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Genomic mutations and proof of causation between dysplasia and SCC in medico-legal cases- a useful approach or a waste of resources?

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Seminal work has suggested[1,2] possible clinical implications of field cancerization in oral stratified squamous epithelium. Since then, several studies examined clonal relationships between dysplasia and oral squamous cell carcinoma (OSCC)[3,4]. It is now obvious, that the relationship between dysplasia, at a specific oral cavity site and a subsequent squamous cell carcinoma, arising at the same site several years later, is complex and not a simple

progression[5]. Those of us that see patients with various mucosal abnormalities in a maxillofacial clinic, often treat lesions with low (LGD) or high grade dysplasia (HGD).

Surgical excision has been the preferred modality, when active intervention has been deemed appropriate, due to the risk of malignant transformation which can be as high as 12.1%[6]. Often patients will have a single lesion that will be excised, resulting in complete healing. Evidence-based patient specific models relating to a detailed risk of malignancy, for this group of patients, do not exist and it may be appropriate for these patients to be discharged to primary care.

It is of note that at present we are lacking credible evidence in order to formulate a specific follow-up regimen, in terms of frequency and duration. Occasionally, patients who have been discharged from secondary care will be referred back several years later with an OSCC. Understandably, this can raise questions from patients relating to the initial management and may lead to medico-legal disputes. In an attempt to 'prove negligence' and sub-optimal clinical care at the initial treatment episode, legal teams may attempt to link the two lesions with the use of genomic technology.

Such an approach may raise several issues. Recent genomic work indicated that point mutations accumulate from normal tissue to LGD, HGD and OSCC but there is no step-wise appearance of a wave of sub-clones[5]. In addition, dysplasia samples have mutations not found in an OSCC that developed in the same site as the original dysplasia several years later. Most importantly although several copy number changes and point mutations can be identified in early oral epithelial dysplasia, at present we are unable to identify those patients that will develop an OSCC. Mutated genes are demonstrated in patients with LGD in field cancerization, but their clinical significance remains unknown. Recent characterization of fully invasive disease[4] has suggested that gene changes were far more heterogeneous, with only six genes mutated in over 10% of samples, and none of those in more than 25%[4].

A genomic progression from normal tissue through pre-cancerous stages to fully invasive disease has not been characterized in HNSCC[5]. Limited work has demonstrated a considerable variety in terms of evolutionary relationships and differentially expressed pathways between OSCC and oral dysplasia. Taking into account the above, an attempt by legal representatives or 'expert witnesses' to link an early dysplastic lesion to a subsequent

OSCC using genomics is a dangerous oversimplification and may be seen as a waste of resources.

Conflict of interest: The authors have no conflict of interest to declare

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