Profiling Cancer Risk in Oral Potentially Malignant Disorders – a Patient Cohort Study

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Abstract

Background: Oral potentially malignant disorders harbour variable and unpredictable risk for squamous carcinoma development. Whilst current management strategies utilise histopathological diagnoses, dysplasia grading and targeted intervention for ‘high risk’ lesions, clinicians are unable to predict malignant potential.

Methods: Detailed, retrospective clinico-pathological analysis of potentially malignant lesions undergoing malignant transformation, from a 590 patient cohort treated by interventional laser surgery and followed for a mean of 7.3 years, was undertaken. Clinical outcome was documented at study census date (31 December 2014).

Results: 99 patients (16.8%) developed cancer: 71 (12%) seen ‘unexpectedly’ upon excision and 28 (4.8%) progressing to malignancy at a median of 87.3 months post-surgery. 30 ‘unexpected’ excisions were micro-invasive (42.3%) arising primarily in severely dysplastic precursors (75%) at ventro-lateral tongue and floor of mouth sites (54.5%); 1 patient (1.4%) had a cancer-related death, whilst 58 (81.7%) were disease free. 19 of 28 ‘progressive’ cancers (67.9%) arose at new sites, with erythroleukoplakia a significant predictor of malignancy ($p=0.0019$). 9 (32.1%) developed at the same precursor site, with 6 (77.7%) on the ventro-lateral tongue and floor of mouth. 3 (10.7%) were micro-invasive, 9 patients (32.1%) died from metastatic disease and 12 (42.9%) were disease free ($p<0.001$).

Conclusion: Squamous carcinoma may arise at the site of a precursor lesion as transformation or new-site development via field cancerisation. Whilst interventional surgery facilitates early diagnosis and treatment of occult disease, thus reducing risk from same-site transformation, new-site cancer is a significant long-term risk for potentially malignant disorder patients.

Introduction

Invasive oral squamous cell carcinomas (OSCC) are preceded by potentially malignant disorders (PMD), distinct mucosal lesions including leukoplakia, erythroplakia, or erythroleukoplakia and widespread disorders such as proliferative verrucous leukoplakia (PVL)[1,2]. Characteristic of PMD is the variable presence of epithelial disorganisation and dysmaturation, identified microscopically as dysplasia and subjectively graded for severity[1,2]. The natural history of PMD remains poorly understood, however, with varying malignant transformation rates quoted between 0.13 to 36.4% occurring over periods of 1 to 30 years[3]; systematic review estimates an overall 12% cancer risk over a mean transformation time of 4.3 years[4].

In a recent editorial, Guneri & Epstein[3] highlighted clinicians' inability to predict PMD behaviour or quantify the risk of malignant transformation emphasizing our poor understanding of carcinogenesis. Contemporary PMD management relies upon incision biopsy for histological confirmation followed by surgical excision for definitive diagnosis and effective treatment of lesions deemed 'high risk'[5-7]. Whilst controversy may exist over the assignment of risk, early diagnosis and intervention during the progression of dysplasia to OSCC should have potential to improve patient prognosis and reduce morbidity and mortality; this hypothesis remains largely unproven however[1].

Long-term observational studies of PMD patients have been advised to improve knowledge of disease progression, to determine predictors of clinical outcome and establish realistic time-scales for malignant transformation[3,8].

In a previous study we demonstrated a degree of efficacy for interventional management by reviewing clinical outcome in 590 'high risk' PMD patients undergoing CO_2 laser surgery and followed for up to 19 years post-treatment (mean 7.3yrs); 438 patients (74.2%) became disease free, 53 (9%) had persistent disease, and 99 (16.8%) developed OSCC.[7] Features associated with malignant transformation included eryrthroleukoplakic appearance, presence of severe dysplasia in initial biopsies and origin on ventro-lateral tongue and floor of mouth sites[7].

The specific purpose of this paper is to re-evaluate the clinico-pathological data for these 99 transforming PMD patients and thereby identify features predictive of cancer, enhance understanding of the carcinogenic pathway and clarify the likely time-course for malignant transformation in PMD patients.

Method

Caldicott Approval from Newcastle University / Newcastle upon Tyne Hospitals NHS Foundation Trust facilitated anonymized, retrospective data collection from medical records, operating books and original pathology reports from PMD patients treated by laser in Maxillofacial Surgery between August 1996 and December 2014. Inclusion criteria for this analysis required patients to have been new presentations of single-site PMD disease with a confirmed diagnosis of OSCC. Demographic and clinico-pathological data required patient age and sex, appearance and site of presenting PMD, histopathology diagnoses (pre-operative incision and post-laser excision biopsies), OSCC appearance, site and histopathology, and clinical outcome at study census date (31 December 2014).

All biopsies and CO_2 laser surgeries were carried out by the first author (PJT), or colleagues working under direct supervision, to well-established guidelines and within 6 to 12 weeks of PMD presentation to avoid disease progression[5]. Formalin-fixed tissue specimens were assessed via standardized histopathology examination by oral pathologists at the Royal Victoria Infirmary using agreed diagnostic criteria, peer review and consensus grading[7]. The World Health Organization (WHO) system was used and dysplasia classified as mild, moderate and severe or carcinoma-in-situ (CiS); micro-invasive and invasive OSCC categories were distinguished. Diagnoses of hyperkeratosis, lichenoid inflammation (LI), PVL and chronic hyperplastic candidosis (CHC) were also made.

All OSCC patients were referred to Newcastle multi-disciplinary head and neck clinics for further assessment and management along established oncology care pathways. Clinical outcomes were stratified as: disease free, further disease or cancer-related death.

Statistical Analyses

Descriptive Statistics were used to summarise patient demography, clinico-pathological features, clinical outcome and follow-up data. Fisher's exact test, Student's t-test and Chi-square testing were used as appropriate to compare clinico-pathological features, assessed as categorical variables, potentially influencing clinical outcome. Due to low study numbers in each category, P values were computed using Monte Carlo simulation and natural logarithmic transformation applied prior to analyses of time influence. Univariate Cox regression analyses of clinico-pathological factors potentially influencing time to malignant transformation, including patient sex, age, precursor lesion site, appearance and histopathology were also performed. Statistical analyses were carried out using SPSS, version 19.0 (Statistical Package for the Social Sciences, Chicago, IL, USA), R Environment for Statistical Computing (version 3.2.5) and SAS/STAT® 9.3 software (SAS Institute Inc, Cary, USA).

Results

Two distinct OSCC presentations were recognised in the 99 patients: 71 were identified immediately and 'unexpectedly' upon histopathological assessment of laser excision specimens, whilst 28 cases 'progressed' to malignancy at same or new sites during follow-up.

Unexpected OSCC Diagnosis

Data for the 71 'unexpected' OSCC cases are listed in Table 1, comprising 50 males (age range 47-83yrs; mean 62.6yrs) and 21 females (age range 33-89yrs; mean 65.3yrs). Initial lesion appearance included 38 leukoplakias (53.5%), 29 erythroleukoplakias (40.9%) and 4 erythroplakias (5.6%). 48 lesions (54.5%) arose on the ventro-lateral tongue and floor of mouth, with other individual sites less frequently involved. 66 presenting lesions (93%) exhibited dysplastic features on histopathological examination, with severe dysplasia or CiS in 52 (73%). All OSCCs were completely excised by laser, with 30 (42.3%) classed as micro-invasive.

Clinical outcome at study census showed 58 patients disease free (81.7%), 12 developing further PMD disease (16.9%) and 1 OSCC-related death (1.4%).

Progression to OSCC

Table 2 documents clinico-pathological profiling for precursor PMDs and subsequent OSCC lesions in the 28 'progression' cases including cancer site, time to malignant transformation and clinical outcome. Patients comprised 16 males (age range 34-84yrs; mean 60.7yrs) and 12 females (age range 45-92yrs; mean 65.3yrs). 19 precursor lesions presented as leukoplakia (68%), with 6 erythroleukoplakias (21%) and 3 erythroplakias (11%). 15 (53.6%) arose on the ventro-lateral tongue and floor of mouth, with other sites again infrequently affected. 27 lesions (96.4%) exhibited dysplasia on initial biopsy, with 17 (60.7%) showing severe dysplasia or CiS. 18 OSCCs presented as erythroleukoplakia (64%) with 10 leukoplakias (36%); only 3 OSCCs (10.7%) were micro-invasive. In terms of clinical outcome, 12 patients (42.9%) were disease free, 7 (25%) developed further PMD and 9 (32.1%) died from metastatic OSCC.

Change in lesion appearance to erythroleukoplakia was a specific OSCC predictor within the 'progression' group (Fisher's exact test: p=0.0019), whilst comparison between 'unexpected' and 'progression' groups highlighted both an increased proportion of invasive OSCCs (Chi-squared test: x^2=8.99; p=0.004) and poor clinical outcome including OSCC-related deaths (Chi-squared test: x^2=23.75; p<0.001) as a result of 'progressive' disease. Patient sex, age, precursor lesion site, appearance and histopathology were not predictive of behaviour; Table 3.

9 OSCCs arose at the same-site as PMD precursor, with 6 (77.7%) arising on ventro-lateral tongue and floor of mouth. For 19 OSCCs developing at new-sites, there were no clear relationships between precursor and subsequent site, although ventro-lateral tongue and floor of mouth precursors were less frequent (8 or 42.2%). Same-site transformation occurred between 3 and 48 months (mean 28 months), whilst new-site OSCC generally took longer, from 9 to 204 months (mean 61.3 months), although the difference was not statistically significant (Student's t-test: p=0.21). Median time to malignancy in the 28 cases was 87.3 months (95% CI 59.9 to 149.2). Analyses of clinico-pathological variables potentially influencing time to malignancy in the 28 cases are summarised in Table 4, but none were significant.

Discussion

Transformation of an identifiable precursor lesion into invasive OSCC must rank as the ultimate PMD treatment failure, yet prediction of 'high-risk' behaviour and cancer development remains elusive in clinical practice. Published transformation rates vary widely between 0.13 and 50%, with 'average' times ranging from 0.5 to 17 years[3,9-16]; such data are unhelpful in counselling individual patients in clinical practice, although it is generally believed that risk increases for lesions exhibiting severe dysplasia and over prolonged follow-up[11,13,14]. Warnakulasuriya & Ariyawardana[17] reviewed 24 observational studies of oral leukoplakia and identified advanced age, females, lesion greater than 200mm^2 in size, non-homogenous clinical appearance and severe dysplasia as high risk. Other authors, however, have not found clinical or pathological observations to correlate reliably with malignant transformation, with currently available biomarkers of little practical use[3,18-20].

This paper presented a clinico-pathological review of 99 PMD patients developing OSCC in a 590 cohort undergoing laser treatment[7]. Identifying and excising 71 'unexpected' cancers, particularly early stage micro-invasive tumours, is undoubtedly a diagnostic and treatment success, demonstrating efficacy of intervention and supporting the hypothesis that patient morbidity and mortality can be reduced[1,7,21]; 81.7% of these patients were disease free with only 1 cancer-related death. In contrast, a further 28 patients developed post-treatment OSCC, 19 at new sites, at a median time of 87.3 months. Whilst long-term follow-up facilitated early OSCC recognition, it is notable that these clinical outcomes were significantly worse with 9 cancer-related deaths and only 42.9% of patients disease free at census ($p<0.001$).

Few studies have reported upon defined PMD cohorts undergoing standardised treatment, so it is difficult to compare data with other publications. Saito et al[22] reported 6.3% transformation in 142 patients treated by surgery for leukoplakia, although only 91 lesions were dysplastic, whilst Ho et al[15] observed a 25% rate in 91 patients monitored over a median 40.3 month period, but provided no treatment details. We have previously identified occult OSCC in 9% of 169 laser excisions[23], but this current series presents the largest and longest observed cohort.

The clinician's dilemma remains how to identify and predict PMDs at greatest risk of cancer. Precursor lesions in this Northern England population most frequently

presented as leukoplakia (57) on ventro-lateral tongue and floor of mouth sites (63), consistent with previous reports and reflective of inherent disease susceptibility[5,6,24]. Of clinical relevance is the observation that ventro-lateral tongue and floor of mouth were at particular risk of same-site malignant transformation, both 'unexpected' and 'progressive', although seemed less likely to be the primary focus in cases of new-site OSCC. Erythroleukoplakia, either as a precursor in 'unexpected' cases or as a change in appearance during 'progression' was associated with OSCC development, confirming earlier observations and highlighting the importance of its early recognition[7,17].

Review of precursor histopathology did not show a reliable predictive role, although 52 of 71 'unexpected' (73.2%) and 17 of 28 'progression' cases exhibited severe dysplasia or CiS on initial biopsy, supporting earlier reports regarding high-grade dysplasia risk[13,17]. Finding micro-invasive cancers in substantive numbers within the 'unexpected' group emphasised not only the difficulty in identifying early cancer change clinically[21], but also the efficacy of intervention via excision because clinical outcome was demonstrably better in these patients[7]. In contrast, despite early recognition during follow-up, the increased number of invasive OSCCs in the 'progression' group was associated with poor clinical outcome and an increased number of cancer-related deaths.

Time to malignancy varied substantially between 3 to 204 months, although same-site transformation generally occurred earlier than new-site cancer development, probably reflecting variable influence of field change cancerization. Lack of statistical significance in the 'progression' group may relate to the limited sample size of 28 cases.

It is the authors' opinion that clarifying terminology will assist future observational studies and therefore advise restricting the term 'malignant transformation' to PMDs exhibiting same-site OSCC, whilst distinguishing 'cancer development' for those with new-site disease. Intervention to excise localised lesions may indeed prevent or effectively treat 'malignant transformation' but the risk of subsequent 'cancer development' remains. Active surveillance during patient follow-up is thus an essential component of interventional therapy and allows early signs of further disease to be recognised and treatment initiated[5-7].

The precise interplay of epidemiological, diagnostic, histopathological, and bio-molecular factors remains complex, however, with carcinogenesis arising from intrinsic and extrinsic influences acting both synchronously and metachronously throughout ill-defined areas of mucosal field change[1].

Although this was neither a prospective nor randomized controlled trial and was limited in population size from a single-centre, review of clinico-pathological and patient outcome data has provided additional insight into cancer risk within a defined PMD cohort. Interventional laser surgery facilitates early diagnosis and effective treatment of occult 'unexpected' OSCC and reduces morbidity and mortality from same-site transformation, but new-site cancer retains lethality and is a significant long-term risk for all PMD patients.

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Competing Interests

None declared.

Ethical Approval

Newcastle University / Newcastle upon Tyne Hospitals NHS Foundation Trust Caldicott Guardian Approval for Anonymised Patient Data Collection & Retrospective Review of Hospital Records ID 4143 (2015)

Patient Consent

Not required.

References

1. Thomson PJ. Oral Carcinogenesis. In: PJ Thomson (ed) *Oral Precancer – Diagnosis and Management of Potentially Malignant Disorders. Chichester:* Wiley-Blackwell; 2012. p31-47.

2. van der Waal I. Potentially malignant disorders of the oral and oropharyngeal mucosa; terminology, classification and present concepts of management. *Oral Oncology* 2009 **45** : 317-323.

3. Guneri P, Epstein JB. Why are we still unable to accurately determine the malignant potential or the behaviour of oral mucosal lesions? *Oral Oncology* 2017 http://dx.doi.org/10.1016/j.oraloncology.2017.04.011.

4. Mehanna HM, Rattay T, Smith J, McConkey CC. Treatment and follow-up of oral dysplasia – a systematic review and meta-analysis. *Head & Neck* 2009 **31** : 1600-1609.

5. Thomson PJ, Wylie J. Interventional laser surgery: an effective surgical and diagnostic tool in oral precancer management. *International Journal of Oral & Maxillofacial Surgery* 2002 **31** :145-153.

6. Diajil AR, Robinson CM, Sloan P, Thomson PJ. Clinical outcome following oral potentially malignant disorder treatment: a 100 patient cohort study. *International Journal of Dentistry* 2013 Article ID 809248, 8 pages http://dx.doi.org/10.1155/2013/809248.

7. Thomson PJ, Goodson ML, Cocks K, Turner JE. Interventional laser surgery for oral potentially malignant disorders: a longitudinal patient cohort study. *International Journal of Oral & Maxillofacial Surgery* 2017 **46** : 337-342.

8. Arduino PG, Bagan J, El-Naggar AK, Carrozzo M. Urban legends series: oral leukoplakia. *Oral Diseases* 2013 **19** : 642-659.

9. Schepman KP, van der Meij EH, Smeele LE, van der Waal I (1998). Malignant transformation of oral leukoplakia: a follow-up study of a hospital-based population of 166 patients with oral leukoplakia from The Netherlands. *Oral Oncology* **34** : 270-275.

10. Cowan GC, Gregg TA, Napier SS, McKenna SM, Kee F (2001). Potentially malignant oral lesions in Northern Ireland: a 20-year population-based perspective of malignant transformation. *Oral Diseases* 7 : 18-24.

11. Shiu MN, Chen TH (2003). Intervention efficacy and malignant transformation to oral cancer among patients with leukoplakia. *Oncol Report* **10** : 1683-1692.

12. Hsue SS, Wang W-C, Chen C-H, Lin C-C, Chen Y-K, Lin L-M (2007) Malignant transformation in 1458 patients with potentially malignant oral mucosal disorders: a follow-up study based in a Taiwanese hospital. *J Oral Pathol Med* 36 : 25–29.

13. Speight PM (2007). Update on oral epithelial dysplasia and progression to cancer. *Head and Neck Pathol* 1 : 61-66.

14. Warnakulasuriya S, Kovacevic T, Madden P, Coupland VH, Sperandio M, Odell E, Moller H (2011). Factors predicting malignant transformation in oral potentially malignant disorders among patients accrued over a 10-year period in South East England. *J Oral Pathol Med* 40 : 677-683.

15. Ho MW, Field EA, Field JK, Risk JM, Rajlawat BP, Rogers SN, Steele JC, Triantafyllou A, Woolgar JA, Lowe D, Shaw RJ (2013). Outcomes of oral squamous cell carcinoma arising from oral epithelial dysplasia: rationale for monitoring premalignant oral lesions in a multidisciplinary clinic. *British Journal of Oral & Maxillofacial Surgery* **51** : 594-599.

16. Field EA, McCarthy CE, Ho MW, Rajlawat BP, Holt D, Rogers SN, Triantafyllou A, Field JK, Shaw RJ (2015). The management of oral epithelial dysplasia: The Liverpool algorithm. *Oral Oncology* **51** : 883-887.

17. Warnakulasuriya S, Ariyawardana A (2015). Malignant transformation of oral leukoplakia: a systematic review of observational studies. *J Oral Pathol Med* doi: 10.1111/jop.12339.

18. Arduino PG, Surace A, Carbone M, Elia A, Massolini G, Gandolfo S, Broccoletti R (2009). Outcome of oral dysplasia: a retrospective hospital-based study of 207 patients with a long follow-up. *J Oral Pathol Med* **38**: 540-544.

19. Watabe Y, Nomura T, Onda T, Yakushiji T, Yamamoto N, Ohata H, Takano N, Shibahara T (2015). Malignant transformation of oral leukoplakia with a focus on low-grade dysplasia. *Journal of Oral & Maxillofacial Surgery, Medicine & Pathology* http://dx.doi.org/10.1016/j.ajoms.2015.02.007.

20. Goodson ML, Sloan P, Robinson CM, Cocks K, Thomson PJ (2015). Oral Precursor Lesions and Malignant Transformation – Who, Where, What and When? *British Journal of Oral & Maxillofacial Surgery* **53**: 831-835.

21. Pentenero M, Navone R, Marino R, Gassino L, Broccoletti R, Gandolfo S (2011). Clinical features of microinvasive stage I oral carcinoma. *Oral Diseases* **17**: 298-303

22. Saito T, Suguira C, Hirai A, Notani K, Totsuka Y, Shindoh M, Fukuda H (2001). Development of squamous cell carcinoma from pre-existent oral leukoplakia: with respect to treatment modality. *International Journal of Oral & Maxillofacial Surgery* **30**: 49-53.

23. Goodson ML, Thomson PJ (2011). Management of oral carcinoma: benefits of early precancerous intervention. *British Journal of Oral & Maxillofacial Surgery* **49:** 88-91.

24. Thomson PJ, Potten CS, Appleton DR (1999). Mapping dynamic epithelial cell proliferative activity within the oral cavity of man: a new insight into carcinogenesis. *British Journal of Oral & Maxillofacial Surgery* **37**:377-383.

TABLE 1: CLINICO-PATHOLOGICAL FEATURES OF PRECURSOR PMD LESIONS IN WHICH LASER EXCISION REVEALED UNEXPECTED SCC (*Number = 71*)

Year	Age	Sex	PMD Lesion	Site	Incision Biopsy Histopathology	SCC Histopathology	Clinical Outcome
1997	89	F	ELK	Buccal	Severe Dysplasia	miSCC	Further PMD
1997	64	M	LK	Lateral Tongue	Moderate Dysplasia	SCC	Disease Free
1997	71	F	LK	Buccal	Hyperkeratosis	SCC	Disease Free
1998	50	M	ELK	Lateral Tongue	CiS	miSCC	Disease Free
1998	62	M	ELK	Lateral Tongue	Severe Dysplasia	SCC	Disease Free
1998	69	F	LK	FOM	CiS	miSCC	Further
1998	64	M	ELK	Fauces / RM	Severe Dysplasia	SCC	Further
1998	51	F	ELK	Lateral Tongue	Severe Dysplasia	miSCC	Disease Free
1998	54	M	EK	Fauces / RM	CiS	SCC	Disease Free
1998	72	M	LK	Lateral Tongue	CiS	SCC	Disease Free
1998	83	F	ELK	Lateral Tongue	Severe Dysplasia	SCC	Disease Free
1998	52	M	ELK	Buccal	CHC	SCC	Disease Free
1999	48	M	LK	Lateral Tongue	Severe Dysplasia	SCC	Disease Free
1999	66	F	LK	Lateral Tongue	Severe Dysplasia	SCC	Disease Free
1999	69	M	LK	FOM	Moderate Dysplasia	miSCC	Disease Free
1999	58	F	ELK	Lateral Tongue	Severe Dysplasia	SCC	Disease Free
1999	81	M	ELK	FOM	Moderate Dysplasia	SCC	Disease Free
1999	56	M	ELK	FOM	CiS	miSCC	Disease Free
1999	49	M	ELK	Palate	CiS	miSCC	Disease Free
1999	61	M	ELK	FOM	CiS	miSCC	Disease Free
1999	47	M	ELK	Lateral Tongue	Severe Dysplasia	SCC	Disease Free
1999	68	M	LK	Buccal	Severe Dysplasia	SCC	Further PMD
2000	68	M	LK	Ventral Tongue	CiS	miSCC	Further PMD
2000	66	F	LK	Palate	CiS	SCC	Disease Free
2000	67	M	LK	Lateral Tongue	CiS	SCC	Disease Free

2000	68	M	LK	FOM	CiS	miSCC	Disease Free
2000	59	M	LK	Palate	CiS	miSCC	Disease Free
2001	59	M	EK	Fauces / RM	CiS	miSCC	Disease Free
2001	67	M	ELK	Fauces	CiS	miSCC	Disease Free
2001	69	F	LK	Buccal	CiS	miSCC	Disease Free
2002	69	M	LK	Ventral Tongue	Hyperkeratosis	SCC	Disease Free
2002	83	M	ELK	FOM	Severe Dysplasia	SCC	Disease Free
2003	84	F	LK	Alveolus	Severe Dysplasia	miSCC	Disease Free
2003	61	F	LK	Lateral Tongue	Severe Dysplasia	miSCC	Disease Free
2003	73	M	LK	Ventral Tongue	CiS	miSCC	Disease Free
2003	57	F	LK	Lateral Tongue	CiS	SCC	Further PMD
2004	68	F	LK	Lateral Tongue	Hyperkeratosis + Lichenoid Inflammation	miSCC	Disease Free
2004	73	M	LK	FOM	CiS	miSCC	Disease Free
2004	55	M	ELK	Lateral Tongue	CiS	miSCC	Disease Free
2004	79	M	LK	FOM	Severe Dysplasia	miSCC	Disease Free
2004	81	M	ELK	Lateral Tongue	CiS	SCC	Disease Free
2004	61	M	LK	Lateral Tongue	CiS	SCC	Further PMD
2004	77	F	LK	Ventral Tongue	Mild Dysplasia	SCC	Disease Free
2004	65	F	LK	FOM	Severe Dysplasia	SCC	Disease Free
2005	59	M	ELK	FOM	Severe Dysplasia	SCC	SCC Death
2005	49	M	ELK	FOM	CiS	SCC	Disease Free
2005	48	M	ELK	Lateral Tongue	Severe Dysplasia	miSCC	Disease Free
2006	60	M	LK	Dorsum Tongue	Mild Dysplasia	miSCC	Further PMD
2006	51	M	ELK	RM	Severe Dysplasia	SCC	Disease Free
2007	60	M	LK	Lateral Tongue	CiS	SCC	Disease Free
2007	64	F	ELK	Lateral Tongue	Moderate Dysplasia	SCC	Disease Free
2007	82	M	EK	Fauces	CiS	SCC	Disease Free

2007	52	M	LK	Lateral Tongue	Moderate Dysplasia	SCC	Disease Free
2007	59	M	ELK	Buccal	Moderate Dysplasia	miSCC	Disease Free
2007	33	F	LK	Dorsum Tongue	PVL	SCC	Disease Free
2007	63	M	ELK	Ventral Tongue	Severe Dysplasia	SCC	Disease Free
2007	62	M	EK	Palate	Severe Dysplasia	miSCC	Disease Free
2007	74	F	LK	Buccal	Mild Dysplasia	miSCC	Disease Free
2008	70	M	LK	Lateral Tongue	Mild Dysplasia + Lichenoid Inflammation	SCC	Further PMD
2008	61	M	LK	FOM	Severe Dysplasia	SCC	Disease Free
2009	67	M	LK	Ventral Tongue	Moderate Dysplasia	SCC	Disease Free
2010	65	M	ELK	FOM	Severe Dysplasia	SCC	Disease Free
2010	58	M	LK	Lateral Tongue	Mild Dysplasia	miSCC	Disease Free
2011	66	M	LK	FOM	Severe Dysplasia	miSCC	Disease Free
2012	74	F	ELK	Alveolus	Mild Dysplasia	SCC	Disease Free
2012	65	M	LK	Fauces	Severe Dysplasia	SCC	Further PMD
2013	67	M	ELK	Lateral Tongue	CiS	SCC	Further PMD
2013	57	F	LK	FOM	Severe Dysplasia	SCC	Disease Free
2013	51	M	ELK	Lateral Tongue	Severe Dysplasia	miSCC	Disease Free
2013	58	M	LK	Lateral Tongue	Mild Dysplasia	miSCC	Further PMD
2013	36	F	ELK	Fauces	CiS	SCC	Disease Free

LK: leukoplakia; ELK: erythroleukoplakia; EK: erythroplakia; FOM: floor of mouth; RM: retromolar region; PVL: proliferative verrucous leukoplakia; CiS: carcinoma-in-situ; miSCC: micro-invasive squamous cell carcinoma; SCC: squamous cell carcinoma; PMD: potentially malignant disorder

TABLE 2: CLINICO-PATHOLOGICAL PROFILING OF PRECURSOR PMD LESIONS AND THEIR TRANSFORMED SCCs (*Number = 28*)

Year	Age	Sex	PMD Lesion	Precursor Histopathology	Precursor Site	SCC Lesion	SCC Site	SCC Histopathology	MT (months)	MT Site	Clinical Outcome
1996	88	F	LK	Moderate Dysplasia	Buccal	LK	Alveolus	SCC	204	New	SCC Death
1996	45	F	LK	Hyperkeratosis + Lichenoid Inflammation	Alveolus	LK	Palate	SCC	30	New	SCC Death
1997	58	M	LK	CiS	Fauces / RM	ELK	RM	miSCC	48	Same	SCC Death
1998	72	M	EK	CiS	Fauces / RM	LK	Lateral Tongue	SCC	8	New	Disease Free
1998	76	M	EK	CiS	Buccal	ELK	Alveolus	SCC	86	New	SCC Death
1999	61	F	LK	Moderate Dysplasia	Ventral Tongue	LK	Lateral Tongue	miSCC	15	New	SCC Death
1999	92	F	LK	Moderate Dysplasia	Lateral Tongue	LK	Buccal	SCC	12	New	Disease Free
2000	51	F	LK	Moderate Dysplasia	Palate	ELK	Alveolus	SCC	124	New	Further PMD
2000	84	M	LK	CiS	Lateral Tongue	ELK	FOM	SCC	133	New	Disease Free
2000	62	M	LK	CiS	Labial Commissure	ELK	Dorsum Tongue	SCC	147	New	SCC Death
2001	56	F	ELK	CiS	Fauces / RM	ELK	Palate	SCC	158	New	Disease Free
2002	60	M	LK	Moderate Dysplasia	Labial Commissure	LK	Labial	SCC	9	New	Disease Free
2003	47	M	LK	Severe Dysplasia	Lateral Tongue	ELK	Lateral Tongue	miSCC	35	Same	Disease Free
2003	72	M	LK	CiS	Lateral Tongue	LK	FOM	SCC	12	New	Further PMD
2003	54	F	LK	Moderate Dysplasia	Alveolus	ELK	Buccal	SCC	69	New	Further PMD
2003	48	M	ELK	Severe Dysplasia	Lateral Tongue	ELK	Lateral Tongue	SCC	59	Same	Further PMD
2006	62	F	LK	Mild Dysplasia	Lateral Tongue	ELK	Palate	SCC	18	New	SCC Death
2007	59	M	ELK	Severe Dysplasia	Lateral Tongue	ELK	Palate	SCC	70	New	Disease Free
2007	58	M	LK	CiS	Fauces / RM	ELK	FOM	SCC	17	New	SCC Death
2008	74	F	LK	Mild Dysplasia	Palate	ELK	Palate	SCC	3	Same	Disease Free
2008	58	M	LK	Severe Dysplasia	FOM	ELK	FOM	SCC	4	Same	Disease Free

2008	74	F	LK	Mild Dysplasia	Buccal	LK	Labial	SCC	28	New	SCC Death
2008	73	M	EK	CiS	FOM	LK	FOM	SCC	16	Same	Disease Free
2009	62	F	ELK	Severe Dysplasia	Lateral Tongue	ELK	Lateral Tongue	SCC	24	Same	Disease Free
2010	34	M	LK	Mild Dysplasia	Ventral Tongue	ELK	Ventral Tongue	SCC	42	Same	Further PMD
2010	51	M	ELK	Severe Dysplasia	Lateral Tongue	ELK	Fauces	SCC	9	New	Further PMD
2010	59	M	ELK	Severe Dysplasia	FOM	ELK	Labial	SCC	16	New	Disease Free
2012	65	F	LK	Severe Dysplasia	FOM	LK	FOM	SCC	21	Same	Further PMD

LK: leukoplakia; ELK: erythroleukoplakia; EK: erythroplakia; FOM: floor of mouth; RM: retromolar region; PVL: proliferative verrucous leukoplakia; CiS: carcinoma-in-situ; miSCC: micro-invasive squamous cell carcinoma; SCC: squamous cell carcinoma; PMD: potentially malignant disorder

TABLE 3: COMPARISON OF CLINICO-PATHOLOGICAL VARIABLES BETWEEN 'UNEXPECTED' OSCC (n=71) AND PROGRESSION OSCC (n=28)

Clinico-Pathological Variable	Chi Square	p-Value
Sex	1.59	0.25
Age	0.79	0.50
Precursor Site	12.56	0.24
PMD Lesion Appearance	3.59	0.16
Precursor Histopathology	5.65	0.74
miSCC vs SCC	8.99	*0.004*
Clinical Outcome	23.75	*<0.001*

miSCC: micro-invasive squamous cell carcinoma; SCC: oral squamous cell carcinoma

TABLE 4: CLINICO-PATHOLOGICAL VARIABLES INFLUENCING TIME TO CANCER DEVELOPMENT (PROGRESSION GROUP n=28)

Clinico-Pathological Variable	p-Value
Sex	0.58
Age	0.46
Precursor Site*	-
PMD Lesion Appearance	0.55
Precursor Histopathology	0.96

**Insufficient data available in category for analysis*