiating transition from benign hyperplasia towards dysmaturation and dysplastic tissue formation, followed by loss of replicative senescence and unlimited proliferation in a stage of 'pre-malignancy' which if unchecked leads to carcinoma-in-situ and then invasive OSCC. Loss of cell cycle control and abnormal cell proliferation are thus fundamental mechanisms driving carcinogenesis, with quantitative proliferation indices putative markers of malignant potential, tumour growth and ultimately prognosis[1,5-7].

Oral epithelial cells destined for 'pre-malignant' change are those most likely to already possess an inherently high proliferative activity. Using in-vitro labelling studies to characterize oral epithelial activity, we have demonstrated a significant

increase in proliferation indices for both increasingly severe dysplasia and worsening grades of OSCC differentiation[8-10]; overall, increasing numbers of epithelial cells committed to cell division are characteristic of dysplastic PMD lesions[11,12]. Of particular interest is the additional observation that 'apparently normal-looking' mucosa from OSCC patients may also exhibit abnormal proliferation profiles similar to that seen in dysplastic or neoplastic tissue[8].

'Pre-malignant fields' probably precede tumour formation, with OSCC arising in a field sub-clone following specific, additional genetic damage; the field expands through oral epithelium at the expense of normal surrounding mucosa due to its inherently high proliferation rate[9]. Resultant tumour proliferation rates may well be determined by the proliferative rate of the 'pre-malignant' epithelium in which they arise, with speed of proliferation particularly important[13]. Recognition of a 'pre-malignant field' is important in prevention, therapy and prognosis, especially for clinically presenting PMD patients, although it is concerning that neither clinical nor histopathological features reliably identify this change[1].

Further research is undoubtedly warranted into the clinical application of cell proliferation measurement and predictive analysis of OSCC precursor lesions. Whilst recent research has focused upon molecular biology, quantifiable cell proliferative changes probably reflect the overall status of genetic damage in tissue much better than individual oncogene alterations and may have prognostic significance[5].

Position

To reliably characterize epithelial proliferative activity within the human oral cavity, it is essential to delineate pre-existing anatomical site variability. By harvesting normal mucosa from varying sites during oral surgery procedures and measuring in-vitro proliferation indices, we demonstrated significantly increased activity and prolongation of S-phase DNA synthesis on the floor of mouth and ventrolateral tongue, sites known to exhibit predilection for OSCC development; in contrast, low risk regions such as palatal mucosa and tongue dorsum showed corresponding reduction in epithelial activity[14]. Demonstration of inherently high proliferative cell activity is strongly suggestive of an underlying predisposition to carcinogenesis[14],

and both increased proliferative activity and chromosomal instability in site-specific lesions may offer predictive roles in identifying early signs of dysplasia and quantifying cancer risk[15-17].

In a study of 26 patients presenting with unilateral PMD or OSCC who underwent 'mirror image' biopsy sampling from apparently normal contralateral mucosa, we found that 15 exhibited occult dysplasia or early OSCC development[18]. Highly supportive of field change carcinogenesis within the oral cavity, these observations also confirmed floor of mouth and ventro-lateral tongue sites to be at increased susceptibility to field change dysplasia[18].

Whilst 'field cancerization' theories propose that carcinogen-induced changes exist throughout both oral cavity and upper aerodigestive tract, a particular subgroup of PMD patients exhibit a high incidence of multiple lesion and multi-focal tumour development[19]. Detailed follow-up studies have shown that multiple-site disease affects up to 24% of patients, occurs significantly more frequently in tobacco smokers and with low fruit and vegetable dietary intake, although dysplasia within individual lesions is less severe and buccal mucosa sites are more frequently involved[20]. In contradistinction, single PMD lesions exhibit more severe dysplasia, have higher epithelial proliferative indices and present commonly on the floor of mouth and ventrolateral tongue[20].

A higher incidence of malignant transformation (MT) is seen in multiple lesion disease, probably reflecting widespread mucosal instability[20]. Although a challenging management problem, a pragmatic approach to rationalize diagnosis and targeted intervention utilises a multiple 'field mapping' biopsy technique[21]. The soft palate, faucial pillars, floor of mouth and ventral tongue are recognised as sites most at risk of severe dysplasia; individual PMD lesions, however, respond well to CO_2 laser excision[21,22].

Recognition of dysplastic change in clinically normal mucosa co-existing with PMD lesions probably represents an early 'pre-malignant' event and the initiation of field change[23]. Regular and careful clinic review is of special importance during the management of field change patients in order to identify dysplastic disease or diagnose OSCC, potentially at multiple oral sites, at the earliest possible stage. Prolonged follow up strategies and multiple treatment interventions in specialist

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clinics require significant resource allocation but this appears increasingly justifiable and in the best interests of patients[24,25].

Progression

The 'progression model' of oral carcinogenesis emphasizes that initial, irreversible genotypic damage produces tissue disorganisation and dysmaturation which, if allowed to progress, lead inexorably towards invasive OSCC[1]. Recognition of PMD lesions is relatively straightforward upon oral cavity inspection, but our ability to identify and treat 'high risk' lesions and 'at risk' patients at the earliest stage of disease remains problematic, although this is fundamental to a successful interventional management strategy[25,26].

It is recognised that PMD appearance, specifically proliferative verrucous leukoplakia (PVL), non-homogenous leukoplakia, erythroleukoplakic lesions and erythroplakia, may be associated with persistent and progressive disease, but these are generalised observations and do not reliably inform individual patient management[22,26].

Detailed characterization of phenotypic epithelial changes during carcinogenesis, however, have demonstrated not only increased cell proliferation within increasingly dysplastic and neoplastic tissue but also hierarchical disruption whereby enhanced proliferative activity extends into supra-basal layers; the latter in particular is associated with poor clinical outcome, PMD persistence and recurrence, MT and lymph node metastasis[10,27-30]. Whilst the importance of increased proliferation in oral dysplastic lesions is now recognised, many studies are limited by their observational, cross-sectional nature. We therefore followed PMD patients for 5-years post-treatment and confirmed a significantly increased risk of progressive disease when proliferative labelling indices in tissue specimens exceeded median values for site-specific mucosal lesions[31].

In the absence of readily available predictive biomarkers, long term clinical follow-up of affected patients becomes mandatory for meaningful analysis of PMD disease progression and MT risk[1,25]. Active patient surveillance, preferably in dedicated

specialist clinics, facilitates the recognition of recurrent or further PMD disease, helps identify early signs of MT, rationalizes timing and coordination of further treatment intervention, and provides opportunities to modify risk factor behaviour and assess long-term patient risk[26].

Prediction

It is frustrating that we remain unable to predict clinical outcome for newly presenting PMD patients or individual mucosal lesions in contemporary clinical practice[26]. However, follow-up of patients undergoing coordinated treatment intervention has allowed detailed documentation of clinical outcome and helped define specific categories of disease free (DF), further PMD disease, MT (same-site) and OSCC development (new-site); these outcome categories are valuable tools in interpreting patient treatment data[4].

Retrospective analyses of patient cohorts have also confirmed the following consistent and predictive clinico-pathological observations:

1. DF status is common in cases of mild dysplasia, but is significantly less likely for erythroleukoplakia and lichenoid lesions,
2. Further PMD disease is more frequent following PVL treatment and in the absence of laser excision surgery,
3. OSCC risk is greatest in erythroleukoplakia, in severe dysplasia and in lesions arising on the floor of mouth and ventro-lateral tongue[8].

As a general observation, the incidence of further PMD disease increases with the length of patient follow-up, whilst non-homogeneous leukoplakia, extensive lesions, more severe dysplasia and floor of mouth and ventral tongue sites all appear to be at greater risk of progressive disease[32]. Continued tobacco smoking and alcohol use following treatment are also risk factors for developing further PMD[33,34].

It is possible, therefore, to delineate 'high risk' and 'low risk' patients on the basis of available clinico-pathological features, although it is recognised that this is primarily patient cohort based[26]. In the future, it is hoped that individual patient profiling,

genomic sequencing and personalised medicine will improve the specificity of predictive diagnosis and targeted treatment intervention.

Prevention

In order to improve patient survival and reduce the morbidity following OSCC diagnosis, it is imperative for clinicians to utilize the 'PMD window' to identify MT at the earliest possible stage and to intervene effectively to halt disease progression. Whilst we have shown that surgical excision of PMD lesions can decrease the risk of same-site MT, it does not eliminate the subsequent risk of new-site OSCC development[35].

Unfortunately, there is also considerable public ignorance regarding OSCC and PMD, and the patient population most 'at risk' rarely attends for oral examination or dental care[26]. As general population screening programmes for OSCC are ultimately flawed health care interventions, a more pragmatic approach is to identify and specifically target those patient groups deemed to be 'high risk' for OSCC development[26,36]. The pragmatic difficulty, of course, is how to consistently identify this population prior to disease presentation. Profiling 'high-risk' patients in European studies have emphasized the following features: male gender, short stature, low socio-economic status, manual occupation or unemployment, addiction to tobacco and alcohol, diets low in fruit and vegetables, and poor oral hygiene and irregular dental care[26]. It is recognised that the detailed influence of these features will vary between global regions.

Overall, the ultimate clinical management goal remains the prevention of OSCC development, with all 3 tiers of preventive medicine intrinsically linked throughout the process of diagnosis and management:

1. Primary prevention, to avoid disease development, removes the principal risks factors of disease and promotes protective behaviour within a community or

population; in particular, eliminating the use of tobacco products, avoiding excessive alcohol consumption and improving diet and nutrition.

2. Secondary prevention, to detect PMD or early OSCC at a stage when intervention leads to cure or significantly reduced morbidity and mortality; this requires an effective interventional management strategy targeting the 'high-risk' population.

3. Tertiary preventive strategies attempt to reduce the risk of disease recurrence and minimize disease-related complications in treated patients, and rely on appropriate specialist clinical service provision and dedicated patient follow-up protocols.

Table 1 summarizes preventive strategies influencing OSCC diagnosis and management; it is notable how many are concentrated towards secondary prevention in the 'high risk' patient population.

An important clinical consequence is the realization that patient surveillance, regular clinic monitoring and risk factor profiling remain pertinent for all PMD patients even following successful treatment intervention[26]. Indeed, long-term patient surveillance has enhanced our understanding of PMD natural history, helped identify and treat the 'high risk' patient, ensured recognition and modification of risk factor behaviour, and highlighted the significance of multiple-lesion presentation and field change cancerization[20,26].

Conclusions

For many years, early diagnosis of OSCC and PMD management have been areas of clinical practice in which variability in decision making and lack of high-quality evidence confounded treatment[36]. It is hoped that recent clarification and rationalization of interventional management strategies will facilitate demonstrable improvements in clinical care, although it is recognised that it takes time to change established patterns of clinicians' decision making[22,25,32,38,39].

By combining an understanding of oral epithelial proliferation and anatomical position variance with enhanced knowledge of PMD progression and prediction of clinical behaviour, it is hoped that rationalized preventive strategies may be targeted

appropriately to aid in the early diagnosis and management of individual patients at risk of carcinogenesis. Only in this manner are we likely to truly improve the outcomes for our patients with OSCC.

Competing Interests

None declared.

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TABLE LEGEND

TABLE 1: PREVENTIVE STRATEGIES IN EARLY OSCC DIAGNOSIS AND MANAGEMENT

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Preventive Strategy	Knowledge Base	Target Population	Clinical Intervention
Primary	Patient Profiling Risk Stratification	General	Patient Education Identify & Eliminate Risk Factors
Secondary	Abnormal Cell Proliferation Anatomical Position Disruption of Tissue Hierarchy Field Change Multiple-Site Disease Progressive Disease	'High-Risk'	Mirror Image Biopsies Field Mapping Biopsies Interventional Surgery
Tertiary	Clinical Outcome Data	Treated Patients	Patient Surveillance Further Intervention